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Complementary and Alternative Medicine: Botanicals/ Homeopathy/ Herbal Medicine

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PREFACE

As the challenges of modern healthcare grow, the exploration of complementary and alternative medicine (CAM) is more relevant than ever. This book, *Complementary and Alternative Medicine: Botanicals/Homeopathy/Herbal Medicine*, brings together the therapeutic knowledge of botanical, homeopathic, and herbal remedies with insights from contemporary research. It aims to offer practical applications of natural medicine for both human and veterinary health, with a particular focus on combating antibiotic resistance, managing chronic diseases, and providing natural alternatives for disease prevention. The initial sections examine the medicinal power of plants like *Moringa oleifera* and *Nigella sativa*, demonstrating their efficacy against parasites, diabetes, and multi-drug-resistant infections. The versatility of plants such as *Silybum marianum* and *Citrullus colocynthis* is highlighted in formulations for managing chronic health conditions, while studies on herbs and plant extracts offer promising strategies for treating bacterial infections in both humans and animals. Throughout, the book provides a comprehensive look at how herbal approaches can address pressing health challenges, including antibiotic resistance and animal health issues in agriculture. Further, this collection explores the use of homeopathic remedies for disease management in poultry, cattle, and other animals. Ancient botanical remedies, such as those used for rinderpest in buffalo and gastrointestinal infections, are revisited through a modern lens, showing how these therapies can offer gentler alternatives to conventional treatments. As the global community increasingly seeks sustainable health practices, the resurgence of plant-based medicine offers exciting possibilities for animal health, from controlling parasites to managing bacterial infections. In addition to practical applications, the book delves into scientific research on the pharmacological potential of many plants traditionally used in folk medicine. Reviews of the bioactive compounds in *Moringa oleifera*, for instance, demonstrate its broad therapeutic uses, while sections on medicinal plants for diabetes and inflammation management underscore the relevance of herbal medicine in chronic disease prevention. From botanical alchemy to the application of phytochemicals in combating infectious diseases, these insights reveal how age-old remedies are gaining renewed validation and significance in modern healthcare. The benefits of CAM extend beyond treating specific conditions. Topics on immunostimulation, stress reduction in farmed fish, and natural strategies for reducing inflammation show the potential of CAM in enhancing overall health. Discussions on quality standards and ethnobotanical practices also highlight the importance of authentic sources and traditional knowledge, ensuring that CAM applications are both safe and effective. As this book shows, the convergence of CAM with scientific innovation holds the promise of a holistic approach to health, preventive care, and sustainability. By integrating herbal medicine, homeopathy, and botanical research, *Complementary and Alternative Medicine: Botanicals/Homeopathy/Herbal Medicine* provides a comprehensive resource for practitioners, researchers, and anyone interested in the evolving role of natural therapies in addressing some of today's most complex health challenges.

Editor

Contents

Chapter 01

The Antiparasitic Effect of Botanicals with Special Reference to *Moringa* against *Cryptosporidium* Species

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ABSTRACT

Cryptosporidium (*C.*) belongs to the phylum Apicomplexa. There are different species of *Cryptosporidium* in which *C. parvum* is the main zoonotic agent. *C. parvum* causes gastrointestinal infections in animals. The transmission of *C. parvum* occurs through contaminated food and water. Its life cycle depends upon only a single host and sporozoites released attach to the epithelial lining of the small intestine. *Cryptosporidium* causes economic losses due to decreased milk productivity, mortality due to severe dehydration, and low reproductive performance. Different drugs are used for the treatment of *Cryptosporidium*. Nitazoxanide is the only FDA-approved that is used against *Cryptosporidium* infection. However, these drugs cause resistance in animals. Then alternative strategies are used for the treatment of infection. Plant extracts are used against *Cryptosporidium* that inhibit larvae migration and hatching of eggs. Bioactive compounds like flavonoids, alkaloids, tannins, and ascorbic acid, of different plants show their efficiency. Different extracts are present in plants that show their effect on the motility of larvae, and egg hatching. Of all medicinal plants, *Moringa oleifera* has great importance in the treatment of *Cryptosporidium*. It has antioxidant, anti-inflammatory, and antibiotic properties, and certain compounds treat intestinal lesions. *M. oleifera* is used for the treatment of parasitic infections in animals. Zinc, iron, and magnesium are also present in it. Zinc is used to increase metabolism, iron increases the growth of animals, and magnesium is used to increase milk production. *Cryptosporidium* can be prevented by treating the contaminated water with moringa seed extract.

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INTRODUCTION

Cryptosporidium (C.) is a protozoal parasite that is present throughout the world (Galuppi et al., 2016), and it belongs to the phylum Apicomplexa (Hassan et al., 2021). It causes the gastrointestinal tract infection in domestic animals. Cryptosporidiosis causes intense diarrhea in ruminants and causes economic losses because of decreased growth, performance, and production of animals (Tomazic et al., 2018). *Cryptosporidium* species that infect the cattle are *C. parvum*, *C. anderson, C. bovis*, and *C. ryanae*. On the other hand, *C. parvum* is the only species that is linked to the characteristic symptoms of cryptosporidiosis in cattle and the primary source of infection in pre-weaned calves. *C. parvum* is the main zoonotic agent of cryptosporidiosis and may also infect several animal species (Pinto et al., 2021). *C. parvum* is the most pathogenic species in cattle and humans while other species have few cases. The zoonotic importance of *Cryptosporidium* is identified by knowing the effect of infection on public health (El-Alfy and Nishikawa, 2020). *C. parvum* is a vital species among all species of the genus *Cryptosporidium* and has zoonotic potential so it needs high consideration to be controlled (Sayed, Hamza, Galal, Sayed, & Gaber, 2016).

C. parvum is an obligate intracellular parasite that attaches to the epithelial lining of the gastrointestinal tract of the host and causes infection (Sayed et al., 2016). In cattle, *C. parvum* causes a severe gastrointestinal infection which also causes a decrease in the growth rate, and reduces milk production, anorexia, and weight loss. This parasite has a simple life cycle and depends on a single host species during its life cycle (Tarekegn et al., 2021). The oocyst of *Cryptosporidium* has two forms one is an environmental form which is a thick-walled oocyst. This oocyst gets ingested by the consumption of contaminated fodder or water. When thick-walled oocyst is ingested, it undergoes excystation due to changes in temperature, action of bile salt, and pH. The second form is sporozoites which are released from the oocyst. Sporozoites are released and attach to the epithelial lining of the gut (Pinto and Vinayak, 2021). The transmission of oocyst has critical importance in the life cycle of *Cryptosporidium spp* (Mohammed, Degefu, & Jilo, 2017).

In cattle, the transmission of *C. parvum* is through the fecal-oral route (Shaw et al., 2021). In the summer season, chances of infection are more due to the high intake of water and other activities like swimming but in winter these activities are decreased so the chance of infection is also reduced (Khan et al., 2022). In veterinary clinics, *Cryptosporidium* is diagnosed by fecal sample. Molecular methods are also used for species differentiation which include polymerase chain reaction (PCR) (Thomson et al., 2017). The *C. parvum* oocysts in food are detected by aptamers (Petersen et al., 2014). Different techniques are used for the detection of oocysts which include Allen and Ridley's formal method, centrifugation method, and sucrose flotation method. The most sensitive method between them is the formol-ether method. Detection in fecal samples is difficult due to the small size of the oocyst. For the identification of oocysts in stool samples different staining techniques are used including Nigrosine staining, safranin staining, Giemsa staining, and Ziehl staining (Siddique et al., 2021). Proper diagnosis of the *Cryptosporidium* is necessary to estimate the need for control of the disease (Gerace, Presti, & Biondo, 2019).

Different drugs are used to treat cryptosporidiosis. Nitazoxanide, clofazimine, glycopeptide occidiofungin, pyrazolopyridine derivates, paromomycin, and metronidazole, etc. are examples of some anti-cryptosporidium medicines. However, by use of these drugs except Nitazoxanide, shows no effective treatment. Clinical symptoms of cryptosporidiosis are only improved with paromomycin (Ali et al., 2024) (Namazi & Razavi, 2024). For the control of cryptosporidiosis in livestock, the drug Halofuginone lactate is used (Aboelsoued and Abdel Megeed, 2022). Nitazoxanide drug approved by the US Food and Drug Administration is used but this drug is ineffective in weak immune patients (Ranasinghe, Zahedi, Armson, Lymbery, & Ash, 2022). When these anti-parasitic drugs are used continuously against infection, resistance to the parasite may be developed (Ranasinghe et al., 2023). The oocyst which is the infective stage of *Cryptosporidium* has a thick outer shell that helps to live outside of the body. Oocysts can survive for a long period due to their outer thick shell causing resistance to different environmental conditions and disinfection of chlorine. When drugs cause resistance in animals, then as alternative strategies medicinal plants are being suggested as anti-parasitic drugs to cure parasitic infections (Nassar, 2022). As alternative approaches, some researchers used medicinal plants as new and effective drugs for the treatment of cryptosporidial infection (Namazi & Razavi, 2024).

Moringa oleifera is a medicinal plant that belongs to the family Moringaceae and it is widely distributed in north-eastern India, Pakistan, Afghanistan, and Bangladesh (Yerena-Prieto et al., 2022). There are some regional names for *M. oleifera* which include the drumstick tree, Kelor, mlonge, saijhan, benzolive, miracle tree, Marengo, mulangay, and Sanjana. It has an antioxidant property and consists of ascorbic acid, carotenoids, saponins, flavonoid, and phenolic content. These all have their role against oxidation. The extract of moringa leaves improves intestinal lesions and increases the level of antioxidants that defend against oxidative stress in the body (Namazi and Razavi, 2024).

It is used as a drug that has the potential to treat animals with infection of parasitic worms. This is commonly used for helminth parasites but has also shown some antiprotozoal activity. Due to the soluble lactin in its seed extract, it shows larvicidal properties. It stops the development of larvae due to their heamagglutinating activity (Fatima et al., 2014). Antibiotic and fungicidal activity is also present in the moringa plant due to their pterygosperium and related compounds. Every part of the moringa plant has different properties that are effective against infection (Haldar and Kosankar, 2017).

Transmission of *Cryptosporidium parvum* in Cattle

Transmission of *Cryptosporidium* in cattle is associated with zoonotic transmission. *C. parvum* is transmitted through food and water. *C. parvum* causes gastrointestinal infection and some species of *Cryptosporidium* are related to respiratory cryptosporidiosis. The infective stage is the oocyst stage that causes infection when it is excreted in the environment and transmission also occurs through the contaminated environment. When cattle ingest the infective stage (oocyst), its excystation occurs in the small intestine and releases the sporozoites. These sporozoites invade the wall of the intestine and asexual multiplication occurs. Sporozoites change into merozoites followed by sexual multiplication and formation of macrogamonts and macrogamonts. By following the fertilization of macrogamonts, oocysts are produced that sporulate within the host before being shed in host faces (Robertson et al., 2020). *C. parvum* is transmitted by ingestion of thick-walled oocyst from different sources. The main sources of transmission are contaminated water and food (Shafiq et al., 2015). Animals are often bathed with contaminated water and also drink this water that favour the transmission of *Cryptosporidium* (Abbas et al., 2022). The climatic conditions and weather fluctuations have an impact on the transmission of *Cryptosporidium* species. The role of climatic conditions is vital in the suspension of oocyst in water, contamination of water sources, and the temperature, and rainfall also affect transmission of this parasite (Fig. 1) (Golomazou et al., 2024)

Life cycle

Cryptosporidium is present everywhere in nature and it requires only a single host to complete its life cycle. Many stages are completed in its life cycle which include asexual and sexual replication. *Cryptosporidium* is an intestinal parasite which reproduce asexually and undergoes a cycle of merogony and sexual gamogony. It has a complicated life cycle. Three developmental stages occur in this parasite; meronts, gamonts, and oocyst. Multiple stages are present in an asexual division that follows the sexual division and development of the oocyst through fertilization. Oocysts come into the environment through faces. Because of the appropriate moisture and moderate temperature, oocysts bear the environmental conditions and live in the water and soil for several months. Due to their small size, oocysts transfer to another place through water sources and air. Two types of oocysts exist; thin-walled and thick-walled oocyst. Thin-walled oocysts present in the host intestine and cause intestinal lesions and thick-walled excreted in the environment and cause infection after ingestion of oocyst through oral uptake. After ingestion of oocyst, excystation occurs in the intestine and changes into sporozoites. Based on *Cryptosporidium* spp., sporozoites invade the gastric and intestinal epithelium. Inside the host, the next stage of asexual proliferation merogony occurs. The shape and size of merozoites and sporozoites are the same, only nucleus difference is present. In merozoites, the nucleus is located in the center than sporozoites. Merozoites attach to the epithelial cell and spread the infection to other intestinal sites (Abbas et al., 2022). Merozoites form two types of meronts. Gametogany is formed by merozoites and micro-macro gametes are formed by the division of Gametogany, followed by fertilization of gametes, which further fertilize to zygote. Thick and thin-walled oocysts are formed through the process of sporogony. The wall is created around the oocyst to tolerate the environmental conditions. In the next stage, the infection is transferred from one host to another. The final stage is the formation of infectious sporozoites through sporogony (Pumipuntu and Piratae, 2018; Mamedova and Karanis, 2020; Gururajan et al., 2021; Delling and Daugschies, 2022).

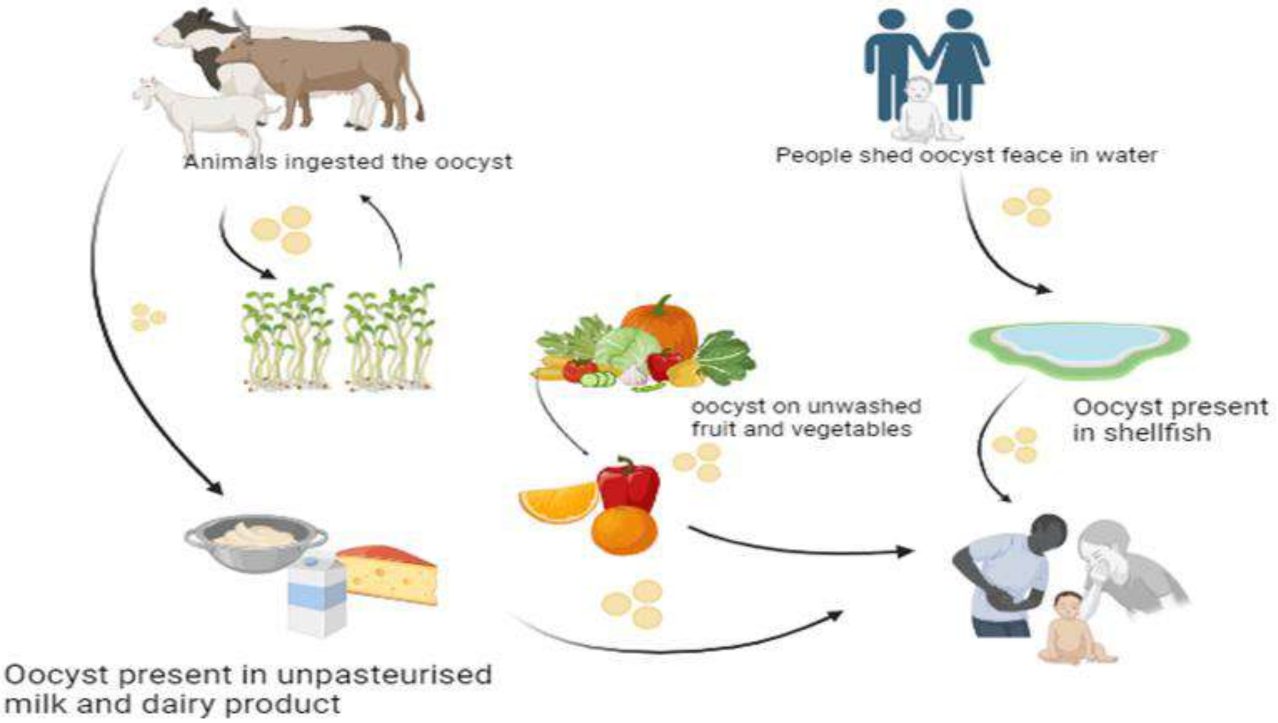

Fig. 1: Transmission of *Cryptosporidium*

Economic Losses

Livestock plays an important role in the development of country economy. However, some factors that pose a threat to livestock production include the different strategies that are used for animal breeding, poor veterinary service, and parasitic diseases. In the world, Pakistan is a milk-producing country, and it fulfills domestic needs. However, the population of Pakistan increased and milk production does not meet the demand of people. Increase the population demand for food and put stress on the price of dairy products. In Pakistan, different factors inhibit the growth of the sector of livestock. Low production of milk and income of farms are the main losses due to livestock diseases (Ashfaq et al., 2015). Parasites that are present in and outside the body of the host get their food. These parasites include helminths, protozoa, lice, and flies that cause gastrointestinal diseases. These diseases cause economic loss in cattle. For the identification of economic loss in cattle due to parasitic disease, different models are used (Rashid et al., 2019). Parasitic disease inhibits the growth and causes disease of blackleg in young cattle. Treatment of reproductive disorders and mastitis is expensive, which also causes major economic loss. Mortality in cattle is due to hemorrhagic septicemia (Ghafar et al., 2020). *Cryptosporidium* causes diarrhea in animals that cause death due to severe dehydration (Khan et al., 2022).

Benefits of Moringa Leaves

Plants have great importance in human life through their medicinal properties and dietary supplements. *Moringa oleifera* is one of the fast-growing, small trees that grow on sandy arid soil and this tress has aesthetically attractive properties (Sujatha and Patel, 2017). This tree may be pollinated by both self-pollination and cross-pollination. There are 13 species of the Moringaceae family. These are dispersed over the globe according to their geography and environment

(Umbreen Shahzad et al., 2019). *M. oleifera* is prevalent in the tropical region of the world sub-Himalayan tract and countries including Pakistan, India, Asia, Africa, Arabia, Philippines, Central America, and Cambodia (Shahzad, Khan, Jaskani, Khan, & Korban, 2013). All parts of this plant contain amino acids, beta-carotene, and phenolic compounds (Gupta and Ahmed, 2020). *M. oleifera* has significant nutritional values and is a rich source of protein, vitamins, and micronutrients that complete the nutritional deficiency of the KPK rural region. The vitamins included in this tree, are vitamin AandC and the micronutrients are Ca, Fe, and K (Haroon et al., 2023). The locally known name of moringa in Pakistan is "Sohanjna" and it is distributed in Punjab, Sindh, and Khyber Pakhtunkhwa (KPK). It is also called a miracle tree due to its nutritional, and medicinal properties (Faisal et al., 2020). *Moringa* is used as an animal feed. During the winter season, with the help of moringa leaves urea-molasses block is made that overcomes the nutritional deficiencies in cattle (Malik et al., 2019). Anti-inflammatory, antibiotics, and antioxidant characteristics are present in moringa leaves. In cattle, *M. oleifera* is used as a protein diet (Mahmood et al., 2022). It shows a great impact on the control of parasites and hinders the disease associated with parasites (Soltan et al., 2017). Magnesium is present in it which increases milk production and the level of iron is also high which increases the growth of animals. Zinc increases the metabolism of protein, fats, and sugar and plays a role in tissue respiration (Su and Chen, 2020).

Plant Bioactive Compound for Control of Gastrointestinal Parasite

The excessive use of chemicals and drugs against gastrointestinal parasites causes anthelminthic resistance, then an alternative method is used for the treatment of infection. These alternative approaches play an important role in the control of GIT parasites in cattle (Zeineldin et al., 2020). The drug resistance is developed against *Cryptosporidium*, then medicinal plants are used as alternative strategies. Drug metronidazole that causes resistance in *Cryptosporidium* (Ojuromi and Ashafa, 2020). Much literature revealed that 139 plants are used for the treatment of diarrhea and abdominal pain, and 30 species are used against protozoal infections (Calzada and Bautista, 2020). Many natural compounds are present in plants that have great efficiency against parasites. These compounds are variable due to their growth environment, and condition, and their harvesting method also plays an important role in the preservation of compounds (Hoste et al., 2015). The effect of plant extract and compounds on anthelmintic activity can be detected by adding them to animals' diet during their infection period (Chagas, 2015).

Different bioactive substances are present in medicinal plants such as flavonoids, alkaloids, and tannins that show their properties against anthelminthic activities. Tannins hinder the hatching of eggs and migration of larvae. It binds with cuticles and causes changes in the movement of larvae, reproduction, absorption, and nutrition. Different parameters are used for showing the effect of plant extract on the GIT parasite from which is part of the species, the dose and type of extract are used. Different types of extract are used; methanolic extract, ethanolic extract, aqueous extract, and acetone extract (Blomstrand et al., 2021). A study by (Akouedegni et al., 2019) revealed that compared to methanolic extract, ethanolic extract of *S. monbin* leaves has a greater influence on larvae motility. Observation of researchers reported that for larvae the aqueous extract shows a greater impact than the ethanolic extract. For larvae migration, the acetone extract of *P. biglobossa* shows a greater effect than methanolic extract, on egg hatching the acetonic extract of plant *cassia alata* plays an important role than aqueous extract. The presence or lack of secondary metabolite in one extract relative to another might be the cause of the variation in activity across the extract of the same plant (Degla et al., 2022). According to a report by Farooq et al. (2008), in the Cholistan desert veterinarians use traditional medicine for the treatment of parasitic disease in cattle. However, the study by Khan (2009) revealed that 35 species of plants were collected from the Cholistan desert of Pakistan and showed the efficiency against parasitic disease in cattle. Tipu et al. (2006) described the efficiency of the anti-coccoidal and anti-parasitic activities, present in leaves and fruits of *Azadirachta indica.* Plant extract is used for the treatment of tick-borne protozoal disease and mastitis in cattle. Different plant species are useful for livestock diseases like gastrointestinal disease, healing of wounds, cough, fever, urinary tract infection, and placental removal (Ahmed and Murtaza, 2015).

Effect of *Moringa* against *Cryptosporidium*

Cryptosporidium is transmitted through contaminated water. When contaminated water along with feces and oocyst of parasites is given to crops, health issues are raised. Water is treated with inorganic and organic chemicals, but this treatment of water is expensive and the emergence of many diseases occurs in animals. The natural way is used for the treatment of water. Among water, *M. oleifera* seeds are used for the treatment of water (Petersen, Petersen, Enemark, Olsen, & Dalsgaard, 2016). The bioactive compound of moringa phenol and alkaloids shows an antiparasitic effect (Elghandour et al., 2023). According to a study, *M. oleifera* extract is used in poor countries as a water purifier and to avoid people with waterborne disease (Mariane de Souza, Beltran, Bergamasco, & Cusioli, 2024).

Conclusion

Cryptosporidium is a gastrointestinal parasite that causes intense diarrhea, lesions in the intestine, blacklegs, mastitis, and dehydration in animals. From *Cryptosporidium* species, *C. parvum* is a main zoonotic agent that causes transmission of infection from animal to human and vice versa. *C. parvum* causes economic loss due to the low production of milk and inhibits the growth of animals. Drugs that are used against infection in animals cause resistance. Medicinal plants are used for the treatment of gastrointestinal infections. Bioactive compounds are present in these plants that show their effect. Of all these plants, *Moringa oleifera* is the plant that is known as a miracle tree due to its magical properties. This plant tolerates adverse climatic conditions. Bioactive compounds like flavonoids, tannins, vitamins, and alkaloids are present in it that show antiparasitic activity. By using these bioactive compounds new drugs are made for the treatment of *Cryptosporidium* in animals. The contaminated water is also treated with moringa seed extract for the prevention of *Cryptosporidium*. However, more research is required to know the benefits of moringa and the application of moringa in animals against *Cryptosporidium*.

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Chapter 02

Development of Antidiabetic Herbal Formulations Based on *Nigella sativa*, *Silybum marianum* and *Citrullus colocynthis*

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ABSTRACT

Diabetes mellitus is considered a complex metabolic disorder that presents a considerable global health burden owing to its rising prevalence and associated complications. Several plant-based formulations are reported to date to have a significant number of phytochemicals that are helpful in combating diabetic complications. Herbal remedies work synergistically to improve body health, especially by alleviating the overall antioxidant status. Moreover, herbal treatments offer a good alternative for a variety of possible side effects associated with conventional medicines. This chapter focuses on the chemical profile, therapeutic benefits, and the antidiabetic properties of herbal formulations containing specifically *Nigella sativa*, *Silybum marianum*, and *Citrullus colocynthis* extracts.

KEYWORDS		
C. colocynthis, Diabetes mellitus, herbal formulations, *N. sativa*, *S. marianum*,	Received: 22-May-2024 Revised: 13-Jul-2024 Accepted: 14-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Diabetes Mellitus (DM) and its Classification

Diabetes Mellitus is a widespread metabolic disorder characterized by chronic high blood sugar levels due to inadequate insulin production, impaired insulin action, or a combination of these factors. Insulin is an important hormone that plays its role and affects the metabolism of proteins, lipids, and carbohydrates in our body (Poznyak et al., 2020). Metabolic imbalances due to insulin resistance primarily impact tissues like fat cells, muscles, and the liver. The intensity of symptoms differs based on the type and duration of diabetes. Hyperglycemia, especially in individuals with low insulin levels, leads to conditions like increased hunger, excessive thirst, difficulty in urination, weight loss, and vision problems. However, certain individuals, particularly those in the initial phases of type 2 diabetes, might not exhibit any noticeable symptoms (Rossi et al., 2019). If left untreated, diabetes can result in serious complications like coma, neuropathy, and in severe cases, fatalities due to untreated ketoacidosis or hyperosmolar syndrome without ketosis (Poznyak et al., 2020).

Diabetes is classified mainly into two types; Type-I diabetes and Type-II diabetes, however, its latest classification is as given in Fig. 1.

Allopathic/Synthetic Approaches to Combat Diabetes

Oral antidiabetic agents treat pathophysiological conditions to control blood sugar levels. Sulfonyl urea's, Dipeptidyl peptidase 4 inhibitors, Sodium Glucose cotransporter 2 inhibitors, and metformin are the most commonly used medicines (Qaseem et al., 2017). To improve the absorption and utilization of glucose thiazolidinedione's are used as insulin sensitizers (Chaudhary et al., 2017). Combining rapid-acting insulin with long-acting basal insulin is effective in glycemic management and mimics physiological insulin formation. Many surgical techniques like Bariatric surgery serve as good alternatives to treat diabetes (Palanisamay et al., 2018). It is important to find out a wide range of alternatives to prevent people from diabetes as it has become a worldwide health problem. Early detection and care are a must to avoid life-threatening consequences (Antea et al., 2022).

Herbal Formulations and their Mode of Action

Using herbal prophylactics, the blood glucose levels are lowered may be due to a rise in the number of β cells of islets of Langerhans to induce more insulin. *Panax ginseng* and *Allium sativum* are known to have cytoprotective properties and protect the functioning of pancreatic β cells (Wickramasinghe et al., 2021). Some other herbal alternatives work by quick uptake and utilization of blood glucose by accelerating the sensitivity of peripheral tissues to insulin. Moreover, many herbal formulations like *Salacia reticulate* and *Phaseolus vulgaris* affects the absorption of sugar in the gut by the inactivation of those enzymes which degrade the sugar content of the food (Tran et al., 2020).

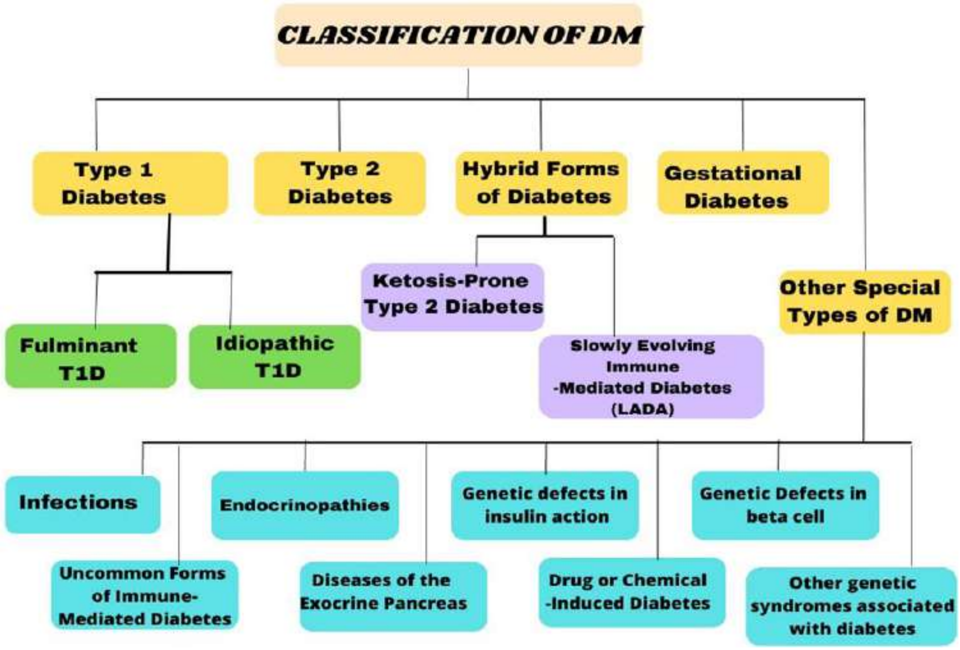

Fig. 1: The latest classification of DM includes various types and subtypes of diabetes (Antar et al., 2023).

Nigella sativa

Dark-colored seeds of black cumin, botanically named *N. sativa* (NS), is a little blooming plant local to southwest Asia. For quite a long time, it has been utilized in conventional medication and as a culinary flavor because of its potential medical advantages. Ongoing logical examination has started to investigate its useful properties, affirming a significant number of its certifiable medicinal purposes and revealing new likely applications (Petruzzello and Melissa, 2024).

Phytochemical Profile of *N. sativa*

Till now, *N. sativa* has been adored for its curative properties. In customary medication, it has been utilized to treat different illnesses, including respiratory diseases, for example, asthma and bronchitis, stomach-related messes, erythrogenic conditions, and skin issues and to boost immune functions (Hannan et al., 2021).

Table 1: Biologically active components of NS (Zielinska et al., 2021)

Active Compounds	Contents
Logefoline	1-8%
Carvacrol	6-12%
Nigellicimine, nigellidine, A-hederin and citronellol	<1% (Trace Amounts)
Vitronellol, saponin, Carvone, N-tlenek nigellicimine, nigellicine and limonene	<1% (Trace Amounts)
T-Anethol	1-4%
4-Terpinol	2-7%
Thymohydroquinone, dithymoquinone and p-cymene	7-15%
Thymoquinone	30-48%

N. sativa plant consists of a rich mixture of thymol, omega-3-fatty acids (ώ3fatty acids), omega-6 fatty acids (ώ6fatty acids), saponins, and flavonoids, thymoquinone and thymohydroquinones. All these bioactive mixtures are a rich blend of highly antioxidative properties that contribute to the treatment of different chronic diseases like diabetes. These bioactive compounds lessen the side effects of various inflammatory illnesses like gut sickness, asthma, and joint pain (Eun et al., 2021).

Therapeutic Potential of *N. sativa*

N. sativa can effectively regulate the performance of the immune system, upgrading its capacity to battle against germs and different illnesses. The immunomodulatory properties of *N. sativa* make it flexible against different microbes (Niu et al., 2021). *N. sativa* has antioxidant and anticancer properties which help to protect the cells from oxidative stress and damage induced by free radicals. The healing potential of *N. sativa* interferes with the progress of malicious growth cells in cancerous tissues. The extract of *N. sativa* has strong hepatoprotective properties as it has healing effects on failed liver function caused by oxidative damage. *N. sativa* supplementation has wonderful neuroprotective effects on improved memory function and improved mental capability in older people (Landucci et al., 2021). *N. sativa* is renowned as a powerful tonic with an eminent history of ordinary consumption as a medicinal plant. It has intense antioxidative behavior which presents it as a potent anticancer substance and is known for its immunomodulatory impacts (Ciesielska et al., 2023). Table 1 enlist different compounds reported in *N. sativa* responsible for its biological effects.

Antidiabetic Potential of *N. sativa*

Traditional herbal medications are well known for their antidiabetic properties including *N. sativa*. A strong bioactive compound thymoquinone is responsible for antidiabetic impacts. Moreover, a combination of a variety of bioactive compounds comprising saponins, flavonoids, and omega fatty acids holds pharmacological benefits (Mahomoodally et al., 2022).

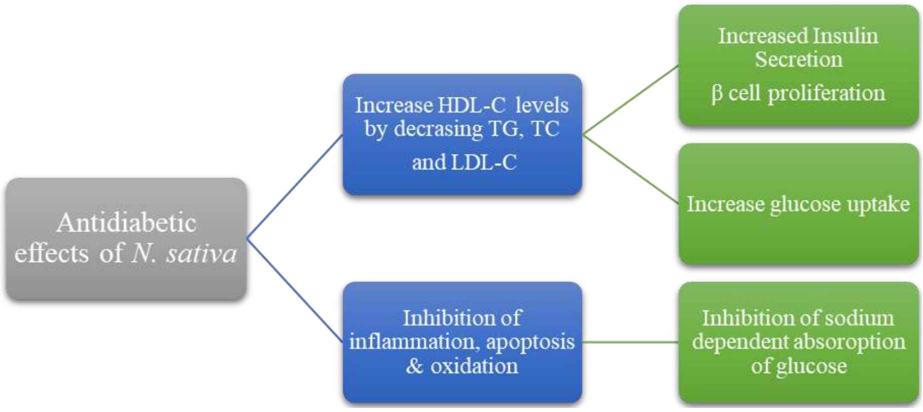

Fig. 2: Proposed antidiabetic effects of NS (Hajar et al., 2022)

The proposed antidiabetic effects of *N. sativa* are shown in Figure 2. Akhtar et al. (2020) evaluated the antidiabetic, hypolipidemic, and antioxidant potential of *N. sativa* seed oil (NSO) and described the significant effects of NSO administration on diabetic rabbits in lowering the serum blood glucose levels and lipid contents with an increase in HDL-C (High-density lipoprotein cholesterol) and vitamin C levels ($p < 0.001$). However, NSO administration has significantly decreased the serum catalase activity along with the decrease in Total Cholesterol (TC), Triglycerides (TGs), Low-Density Lipoproteins (LDL-C), and Very Low-Density Lipoproteins (VLDL-C) levels. *N. sativa* has an important role in lowering blood sugar levels by enhancing insulin sensitivity resulting in the uptake of glucose from peripheral tissues. The shielding effect of NS protects the function of beta cells of islets of Langerhans and their ability to release insulin as it shields the beta cells of the pancreas from damage induced by oxidative stress (Banday et al., 2020). A combination of *N. sativa* with metformin resulted in controlled glycemic levels and reduced insulin barrier. Many studies about the herbal potential of NS on the molecular level affirmed the best antidiabetic effects. A powerful bioactive compound, thymoquinone is known for its astonishing role in the settlement of controlled blood glucose levels and fat digestion by displaying its antidiabetic effects. *N. sativa* has soothing and cell-strengthening properties that moderate the irritation and oxidative stress induced by diabetes and in this way serve as a strong antidiabetic agent. *N. sativa* can be used in combination with other antidiabetic prescriptions to show promising results (Khawandanah, 2019).

Antidiabetic Herbal Formulations Comprising *N. sativa* Extracts

Nigella sativa seeds or extracts have been used commonly in herbal preparations targeted against diabetes. The mechanism of action described so far is the increase in insulin responsiveness, permitting better glucose take-up by pancreatic cells. Table 2 enlists findings of different studies from the supplementation of *N. sativa* on diabetes patients. Saadia et al., (2017) reported the therapeutic effects of *N. sativa* administration to quinine-induced thrombocytopenic rats in elevating the platelet count (PLT) of animals to reduce the risk of thrombocytopenia. Moreover, it was found that *N. sativa* post-treatment in rats elevated the serum catalase, ascorbic acid, and bilirubin levels while the pre-treatment increased the micronutrient levels including iron, nickel, and cobalt. In another study, Saadia et al., (2019) reported that *N. sativa* post-treatment to rabbits was found effective in normalizing the serum alanine transaminase (ALT) levels with a significant increase in catalase levels. However, the *N. sativa* pre-treatment was found effective in maintaining the serum nickel and cobalt concentrations. So, it was suggested that *N. sativa* pre or post-administration to test animals was effective in normalizing the serum concentrations of antioxidants and trace elements.

Silybum marianum

Milk thistle, with the scientific name *Silybum marianum* (L.) Gaertn., is a medicinally significant plant from the Asteraceae family, originally found in the Mediterranean Basin. It thrives in warm, arid soil across various regions including North and South America, southern Australia, Europe, Central and Western Asia, and North Africa. Owing to its competitive nature, milk thistle can grow well in light soils with insufficient water supply. Milk thistle is a plant that can be either annual or biennial and grows up to 2.0 meters tall, with stems ranging from 40 to 200 cm in height (Figure 3). Its leaves are arranged alternately possess a shiny appearance, and possess spiny edges and prominent white veins, typically measuring 50-60 cm long and 20-30 cm wide. The flower heads have an average diameter of about 5 cm (Simora et al., 2020).

Table 2: Effect of *N. sativa* supplements on patients with diabetes (Tavakkoli et al., 2017)

Sr.	Study Design	Dose	Result
1	(RDBP) Random double-blind placebo Trial(control)	N.S oil (3g per day)/forty days	Decrease in body mass index, insulin, and insulin resistance including HDL C (compared with baseline)
2	Prospective study	N.S oil (5mL per day)/six weeks	Decrease in LDL cholesterol and fasting blood sugar (FBS)
3	(RDBP) Random double-blind placebo Clinical trial (Control)	N.S oil extract (1g per day)/ Eight weeks	Decrease in triglycerides, LDL-cholesterol, Total count

(a) (b) (c)

Fig. 3: *S. marianum* (a and b) plant, c) Fructus silybi mariani (Simora et al., 2020).

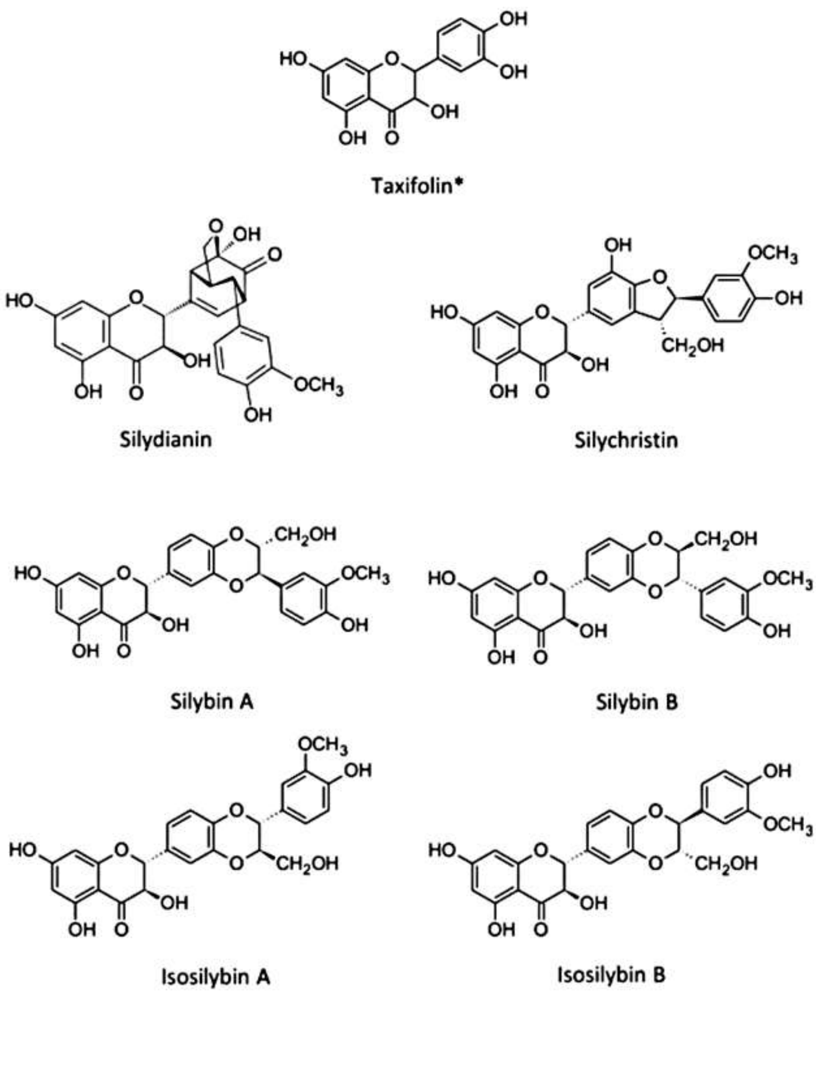

Fig. 4: Chemical structure of silymarin marker compounds (Drouet et al., 2018).other Ingredients

Chemical Constituents of Milk Thistle Extract

The key active compound found in milk thistle is silymarin, which is extracted from the seeds (achenes). Silymarin contains various flavonolignans (flavonolignan isomers), flavonoids, and the most important flavonolignans encompass silybins A and silybins B, silychristin A, isosilybins A and isosilybins B, silydianin and isosilychristin (Fig. 4). Of these compounds, silybin is the most prevalent and biologically active compound, comprising around 60-70%, while silychristin accounts for approximately 20%, silydianin for 10%, and isosilybin for 5%. Additionally, silymarin contains the flavonoid taxifolin (Simora et al., 2020). Apart from flavonolignans and flavonoids, milk thistle also contains sugars (such as rhamnose, arabinose, glucose, and xylose) proteins (25-30 %), sterols (including sitosterol, cholesterol, stigmasterol, and campesterol), tocopherol, and lipids (15-30 %) in the form of triglycerides. Notably, the lipid content consists primarily of palmitic acid (9 %), oleic acid (30 %), and linoleic acid (60 %). Although the lipid-rich oil obtained from milk thistle fruits is nutritionally valuable, it is often regarded as an unwanted byproduct of silymarin extraction. It must be separated from the fruits before silymarin extraction (Aziz et al., 2020). Chemical compound analysis of different parts of *S. marianum* was performed using GC-MS procedures, and the findings are outlined in Table 3.

Table 3: Chemical composition of extracts from seeds, stem, and leaves of *S. marianum* (Javeed et al., 2022).

Extract	Chemical Compounds	Molecular Formula	Molecular Weight
	Methyl stearate	$C_{19}H_{38}0_2$	298.5
	Pentadecanoic acid, 14-methyl-, methyl ester	$C_{17}H_{34}O_2$	270.5
Stem	2-Pentadecanone, 6,10,14-trimethyl	$C_{18}H_{36}O$	268.5
	1,2-Benzenedicorboxylic acid, butyl decyl ester	$C_{22}H_{34}O_4$	362.50
	Carbamic acid, (3-methylphenyl)-, methyl ester	$C_9H_{11}NO_2$	165.2
	11-Octadecenoic acid, methyl ester	$C_{19}H_{36}0_2$	296.5
	Benzene, 1-isocyanato-3-methoxy-	$C_8H_7NO_2$	149.1
	Dibutyl phthalate	$C_{16}H_{22}O_4$	278.34
	Tetradecanoic acid, 12-methyl-, methyl ester	$C_{16}H_{32}O_2$	256.4
	Dibutyl phthalate	$C_{18}H_{36}O$	268.5
	7-Octadecenoic acid, methyl ester	$C_{19}H_{36}O_2$	296.5
Leaves	2-(2-Methoxy-5-methyl-phenyl)-propionaldehyd	$C_{11}H_{14}O_2$	178.2
	2-Undecanone, 6,10-dimethyl-	$C_{13}H_{26}O$	198.3
	Hexadecanoic acid, methyl ester	$C_{13}H_{22}OSi$	222.4
	Silane, (1,1-dimethylethyl dimethyl (phenylmethoxy)-	$C_9H_{10}O_3$	166.2
	Methyl stearate	$C_{19}H_{38}0_2$	298.5
	2-Pentadecanone, 6,10,14-trimethyl	$C_{16}H_{22}O_4$	278.34
	Heptadecanoic acid, 14-methyl-, methyl ester (+/-)	$C_{18}H_{36}0_2$	284.4
Seeds	Silane, (1,1 dimethylethyl) dimethyl (phenylmethoxy)-	$C_{13}H_{22}OSi$	222.4
	Benzene, 1-isocyanato-2-methoxy	$C_8H_7NO_2$	149.1
	Hexadecanoic acid, methyl ester	$C_{18}H_{36}O$	268.5
	8-Octadecenoicacid, methyl ester	$C_{19}H_{36}O_2$	296.5
	Dibutyl phthalate	$C_{16}H_{22}O_4$	278.3

The investigation identified eight, nine, and six chemical compounds, which collectively constituted 99.96%, 99.89%, and 99.95% of the total extract from the stems, leaves, and seeds respectively. Dibutyl phthalate was identified as the primary compound in all extracts. Conversely, Hexadecanoic acid methyl ester and Silane, (1,1-dimethylethyl) dimethyl (phenylmethoxy), were not found in the stem extract. Benzene, 1-isocyanato-2-methoxy, an important compound, appeared in the seed and stem extracts but was absent in the leaf extract. Additionally, Methyl stearate was detected in all extracts except those from the seeds. Several minor compounds were also observed in the extracts, though they exhibited low peak areas. (Javeed et al., 2022).

Therapeutic Properties of *S. marianum*

Silymarin, the active component of milk thistle, is a lipophilic extract derived from the seeds and contains three flavonolignan isomers: silychristin, silydianin, and silybin. Standardized extracts of milk thistle usually consist of 70% to 80% silymarin.

Silymarin, (Fig. 5) with silybin being the predominant physiologically active component (Sapthasri, 2021). These constituents have been employed in treating various conditions such as cancer, inflammatory ailments like arthritis, cardiovascular diseases, autoimmune disorders, and ophthalmological issues (Porwal et al., 2019). The growing interest in plant-based extracts and nutraceuticals arises from their therapeutic potential. Recent studies have revealed milk thistle's effectiveness in addressing diverse disorders. Silybin, a constituent of silymarin, modulates oxidative stress, hepatic fat storage, and blood insulin levels, thereby enhancing hepatic function and mitigating hepatotoxicity (Tajmohammadi et al., 2018). Furthermore, silymarin demonstrates anti-inflammatory properties, particularly beneficial for individuals with arthritis (Shavandi et al., 2022).

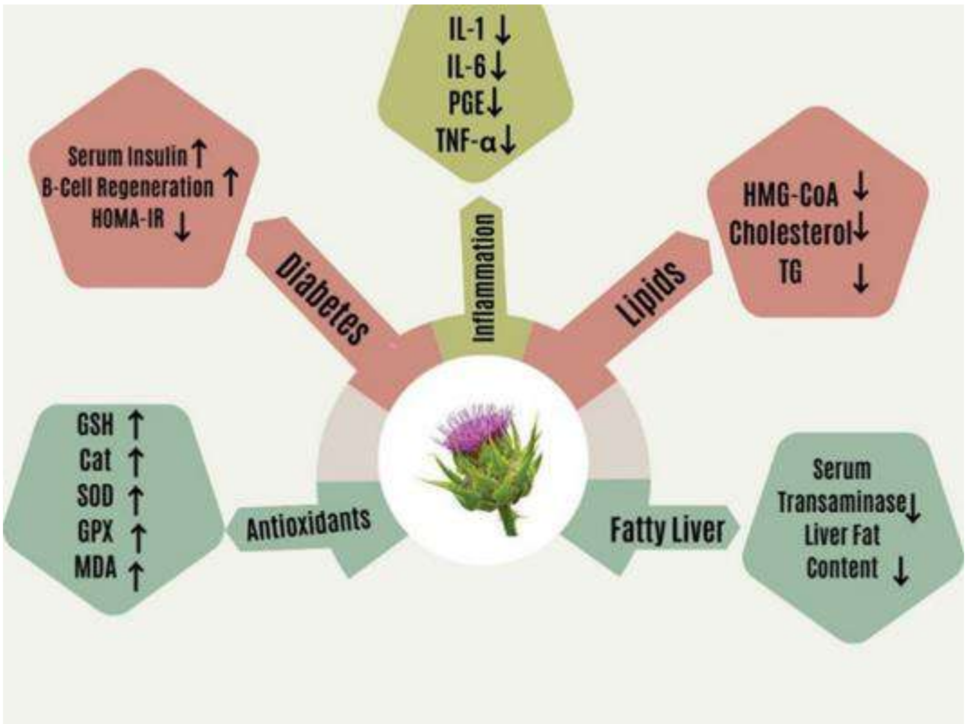

Fig. 5: Pharmacological properties of silymarin (Mohammadi et al., 2020).

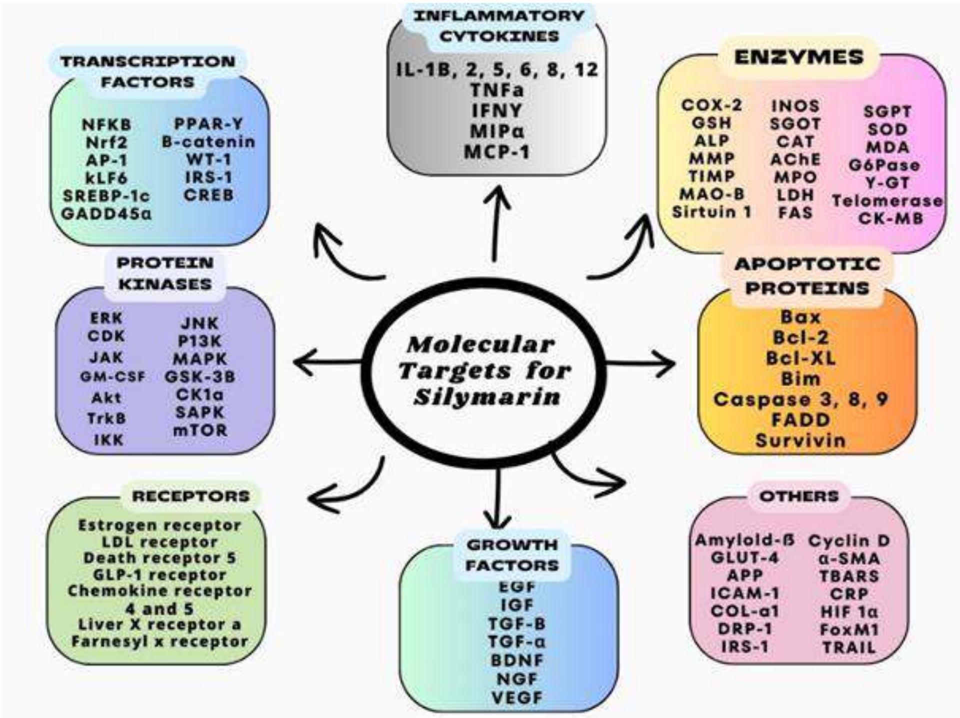

Fig. 6: Various molecular targets for silymarin (Wadhwa et al., 2022)

Anti-diabetic Activity of *S. marianum*

The growing occurrence of diabetes mellitus (DM) poses a significant worldwide health issue. DM is a metabolic condition marked by chronic high blood sugar levels, insulin resistance, and impaired insulin production, often accompanied by increased glucose production in the liver. Silymarin and its components have shown potential hypoglycemic effects, effectively reducing blood glucose levels and enhancing insulin secretion (Sharma et al., 2021). Several experimental investigations of the anti-diabetic activity of silymarin are given in Table 4.

In rat models of diabetes induced by streptozotocin (STZ), administering silymarin orally lowers HbA1c levels and fasting blood sugar. Additionally, it inhibits the activity of glucose-6-phosphatase (G6Pase) and gluconeogenesis. Chronic hyperglycemia damages mitochondria, leading to oxidative stress (Rahimi et al., 2018). Silychristin A, a component of silymarin, protects against ROS-induced apoptosis in pancreatic cells. Inflammation exacerbates diabetes complications. Silymarin reduces the expression of inflammatory cytokines and NF-κB target genes, preserving pancreatic β-cell function (Xu et al., 2018). Ashraf et al., (2020) comparatively evaluated the protective effect of seed oil extracts of *S. marianum* and *N. sativa* administration in cisplatin-induced nephrotoxic mice. *S. marianum* oil extract significantly reduced the elevated blood glucose and blood urea nitrogen (BUN) levels in comparison to *N. sativa* oil extract. SM Oil extract administration also ameliorated the cisplatin-induced lowering of triglyceride levels. Moreover, the histological study showed improvement in kidney cells with slight signs of cellular damage in mice treated with SM oil extract. Figure 7 explains the different antidiabetic mechanisms of silymarin.

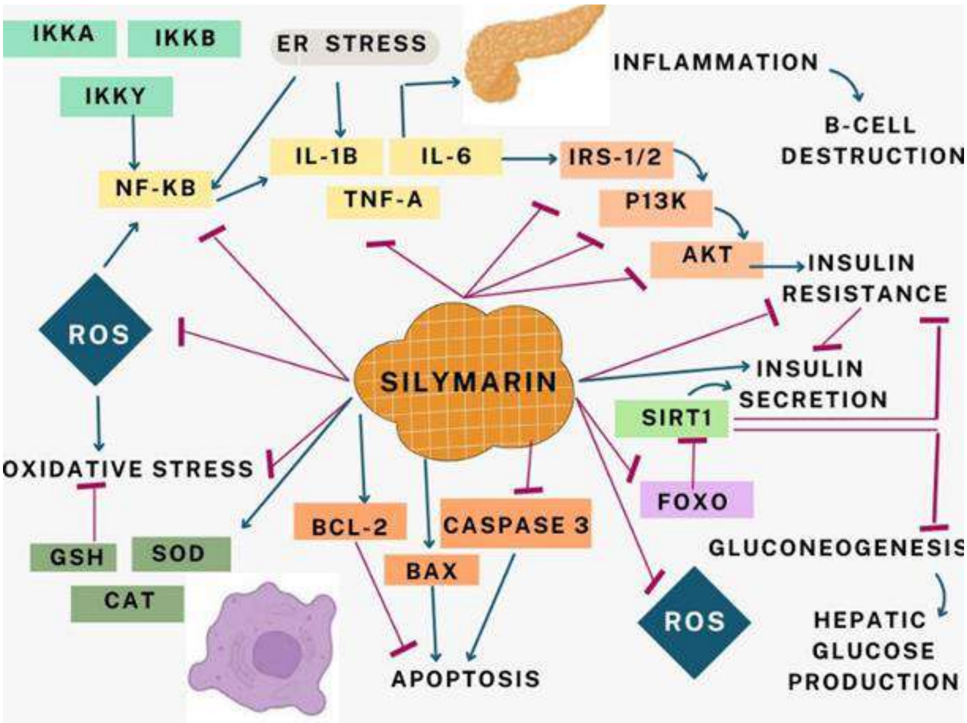

Fig. 7: Various anti-diabetic mechanisms of silymarin (Wadhwa et al., 2022).

Table 4: Experimental investigation of the anti-diabetic activity of silymarin (Wadhwa et al., 2022).

Study Model	Possible Target Site/Mechanism of Action	Dose/Concentration Used
Obesity-induced insulin resistance model and HepG2 cells	Increase in SIRT1 expression Reduction in phosphorylation of FOXO1 and Akt Enhancement in SIRT1 enzymatic activity	30 mg/kg/day p.o. for one month
HFD-induced insulin resistance	Decrease in levels of TNF-a, IL-6, and IL-18 Lowering of SGOT, SGPT, CH, TG, and LDL levels Improvement in insulin sensitivity	30 and 60 mg/kg p.o.
HFD model	Improvement in insulin sensitivity Lowering of hepatic NADPH oxidase expression and NF-kB activity Decrease in CAT, GSH, and SOD activity Reduction in levels of IL-6, TNF-a, NO, and iNOS	30 mg/kg/day p.o. for one month
Pancreatectomy model	Rise in serum insulin levels Enhancement in β cell proliferation Increase in expression of Pdx1 and insulin genes	200 mg/kg p.o.
HFD-induced insulin resistance model and HEK293T cells	Decrease in fasting blood sugar (FBS) levels Suppression of NF-κB signaling pathway Stimulation of Farnesoid X receptor (FXR)	40 µg/mL 50 µM
STZ-and HFD-induced diabetes	Reduction in liver glucose output Enhancement in GLP-1 receptor expression in the duodenum	100 and 300 mg/kg p.o.
STZ-induced diabetes and INSI cells	Reduction in fasting blood sugar (FBS) levels and increase in insulin secretion Increase in protein levels of Bax and cleaved-caspase-3 Decrease in gene expression of Bcl-2 and pro-caspase-3	50 µg/mL 25-100 µ.M
STZ-induced diabetes	Decrease in HbA1C levels Lowering of MDA, SGOT, SGPT, LDH, and CK-MB levels in the heart Reduction in CH, TG, and LDL levels Increased Bcl-2 and decreased Bax levels prevent apoptosis	80 mg/kg p.o. for 21 days
STZ-induced diabetes	Decrease in urotensin II gene expression Lowering of fasting blood sugar (FBS), CK-MB, LDH, MDA, cholesterol (CH), LDL, and nitric oxide (NO) levels	60 and 120 mg/kg/day p.o. for 2 months

Citrullus colocynthis

C. colocynthis, a member of the Cucurbitaceae family, is abundantly found in desert areas around the world including Pakistan (Ahmed et al., 2019). The plant is famous for its nutraceutical and medicinal properties. The fruit of *C. colocynthis* has several names in different languages, Bitter apple or Colocynth in English, in Urdu as Hanjal, Pcitummatti in Tamil, Indrayan in Hindi, and Rakhal in Bengali (Banjo et al., 2021). The plant is famous for its traditional properties and is broadly used for the treatment of different ailments like diabetes, asthma, and jaundice. Each gourd of *C. colocynthis* typically contains 200–300 seeds, and the fruit has a bitter taste. Figure 8. The plants are Perennial vines that provide small, fragrant flowers and display seed-fruit ratio, density, and mesocarp thickness (Aggarwal et al., 2020; Rashid et al., 2021).

A

B

C

Fig. 8: A) The whole plant of *C. colocynthis* B) Fruit C) Seeds

Chemical Composition and Nutritional Profile of *C. colocynthis*

Despite use of different parts *C. colocynthis* in food and pharmaceutical industries, there is a lack of nutritional information available to readers worldwide. Such variations in characteristics can have resulted from national variations in farming practices and agricultural conditions (Berwal et al., 2022). The seed components which appear golden yellow constitute about 23-25% oil. The seeds contain 70% of unsaturated fatty acids and 51% of polyunsaturated fatty acids. The matured fruit contains a high moisture level, constituting more than 90% of its overall weight. In another study, the seeds are reported to contain 4.91g of moisture content per 100g, while 13.19g and 2.00 g of protein and ash content per 100 g respectively (Banjo et al., 2021). Tryptophan, arginine, and methionine are abundant amino acids found in *C. colocynthis* (Hameed et al., 2020). The protein also contained aspartic acid, glutamic acid, glycine, and serine. Another category of equally significant micronutrients that the body needs is minerals. It is thought that all minerals are helpful for preserving the alkalinity of the body's different fluids as well as the correct electrolyte balance (Khan et al., 2023). Table 5: A variety of bioactive substances extracted from *C. colocynthis* together with an explanation of how they work.

Phytochemical Composition of *C. colocynthis*

The therapeutic potential of *C. colocynthis* is contributed by a wide array of bioactive compounds: polyphenols, flavonoids, and cucurbitacin. The crude extract of *C. colocynthis* contains a wide array of phytochemicals that includes saponins, flavones, tannins, phenols, glycosides, flavonoids, alkaloids, steroids, and terpenoids (Bhasin et al., 2020). Different parts of *C. colocynthis* revealed the presence of different types of cucurbitacins A, B, C, D, E, J, and L, different phytochemicals like terpenoids, glycosides, alkaloids, phenolics, steroids, tannins, proteins, carbohydrates, and specific amino acids (Dhakad, 2017). Different compounds reported from *C. colocynthis* are listed in Table 6.

Phenolic compounds are considered among the largest and widest distributed groups of plant metabolites (Ahmed et al., 2019). They exert various *in vitro* and *in vivo* biological actions including cell proliferation, inhibition of angiogenesis, improving vascular endothelial function, causing cardiovascular benefits, and acting against atherosclerosis, including anti-aging effects (Mazher et al., 2020).

Flavonoids represent a class of phenolic compounds produced by plants in response to microbial infection. They have been shown to exhibit *in vitro* antimicrobial activity against a range of microorganisms. They also have good antioxidant and cytotoxic properties. Due to their antioxidant and radical scavenging abilities, flavonoids offer benefits to humans as promising anticancer agents. These compounds are beneficial and provide resistance against diseases (Al-Nablsi et al., 2022).

Table 5: Bioactive compounds isolated from *C. colocynthis* and their mechanism of action (Li et al., 2022)

Sr no	Class	Mechanism of action
1	Flavonoids	They make complexes with cell walls, bind to adhesions, and prevent prostaglandins and autacoid release
2	Alkaloids	They possess antioxidant properties and prevent the release of prostaglandins and autacoids.
3	Saponins	Hold membrane permeabilizing properties, prevent *in vitro* release of histamine
4	Glycosides	Prevent prostaglandin and autacoid release.
5	Lectins	Forms disulfide bridges, blocks viral adsorption or fusion
6	Steroids	Improves sodium and water absorption in the intestine
7	Terpenoids	Prevent autacoids and prostaglandins release, membrane disruption

Cucurbitacins are natural triterpenoid compounds well known for their bitter taste and toxicity, they have significant cytotoxic effects, thus playing a crucial part in drug exploration, notably for the development of anticancer drugs (Li et al., 2021; Marzouk et al., 2022).

Alkaloids have long been recognized for their role in structural and biochemical functions within biological organisms. *C. colocynthis* contains a high concentration of alkaloids (Ponsankar et al., 2020). These compounds serve as defensive molecules within living organisms and have been utilized in healthcare, most importantly steroidal alkaloids which form the majority of beneficial substances. Moreover, phytochemicals, with significant trypanocidal activity were also reported such as phenolics and flavonoids, etc. (Tabani et al., 2018).

Saponins: *C. colocynthis* extract was reported to contain saponins with significant anti-inflammatory activity. Saponins are also used in medicinal formulation and pharmaceutical industries for foaming and frothing effects (Elgerwi et al., 2017). Although saponins are used in medicine from ancient times, still they are among widely recognized bioactive elements in cytotoxicity. Saponins are made up of sterol glycosides and triterpene, which have a pharmaceutical application as an emulsifier and expectorant. Saponins are thus classified as a carbohydrate derivative and can either take the form of tri-terpenoids or steroids (Afzal et al., 2023). They are formed from the combination of phenylpropanoids and acetate derivatives as precursors. Several studies have proven the effectiveness and activity of steroidal saponins in community pharmacies (Alzarah et al., 2021).

Table 6: A comprehensive list of the chemical constituents derived from *C. colocynthis* (Cheng et al., 2023)

Sr.	Class	Compounds
1	Cucurbitacin and its glucosides	Cucurbitacin A, B, C, D, E, I, J, K, L, Iso-cucurbitacin B, Cucurbitacin L 2-O-β-D-glucoside, Cucurbitacin K 2-O-β-D-glucoside, Cucurbitacin J 2-O-β-D-glucoside, Cucurbitacin I 2-O-β-D-glucoside, Cucurbitacin E 2-O-β-D-glucopyranoside, Deoxocucurbitoside B, Dihydrocucurbitacin E, Colocynthosides A, Colocynthosides B, Norcolocynthenins B, Norcolocynthenins A, 16-(2-prop-1-enyl)-25-O-acetyl-2-O-β-D-glucopyranosyl cucurbitacin I, 16-(2-prop-1-enyl)-2-O-β-D-glucopyranosyl cucurbitacin I, 25-p-coumaroyl-3'-acetyl-2-O-β-D-glucocucurbitacin I, 6'-acetyl-2-O-β-D-glucocucurbitacin E, Dihydroisocucurbitacin B-25-acaetate, Dihydro-epi-iso-cucurbitacin D, Khekadaengoside E, Hexanocucurbitacin I 2-O-β-D-glucopyranoside,
2	Phenolic acids	Gallic acid, Syringic acid, P-coumaric acid, Vanillic acid, Sinapic acid, Hydroxycaffeic acid, Protocatechuic acid, Caffeic acid, Chlorogenic acid, Ferulic acid, Gallic acid monohydrate, 3,4-dihydroxyphenylacetic acid, P-hydroxy benzoic acid
3	Alkaloids	8-methylquinoline, 7,8-benzoquinoline, 6-methylquinoline, 6-hydroxyquinoline, 4-methylquinoline, 4-hydroxyquinoline, 2-methylquinoline, 2-hydroxyquinoline, Uracil, Quinoline, Nicotinamide,
4	Flavonoids	Catechin, 6-C-p-methylbenzoylvitexin, Quercetin, Kaempferol, Isovitexin, Isoorientin, Isosaponarin,3-O-methyl ether, Myricetin
5	Steroid and its saponins	22,23-dihydrospinasterol, β-sitosterol, α-spinasterone, α-spinasterol-3-O-β-D-glucopyranoside,
6	Aromatic rings	4-(β-D-glucopyranosyloxy)-benzal alcohol, 4-(β-D-glucopyranosyloxy)-benzaldehyde, Benzyl β-D-glucopyranoside, 4-hydroxybenzyl β-D-glucopyranoside
7	Tocopherols	α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol
8	Coumarin	6-hydroxy-4-methyl coumarin

Therapeutic Potential of *C. colocynthis*

Medicinal plant extracts have been utilized since ancient times as an ingredient in herbal formulations. Herbal drugs are formulated using parts of plants that have applications in the food industry, too. The medicinal plant remedies employ powders, electroactive, liniments, emulsions, and decoctions (Zheng et al., 2020). Bitter apple is used in various diseases like cancer, mastitis, bronchitis, leprosy, and for joint pain. It is also used in complementary medicines for the treatment of inflammatory conditions (Karimabad et al., 2020). Several phytochemicals belonging to different classes have been reported to show inhibitory action against microorganisms. These constituents are also used in a variety of industries, viz. food industry, cosmetics and perfumery. The active ingredients of bitter apples are extracted by using different techniques and then used in various formulations of functional foods and pharmaceuticals. Egusi seed kernels have been in use for a long time in cooking, across Africa (Hameed et al., 2020).

Antidiabetic Potential of *C. colocynthis*

The bitter apple has been in wide usage as an anti-diabetic agent in many countries, thus attracting substantial research studies both in animals and human beings. *C. colocynthis* is a powerful antidiabetic plant, and ethnopharmacological studies have documented and validated its antidiabetic potential in many countries, including India, Nigeria, Morocco, Iran, the Mediterranean region, and Algeria (Sharma et al., 2020). Various dosage forms, delivery methods, and forms of *C. colocynthis* are used to treat diabetes mellitus. For instance, in Algeria, *C. colocynthis* is used under the feet during bathing. There is also a recipe where fruits need to be crushed with the soles of the feet in the morning and then roasted seeds are ingested on an empty stomach (Meybodi, 2020). A few studies conducted on animals have documented the impact of *C. colocynthis* and its complications against diabetes, using various types of extracts, such as methanolic, ethanolic, aqueous, hydroethanolic, hydroalcoholic, etc. Among these, an aqueous extract was most commonly used. Besides this, other forms of plant administration, such as a suspension, oil, powder, etc., have also been used. Several studies have been reported regarding the antidiabetic activity of *C. colocynthis*. According to recent reports, *C. colocynthis* has anti-inflammatory, antioxidant, and hypolipidemic potential, improving the condition of diabetic animals. Kamran et al. (2021) developed the antidiabetic potential of *C. colocynthis in vitro* by an α-glucosidase inhibition assay and *in vivo* by STZ-induced diabetes in rats. Results showed a hypoglycemic effect that was significant at two different doses: 150 mg/kg and 300 mg/kg. The regular administration of *C. colocynthis* extract for 14 days significantly lowered serum glucose. Besides, it showed a remarkable decrease in serum cholesterol and triglyceride levels in diabetic rats compared to the negative control. The hydroethanolic extract of *C. colocynthis* may exert the hypoglycemic effect due to its potential for inhibiting α-glucosidase (Ghauri et al., 2020).

The aqueous extract of *C. colocynthis* in rats with type 2 diabetes revealed its effect on gene expression, particularly in relation to anti-hyperlipidemic and antidiabetic mechanisms. The ability of the *C. colocynthis* extract to decrease the fasting blood glucose, and hepatic, and serum triglycerides both in early and late type 2 diabetes revealed its potential to act via various mechanisms (Afshari et al., 2021). Herbalists in Iran also use *C. colocynthis* fruit in treating diabetes. In a two-month clinical trial conducted on 50 patients with diabetes mellitus, there was a remarkable reduction in HbA1c and fasting blood glucose in patients treated with bitter apple (Mariod and Jarret, 2022).

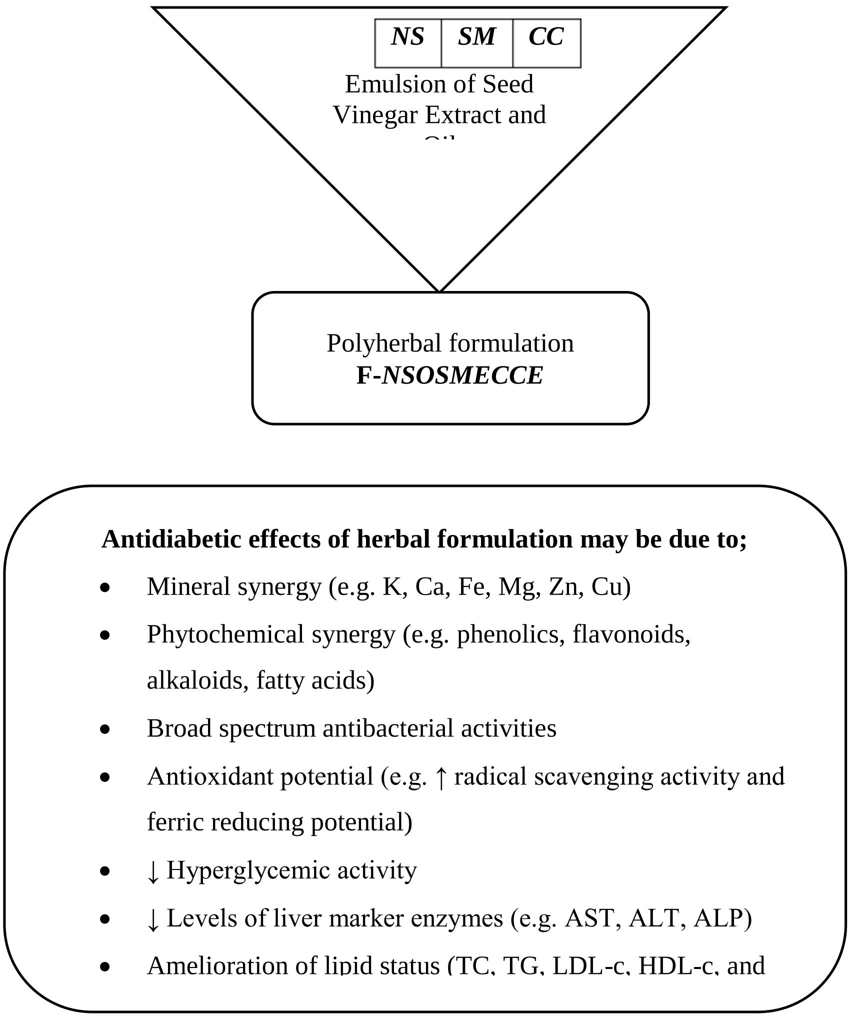

Fig. 9: Schematic mechanism of action of formulated polyherbal emulsion (F-NSOSMECCE) to manage diabetes and its complications.

Antidiabetic Herbal Formulations Comprising *N. sativa*, *S. marianum,* and *C. colocynthis*

Herbal materials are the whole plants or parts of medicinal plants in their natural state, including dried herbs powder, herbs, gums, fresh juices, resins, essential oils and fixed oils. Various methods of processing are adopted in different regions such as steaming, roasting, or stir-baking, which may involve ingredients that include alcoholic beverages, honey, or any other substance depending on the regional factors (Tran et al., 2020). Low solubility is one of the major barriers to the therapeutic utilization of herbal medications. Additionally, despite their potential efficacy, herbal medicinal products often encounter criticism due to deficient standardization and perceived deficiencies in quality (Wu et al., 2021). Herbal extracts face the challenge of compound degradation within the stomach's highly acidic pH, and certain ingredients may undergo liver metabolism before reaching systemic circulation (Lian et al., 2021). With the considerable potential of herbal drugs, numerous researchers are actively exploring the development of innovative drug delivery systems including nanoparticles, microcapsules, microparticles, mucoadhesive systems, sustained and extended-release formulations, solid dispersion, and fast-dissolving tablets (Ahda et al., 2023). The antidiabetic potential of a polyherbal formulation consisting of *C. colocynthis*, *Cinnamomum tamala*, *Asparagus racemomusin*, and *Piper nigrum* in alloxan-induced diabetic rats at two different doses of 200 mg/kg b.w. and 400 mg/kg b.w significantly improve the blood glucose, total glycerides, total cholesterol, SGOT (Serum Glutamic-Oxaloacetic Transaminase), SGPT (Serum Glutamic-Pyruvic Transaminase), VLDL and LDL and HDL level (Folane et al., 2020).

Gardezi et al., (2022) investigated the antidiabetic effects of a polyherbal extract (PHE) containing *N. sativa*, *Cicer arietinum*, *S. marianum*, *C. colocynthis* and *Zingiber officinale* extract. PHE showed a hypoglycemic effect in diabetic rats by lowering the blood glucose level. Akhtar et al., (2022) comparatively evaluated the antidiabetic potential of *N. sativa* seed methanolic extract (NSSE) and *N. sativa* seed oil (NSO) extract in alloxan-induced diabetic rabbits. The finding exhibited that the administration of *N. sativa* seed oil has significantly normalized the serum catalase, ascorbic acid, and total bilirubin levels as compared to the *N. sativa* methanolic extract, proposing that NSO may be used as nutraceutical adjuvant to normal antidiabetic drugs remedies. Akhtar et al. (2023) developed an herbal formulation 'F6- SMONSECCE', prepared from a combination of seeds extract from *S. marianum* oil (SMO), *N. sativa* extract (NSE), and *C. colocynthis* extract (CCE). Figure 9 describes the proposed mechanism of action of herbal formulation developed in the study. The formulation showed the presence of significant amount of total phenolic and flavonoid contents exhibiting the antioxidant potential determined through DPPH radical scavenging and ferric reducing antioxidant power (FRAP) assays. The polyherbal formulation was also administered to diabetic rats which significantly attenuated the blood glucose levels, total cholesterol, total glycerides, LDL-C, and VLDL-C levels with an increase in HDL-C levels. The administration of herbal dose also showed significant normalization of pancreatic and kidney cells in histological study. The formulation was therefore proposed as an antioxidant, antilipidemic, and hypoglycemic remedy against diabetes.

Safety Concerns

It is important to consider the safety aspects of herbal medications though it is used to treat diabetes but a complete information guide should be available about antidiabetic drugs including information about its hidden side effects and toxic effects whenever prescribed in combination (Ekor, 2014). All medical conditions like hepatotoxicity, nephrotoxicity, GIT disturbances, and interaction with other drugs by the use of antidiabetics should be taken into serious consideration and strict supervision by medical professionals is a must (Zhang et al., 2015). Although herbal medications serve as natural remedial options to treat diabetes but still more investigation and research are need of the time to fully explore their medicinal potential (Temitope and Santwana 2021). It is also important to find their diverse mode of action, efficacy, safety profiles, and ideal dosage requirements for better treatment (Kumar et al., 2021). Furthermore, due to the increasing demand for these herbal formulations, it is also important to collaborate among researchers, traditional medical practitioners, and healthcare professionals to revolutionize the discipline of herbal medication to combat different diseases (Hassen et al., 2022).

Wellbeing and Future Contemplations

Despite of miraculous effects of natural antidiabetics, it is important to consult medical experts before using any herbal antidiabetic therapy to avoid possible side effects and complications. Antidiabetic formulations are promising because of their potential benefits to cure diabetes.

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Chapter 03

Medicinal Herbs Extracts as an Alternative Therapeutics Approach against Multi-Drug Resistant Diarrheagenic *Escherichia coli*

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ABSTRACT

Diarrhea is one of the most critical health issues responsible for the high rate of morbidity and mortality in the world. It is major health problem especially in developing countries. Different pathogenic bacteria and viruses cause diarrhea. Among the pathogenic bacteria, *Escherichia coli* (*E. coli)* is the major etiological agent of diarrhea by producing Shiga toxin that may damage the intestine. The diarrhea-genic *E. coli* is treated through the use of antimicrobial agents. The excessive and nonspecific use of antibiotics has resulted the emergence of multi-drug resistant strains of *E. coli,* which creates a serious threat to public health. This chapter provides brief overview of isolation and molecular identification of various multidrug resistive strains of *Escherichia coli* from diarrheal patients of different ecological zone of district Swat, Khyber-Pakhtunkhwa, Pakistan and to evaluate antimicrobial potential of medicinal herbs especially *Limonium cabulicum* against diarrhea-genic *E. coli*. The samples were collected from equal number of male and female diarrheal patients under the age group of five years. For antibiogram studies, ten different antibiotics from all of the four generations were tested following the guidelines of Centers for Disease Control and Prevention (CDC). The study also evaluated local medicinal plant i.e., *Limonium cabulicum* for their antibiotic potential against selective multidrug resistant *E. coli* strains. Sequencing of 16s rRNA and phylogenetic analysis for *E. coli* isolates were also performed in the current study. The data revealed high frequency of *E. coli* isolates were recorded in male children than females. The susceptibility pattern of isolates showed the existence of multi-drugs resistant strain of *E. coli*. Nine out of ten selected antibiotics were non-effective against most strain of *E. coli*. The only effective antibiotic was Fosfomycin. The results of study revealed that *Limonium cabulicum* roots and leaves extracts in ethanol and aqueous solvents had remarkable activities against the tested strains. Sequencing of the 16s rRNA and phylogenetic analysis confirmed the existence of *E. coli* strains in diarrheal patients.

KEYWORDS
Antibiogram; Diarrhea, Diarrhea-genic *E. coli; Escherichia coli;* Medicinal Plants, Multi-Drug resistant; *Limonium cabulicum;* Pathogenic Bacteria

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INTRODUCTION

Diarrhea is the release of three or more liquid stools in 24 hours with abnormal fluids contents or irregular increases in daily stool fluidity than normal (Haricharan, 2010). This disease is common for all age groups but severe in infants and children below the age group of 5 years. The prevalence of diarrhea revealed a major world health problem and responsible for the second-highest rate of mortality and morbidity, especially in under developing countries. The severity of this disease is found in the infant's age group under 5 years and reported as the fourth highest burden of child mortality across the world (Black et al., 2012).

Different pathogenic bacteria including *Salmonella enteritis, Shigella, Campylobacter, Staphylococcus aureus,* *Clostridioides difficile* and *Yersinia* spp. can cause diarrhea. However, *E. coli* is the major causative agent of diarrhea. The pathogenic strains of *E. coli* causing diarrhea include STEC serotypes O157: H7, O103: H2, O118:H6, O26:H16, O26:H11, O111:H8 and O121:H19. The severity of the disease's symptoms varies depending on the toxins produced by *E. coli* in the intestine and may include vomiting, cramping in the muscles and abdomen, and diarrhea (Klein et al., 2002). Symptoms and transmission sources of pathogenic strains of *E. coli* are diverse. For example, the significant reservoir of *E. coli* (O157: H7) is cattle. However, sometimes other mammals including cats, dogs, rabbits, horses, pigs and insects (flies) also involve in the transmission of *E. coli*. Furthermore, contaminated food, vegetable and fruits irrigated by contaminated water are also the possible reservoir for the transmission of *E. coli* (Ferens and Hovde, 2011) (Fig. 1). The transmission of *E. coli* can be prevented by using proper cooked food, adopting the required safety barriers such as masks, gloves, awareness of the cooking policies, applying different scientific methods in sterilization pasteurization, canning, maintaining the water quality and quantity in foods, avoid raw and unpasteurized milk and juices (Taylor et al., 1995; Nicholls et al., 2002). Furthermore, the use of antiseptics for cleaning households, and following the safety precautions measure while pitting and contact with farm animals are also the possible measures for preventing the transmission of *E. coli* (Maunsell and Bolton, 2004).

Fig. 1: Different therapeutic approaches against the major causes of diarrhea.

The specific identification of *E. coli* is also a key for the proper management and control of *E. coli* infection. Different assays were used for the identification of *E. coli*. Biochemical test and genotypic techniques are commonly used for the identification purpose. Among the genotypic techniques 16S rRNA gene sequencing, is most accurate method for identification and characterization of the clinical isolates of *E. coli* (Rousselier et al., 2001; Deshmukh and Roy, 2021)

Materials and Methods

The current study was conducted at the Center for Biotechnology and Microbiology (CBandM) at the University of Swat Khyber Pakhtunkhwa in Pakistan. About 153 miles from Pakistan's capital city of Islamabad, the Swat Valley is situated on the Swat River at the coordinates 35°12′N 72°29′E. As seen in Fig. 2, four Tehsil Headquarter Hospitals (THQs) Madyan, Khawazakhela, Matta, and Kabal, three BHUs, (basic health units) Fatehpur, Islampur, Manglawar. and eight private hospitals in District swat were chosen for sample collection.

For the study, different samples were taken from diarrheic patients, predominantly from THQs and BHUs. The sampling procedure entails the collection of faeces (watery) from diarrheal patients of both genders and of all ages using sterile surgical swabs with labels indicating the patient's age, gender, and location. Using the standards procedure, a non-selective Nutrient ager (NA) media was created for the growth of bacteria from an inherently obtained sample. According to established protocols, MacConkey ager and Sorbitol MacConkey ager (SMAC) were utilized for identification of pathogenic strain O157:H7 *E. coli.*

Following the development of various colonies, the colonies were identified based on their architecture and colors (colony morphology). Following morphological identification, pure cultures were subjected to biochemical confirmation tests for authentic identification. Gram staining revealed that the samples were gram negative, while catalase and oxidase tests revealed that they were catalase positive and oxidase negative. To ascertain whether the microorganisms could produce -galactosidase enzymes that hydrolyzed O-Nitro phenyl—D-Galactopyranoside, the O-Nitro phenyl—D-

Galactopyranoside (ONGP) test was carried out (ONPG). Using the disc approach, the medium was infected with a significant amount of pure culture inoculum and incubated for four hours at 37 ºC. Yellow tint of the disc after 4 hours of incubation indicated ONGP positive for the chosen bacterium sample. The lysine decarboxylase test was used to identify isolated microorganisms that use lysine as a source of carbon and are referred as lysine decarboxylase positive. A further 24 hours were allocated to the medium for incubation, during which it was noted that the application of lysine caused the hue to return to purple from yellow. Another biochemical test to identify bacteria's capacity to convert tryptophan into indole was conducted, which was a sign that the strain can break down tryptophan and create indole.

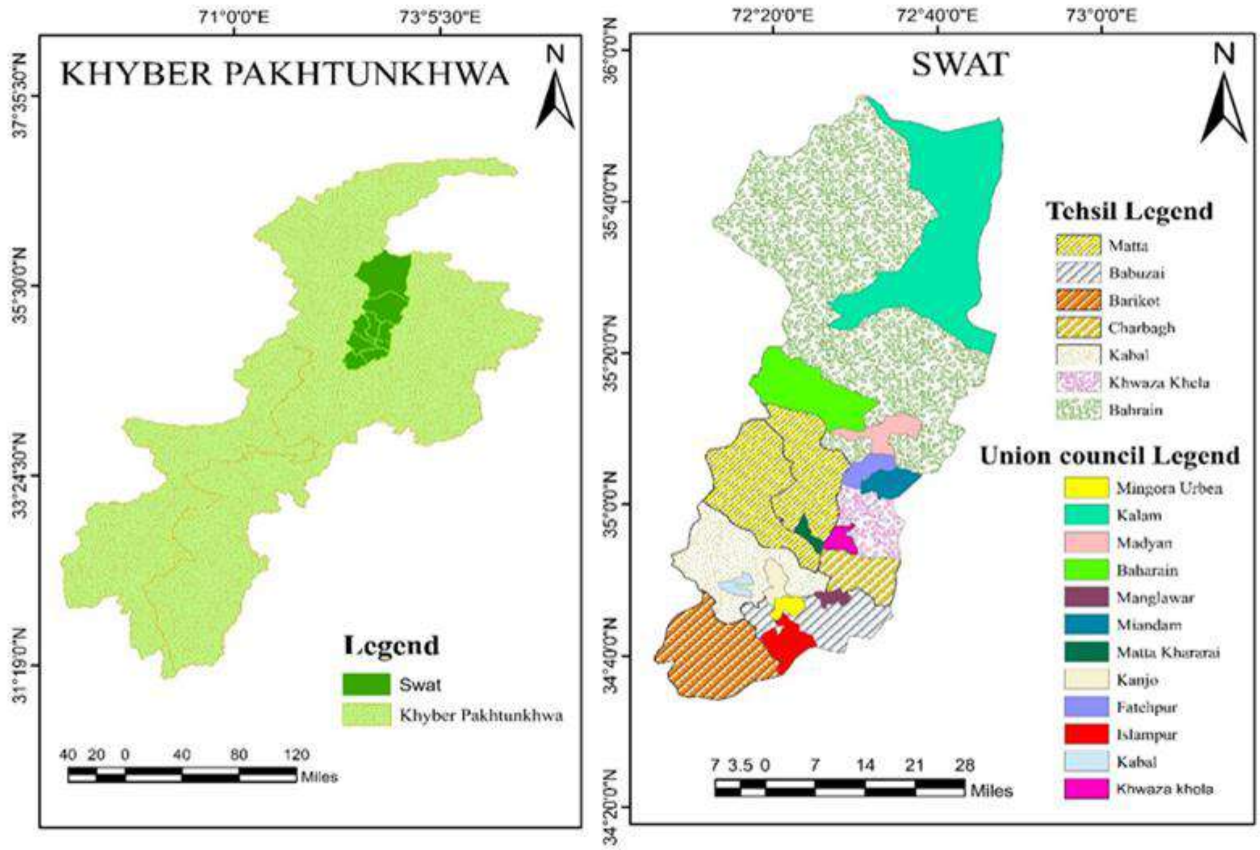

Fig. 2: Map of study area.

For identification purposes, genotypic approaches were also used in addition to other biochemical test procedures. The findings of BLAST in the NCBI database and sequencing the sample's 16s rRNA confirmed the presence of *E. coli* in the samples. Our query sequence from the isolate, according to the phylogenetic analysis, was also shown to be more closely related to *E. coli* strains from Pakistan, India, and Mexico.

By using the Kirby and Bayer-proposed disc diffusion approach, antibiogram patterns was carried out. Ten commonly used antibiotics were utilized in total. Muller Hilton (MH) agar was used to assess the antibiotic sensitivity of the chosen *E. coli* strains, following the manufacturer's recommendations. Premade antibiotic discs were utilized on the plates. Well diffusion method was employed to evaluate the antimicrobial sensitivity of medicinal plants against the diarrheal pathogenic *E. coli*. following National Committee for Clinical Laboratory Standards (NCCLS) protocols.

The Challenges of Antimicrobial Resistance Associated with Diarrhea Worldwide

Antimicrobial agents are used for the control of pathogenic strains of *E. coli*. Without any doubt antibiotics have revolutionized the treatment of bacterial infections of both humans and animals to a great extent. But the prevalence of antibiotic resistance to specific types of bacteria has alarmingly increased in recent years. Among those bacteria that pose the greatest threat to human health because of its growing resistance to antibiotics are the members of the *Enterobacteriaceae* family, particularly *E. coli*. The increase in antimicrobial resistance is a challenge in medical field, and the advance antimicrobial chemotherapy shows less effectiveness against the prevention of highly pathogenic strains of *E. coli* (Table 1). According to Centers for Disease Control and Prevention (CDC) O157: H7 is the most common *E. coli* strain isolated as a pathogen in the United States (Gonzalez-Escalona and Kase, 2019). The study conducted by Mora et al. (2005) reported that the STEC strains of *E. coli* includes O157: H7, O4:H4, O8:H21, O20:H19, O26:H11, O111:H, O118:H16, O128:H and O171:H25 shows highly resistance to more than five antibiotics. The increase in the prevalence and development of multi drug resistance is happening due to the misuse of antibiotics which can pose a great deal of threat to the normal intestinal microbiota and therefore there is an urgent need to develop alternative drugs to treat resistant bacteria (Kaper and O'Brien, 1998; Rhee et al., 2009; Ifeanyi et al., 2015; Mutters et al., 2018; Gharbi et al., 2019)

In developing countries, the situation is getting worsens, as reported by national surveillance data from Mexico, China and Turkey, where *E. coli*-resistant strains has been shown to have a prevalence of > 40% to cephalosporin, quinolones and trimethoprim/sulfamethoxazole (TSX), drugs widely used around the world to empirically treat bacterial infections (Hamad, 2010; Shao et al., 2017). The study conducted on specimens from diarrheal patients in Bangladesh and screened for ETEC between 2005 and 2009 (Begum et al., 2016). The isolates were checked for antibiotic sensitivity and the resistance profile of ETEC isolates was observed as follows: ciprofloxacin 27%, ampicillin 66%, ceftriaxone 13%, streptomycin 48%, azithromycin 27%, doxycycline 44%, erythromycin 96%, nalidixic acid 83% cotrimaxazole 46%, tetracycline 42% and norfloxacin 27%, Furthermore, the antibiotic resistance in ETEC against ciprofloxacin is increased from 13% to 34% in duration of 4 years from 2005-2009.

The study conducted by Hamid et al. (2012) reported that Multi drug-resistant E coli has become a major public health concern in Sudan and many countries, causing failure in treatment with consequent huge health burden. They identified a total of 232 *E. coli* isolates from clinical specimens and tested their antimicrobial susceptibility. Out of the 232 *E. coli* isolates, 214 isolates were characterized as MDR *E. coli* (92.2%). The findings of the study revealed that the antibiotic resistance was recorded as, ciprofloxacin 58.4%, Ofloxacin 55.1%, amoxicillin-clavulanate 50.4%, cefuroxime 92.5%, amoxicillin 97.7%, trimethoprim-sulfamethoxazole 88.3%, amoxicillin 97.7%, gentamicin 35% nalidixic acid 72%, tetracycline 77.1%, ceftriaxone 64%, nitrofurantoin and ceftazidime each, 22.4%, tobramycin and chloramphenicol 18.2% each and amikacin 1.9%. The study reported the total of 53.3% isolates multi-drug-resistant (MDR) diarrheagenic *E. coli* (DEC) has rapidly spread worldwide and represents the most serious threat to the management of diarrhea in developing countries. During the period from March 2011 to January 2012, a total of 450 stool samples of diarrheal children with age of 0– 60 months were studied in Tabriz Iran, to detect enterohemorrhagic *E. coli* (EHEC) enterotoxigenic *E. coli* (ETEC) and tested for antimicrobial susceptibility. Diarrheagenic *E. coli* exhibited high-level resistance to aztreonam (80.7%), amoxicillin (74.4%), and tetracycline (69.3%). The finding of the study reported 86.4% of *E. coli* isolates as MDR (Memariani et al., 2015)

Antibiotics Key Codes

Ampicillin -AMP, Tetracycline- TET, Nalidixic acid-NA/NAL, Cephalosporins-CEP, Imipenem-IPM, Trimethoprim-TMP, Sulfa-Methoxazole-CMX, Chloramphenicol-C/CHL/VCL, Gentamicin-GEN, Streptomycin-STM, Cotrimoxazole-CMX, Azithromycin-AZI, Ciprofloxacin-CPFX/CIP, Teicoplanin-TEC, Quinolones- QNS, Vancomycin- VAN, Aminoglycosides-AMG, Sulfamethoxazole(TS)-SMZ, Amoxicillin-clavulanic acid-AMC, Cefotaxime-CTX, Cefuroxime- CXM, Kanamycin-KAN, Erythromycin-ERY, Spectinomycin-SPT/ SPTCM, Ceftriaxone-CRO.

Medicinal Plants– an Alternative Approach for the Control of Diarrhea-genic *E. coli*

Medicinal plants are getting high consideration among the scientific community due to their long historical background of being sources of natural bioactive compounds for the treatment of different infection caused by pathogens (Seyyed Nejad et al., 2010; Nabavi et al., 2015). The composition of medicinal plants is highly diverse and their extracts have antimicrobial potential against both Gram-positive and Gram-negative bacteria (Mustafa et al., 2019; Fernandes et al., 2022). The medicinal plants contain phenolic, terpenoids, alkaloids, Sulphur and nitrogen-containing compounds which exhibit antibacterial potential, by targeting the different component of microbial cell and generating the reactive oxygen species in the culture (Berni et al., 2018; Manzar Alam et al., 2022). Plant extracts and their compounds have been reported for Immune stimulatory effects (Amirghofran, Hashemzadeh, Javidnia, Golmoghaddam, and Esmaeilbeig, 2011). The extracts of *Tinospora crispa* stimulate innate immune responses in Wistar Kyoto rats (Bukhari et al., 2015). Similarly, the inhibition of arachidonic acid metabolism and cytokine production by eucalyptol has also documented in previous study. The others researchers also reported the anti-inflammatory potential of the bioactive compounds and plant extracts in the *in vivo* and *in vitro* studies (Gurgel et al., 2009; Ferreira et al., 2016). Furthermore, the antibiotic resistance modifying potential in plants extracts also gaining research interest in scientific community. Some plant extracts have shown to increase the antimicrobial potency of antibiotic against multidrug resistant bacterial species and suggested as antibiotic adjuvants (Vaverková et al., 2013; Kuete et al., 2015).

Medicinal plant extract has shown a remarkable antimicrobial potential against Gram-negative bacteria with least side effects (Fig 3) and have long been used for the treatment of gastrointestinal tract infections especially diarrhea. Previous published data revealed the antimicrobial potential of the different medicinal plants against the causative agent of diarrhea especially *E. coli*. For example, the ethanol extracts of *Acacia nilotica*, *Syzygium aromaticum* and *Cinnamomum zeylanicum* inhibited the growth of *E. coli* (Khan et al., 2009a; Khan et al., 2009b). Similarly, the ethanol and methanol extracts of *Oxalis corniculata*, *Punica granatum* and *Syzygium aromaticum* also displayed the antimicrobial potential against pathogenic strains of *E. coli* (Mostafa et al., 2018; Dahal et al., 2019). The extracts of other medicinal plants including *Gaultheria procumbens* leaf, ethenolic solvent of *Aloysia citrodora*, *Hibiscus sabdariffa*, *Phlomis brachyodon*, *Urtica pilulifera*, *Anchusa azurea*, *Pallenis spinose*, *Cirsium englerianum*, *Eucalyptus depauperata*, *Lippia adoensis*, *Discopodium penninervium* , *Rumex abyssinicus*, *Cyperus pustulatus*, *Cassia fi stula*, *Holarrhena antidysenterica*, *Terminalia alata*, *Terminalia arjuna*, *Paederia foetida*, *Zanthoxylum alatum*, *Ocimum sanctum*, *Verbascum Thapsus* and *Bryophyllum* were also effective against pathogenic strain of *E. coli* (O157:H7), reported in the previous studies (Odugbemi et al., 2007; Dahiya and Purkayastha, 2012; Rawat et al., 2015; Ahmad et al., 2021; Tufa et al., 2021). In the present study *Limonium cabulicum* (Local name *Ghawakhai*) was found for the first time to have a strong antibacterial potential against multidrug resistance (MDR) strains of *E. coli*, producing maximum zone of inhibition of (19 mm).

Results

The antibiotics sensitivity test revealed that the diarrheagenic *E. coli* isolates was resistant to Cefoperazone/ Sulbactum (SCF), Norfloxacin (NOR), Ciprofloxacin (CIP), Septran/ Co-Trimexazole (SXT), Chloramphenicol (C), Cefixime (CFM), Trimethoprim (W), Pipemidic acid (PIP) and Nalidixic acid (NA). Furthermore, the findings of the current study showed that Fosfomycin (FOS) is a drug of choice for the control of *E. coli* as shown in the Table 2.

Table 1: Resistance of *E. coli* to antibiotics reported in different countries.

COUNTRY	ANTIBIOTICS AND PERCENTAGE OF RESISTANT *E. COLI* ISOLATES										REFERENCES
Iran	AMP 19.80%	TET 75.50%	NA/NAL 75.50%	IPM 100%	TMP 24%	CMX 24%	GEN 84.60%	CPFX/CIP 91.40%			(Farshad et al., 2012)
Qatar	AMP 70%	TET 35%	CEP 35%	TMP 30%	CMX 30%						(Yassine et al., 2020)
Korea	AMP 76% 10.40%	TET 66% 15.60%	NA/NAL 9.40%	STM 12.40%							(Kim et al., 2014) (Ryu et al., 2012)
Peru south America	AMP 85%	TET 65%	NA/NAL 28%	C/CHL/VCL 65%	CMX 79%						(OCHOA ET AL., 2009)
Vietnam	AMP 77.20%	C/CHL/VCL 29.60%	CPFX/CIP 88.30%	CTX 19.10%	CXM 29.10%						(Weintraub et al., 2005)
China/ Shaanxi china	AMP 75.60%	TET 73.10%	CPFX/CIP 46%	CTX 46%	KAN 65.20%	ERY 65.20%	SPT/ SPTCM 50%				(Baloch et al., 2017; bdelgader et al., 2018)
Ghana	AMP 68%	TET 93.55%	TMP 58.60%	C/CHL/VCL 93.55%	STM 54%	AZI 70.97%	CPFX/CIP 61.29%	TEC 96.77%	(AMC), 70.90%	CRO 58.60%	(Huda et al., 2020)
United States/ Canada	AMP 13.7	CPFX/ CIP 19.30%	(AMC), 13.7								(Okeke et al., 2005)
Bangladesh	TET 89.44%	AZI 100%	ERY 88.89%								(Sobur et al., 2019)
Maxico	AMP 44%	TET 37%	CTX 44%								(Canizalez-Roman et al., 2019)
Japan	AMP 24%	TET 49%	NA/NAL 28%	CEP 18%	TMP 20%	TS 20%					(Nishikawa et al., 2017)
South africa	TET 91%	AZI 92%	TS 90%								(Ateba and Bezuidenhout, 2008)
Salvador, Brazil	AMP 13.30%	TET 13.30%	TMP 13.30%	C/CHL/VCL 13.30%	TS 13.30%						(Lima et al., 2017)
Egypt	AMP 18.90%	TET 27.50%	NA/NAL 1.80%	TMP 11.30%	CMX 11.30%	C/CHL/VCL 2.30%	STM 18.50%	CPFX/CIP 1.40%	CTX 4.50%	KAN 4.10%	(Yamasaki et al., 2018)
Ethiopia	AMP 83%	AMC 75.79%									(Tuem et al., 2018)
Portugal	TET 50%	QNS 50%	VAN 50%	AMG 50%	TS 50%						(Igrejas et al., 2016; Amaro et al., 2021)
England	AMP 5.80%	TET 2.80%	TMP 5.80%	C/CHL/VCL 2.10%	STM 5.80%	AZI 0.20%	CPFX/CIP 2.60%	TEC 5.80%	QNS 5.80%	VAN 2.80%	(Do Nascimento et al., 2017; Jenkins et al., 2020)

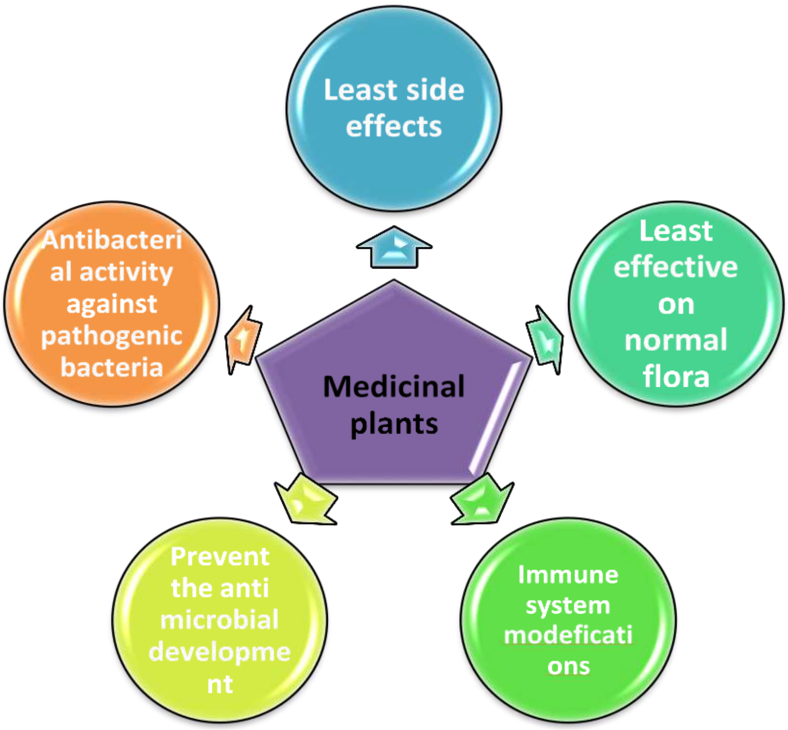

Fig. 3: Importance of medicinal plants as alternative therapeutics

Table 4.1: Antibiotic sensitivity test against pathogenic *E. coli* O157:H7 serotype.

ANTIBIOTICS NAMES	ABBREVIATIONS	DISK CONTENT	ANTIBIOTIC GENERATION	STANDARD DIAMETER OF INHIBITION ZONE (mm)			Average Zone Obtained In (mm)	RESULT
				R	I	S		
Fosfomycin	FOS	50 µg	3rd	≤12	12-16	≥16	27.5	Sensitive
Norfloxacin	NOR	10 µg	2nd	≤13	13-16	≥17	10.25	Resistant
Cefoperazone/Sulbactum	SCF	105 µg	3rd	≤15	16-20	≥21	12.75	Resistant
Ciprofloxacin	CIP	5 µg	2nd	≤15	16-20	≥21	11	Resistant
Septran/Co-Trimexazole	SXT	25 µg	2nd	≤12	12-16	≥16	00	Resistant
Chloramphenicol	C	30 µg	3rd	≤13	13-18	≥18	00	Resistant
Cefixime	CFM	5 µg	3rd	≤13	13-19	≥19	00	Resistant
Trimethoprim	W	1.25 µg	3rd	≤12	12-16	≥16	00	Resistant
Pipemidic acid	PIP	20 µg	2nd	≤13	13-18	≥18	00	Resistant
Nalidixic acid	NA*	10 µg	1st	≤13	14-18	≥19	00	Resistant

The findings of the current study revealed that the extracts of leaves and roots were active against the *E. coli* isolates. Among the tested extracts, the water extract of leaves showed a maximum zone of inhibition (ZI) of 15mm at the concentration of 1000 µg/ml. However, the antimicrobial activity of the plant extracts showed an increase when the concentration of the extract was increased. The water extract at 3000 µg/ml showed a higher ZI of 19mm. Similarly, at the same concentration, the ethanol solvent of the extract also produced a zone of inhibition of 15mm (ZI) against the tested isolates of *E. coli*. The current study also reported moderate anti-*E. coli* activity in n-hexane and ethyl acetate extract of leaves at the concentration of 3000 µg/ml. (Table 3). On the other hand, n-hexane extract did not show any activity at a concentration of 1000 µg/ml.

Among the root extracts of the plant, ethanol solvent extracted samples revealed a higher ZI with 19mm, 18mm, and 15mm at 3000, 2000, and 1000 µg/ml respectively. The extract of the water showed a uniform ZI with 15mm at each tested concentration. Although, the ethyl acetate solvent did not show any activity at both 2000 and 1000 µg/ml, except for a marginal 2mm ZI at 3000µg/ml (Table 3). Similarly, n-hexane extracts of root at 3000 and 2000 µg/ml showed 2mm of ZI, while no antibacterial activity was noted at 1000 µg/ml.

Overall, the average higher ZI was reported for ethanol solvent with 17mm ZI, followed by aqueous solvent with 15mm ZI, respectively. The current study revealed that ethanol and aqueous solvents are the optimum solutions for pant material extraction.

Phylogenetic analysis of sequenced *E. coli* isolates revealed that the bacterial strain isolated from diarrheal patients predominantly occupies the basal nodes. This analysis indicates that the selected strain is most closely related to *Escherichia coli* strain O55:H7 (accession number CP038295), followed by *Escherichia coli* strain LD39-1 (accession number

CP047658). The least similarity was observed with *Escherichia coli* O55:H7 strain DEC5D (accession number CP038386), as depicted in the cladogram (Fig. 4).

Table 3: Average zone of inhibition of *E. coli* isolates produced by root and leaves extracts of *L. cabulicum* at 1000, 2000 and 3000µg/ml

Plants	Parts used	Extract	Concentrations of extracts and Zone of Inhibition		
			1000 µg/ml	2000 µg/ml	3000 µg/ml
L. cabulicum		Ethanol	15±1.0	18±1.1	19±1.4
		Ethyl acetate	0±0.	02±0.9	02±0.5
	Root	N-hexane	0±0	0±0	02±0.7
		Water	15±1.1	15±1.0	15±1.1
		Ethanol	12±0.9	14.4±1.2	15.3±0.7
L. cabulicum	Leaves	Ethyl acetate	4±0.9	7.2±0.9	9.1±1.1
		N-hexane	0±0.7	6.3±0.8	7.4±1.0
		Water	15±1.1	18±0.9	19±1.1

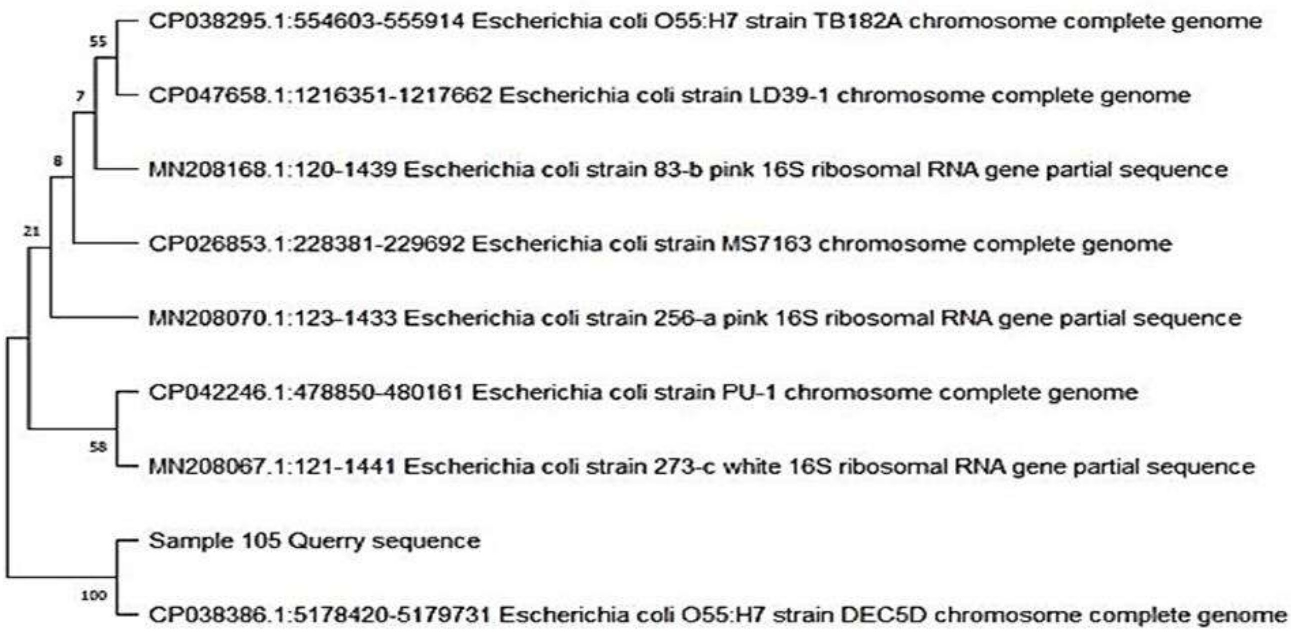

Fig. 4: Cladogram of the phylogenetic analysis

DISCUSSION

Diarrhea is one of the major intestinal diseases responsible for the second-highest rate of mortality and morbidity, across the world, widely in poor countries and also in industrialized and developing countries. Globally diarrhea affects people of all ages; however, children at an early age are more affected than others (Claeson et al., 2004). In 2015, among the under-age-five, ten highest mortality countries, Pakistan was ranked with the third highest neonates' mortalities rate caused by diarrhea (ADIELE, 2019; Rabbani and Qayyum, 2017). Among the most important various etiological agents, the strains of *E. coli* are the one responsible for chronic diarrheal disease (Mobley et al., 2004). These strains of diarrhoea-genic *E. coli* have acquired resistance through horizontal gene transfer and become multi-drug resistant (Gomes et al., 2016). The scientific community in the world is making huge efforts to combat the rising antimicrobial resistance. Traditionally medicinal plants have been utilized for the treatment of various diseases, including severe infectious diseases (Sheetal Verma and Singh, 2008). Therefore, keeping that in mind, the study was designed to evaluate the medicinal plant extracts against the MDR diarrheagenic *E. coli* as an alternative approach to the currently resistant antibiotics.

Fosfomycin was the only antibiotic found to be effective against the pathogen in the current study when isolated pathogenic *E. coli* O157:H7 was tested with 10 different antibiotics. Norfloxacin, cefoperazone/sulbactum, and ciprofloxacin, co-trimaxazole, chloramphenicol, cefixime, trimethoprim, pipemidic acid, and nalidixic acid were all found to be ineffective. The current result is consistent with a study by Pascual et al. (2006). The current study backs up previous findings that Fosfomycin has excellent anti-*E. coli* activity (Vila et al., 2001).

In the current research, the plant *Limonium cabulicum* local name *Ghawakai*, was selected because the other species of the family have been previously studied for their bioactivities. The *L. cabulicum* belongs to the family of *Plumbaginaceae*, which have a rich source of the bioactive compound containing species (Tripathi et al., 2012). However, the current study on the antimicrobial activity of *L. cabulicum* spp. in different extraction solvents against the MDR diarrheagenic *E. coli* is novel and up to date has not been reported elsewhere.

Four different solvents (Ethanol, Ethyl acetate, N-hexane and Water) were used to optimize the extraction from root and leaves of *L. cabulicum*. The extracts of both root and leaves were screened in three different concentrations against the MDR strains of diarrheagenic *E. coli* (Table 3). The findings of the study revealed the effect of extraction solvent on antibacterial potential of root and leaves against diarrheagenic *E. coli*. In the extraction, solvents play a key role in the recovery of phyto active metabolites from plant material (Mutalib et al., 2013). Previous studies have also reported the effectiveness of extraction solvents on the bioactivities of plant (Sahle and Okbatinsae, 2017; Dixon et al., 2019; Habtom and Gebrehiwot, 2019). Overall, water extract of *L. cabulicum* leaves showed the highest zone of inhibition of 19mm (ZI) at 3000 µg/ml, followed by the ethanolic extract with an average of 17mm zone of inhibition. A similar study conducted by Uma et al. (2009) reported the phytochemical antibacterial activity of *Ficus bengalensis* against entero-toxigenic *E. coli* with 16mm and 12mm ZI at 4ml/disk with methanol and aqueous extract respectively. This study showed that even 1000 µg/ml extract of *L. cabulicum* is effective against the diarrheagenic *E. coli*. Similarly, the root extracted samples in ethanol solvent produced a zone of inhibition of 19mm ZI and 18mm at 2000 and 3000 µg/ml, respectively. The results of this study are further supported by Darwish and Aburjai (2010), who have reported more than a dozen medicinal plants' activity against the MDR strains of *E. coli*. The less or no activity of hexane extracts may be due to the least recovery of bioactive compounds from root and leaves of *L. cabulicum* in hexane solvent system. Our findings are aligned with the finding of Aibinu et al. (2007), where 7mm to 28mm zones of inhibition have been reported against MDR *E. coli*. Ethanol and aqueous extracts have the good antibacterial efficacy against both gram-negative and gram-positive bacteria and the anti-microbial potential of the medicinal plants depends on the nature of the solvents for the crude extraction (Rasool Hassan, 2012).

Phylogenetic analysis revealed that the isolated bacterial specie was most closely related to *Escherichia coli* strain O55:H7 (CP038295) and *Escherichia coli* strain LD39-1 (CP047658), with the least similarity to *Escherichia coli* O55:H7 strain DEC5D (CP038386) (Kyle et al., 2012). Notably, the O55:H7 *E. coli* strain has been reported to share significant similarities with the pathogenic O157:H7 strain (Kyle et al., 2012). Our study confirms the isolation of the O55 strain, which is considered the progenitor strain of *E. coli* O157:H7 and is recognized as a foodborne pathogen (Griffin and Tauxe, 1991; Weinroth and Bono, 2022). Furthermore, studies have highlighted the importance of monitoring and controlling the spread of *E. coli* O55:H7, as it can lead to severe foodborne illnesses (Nadon et al., 2017; Hemrajani et al., 2020).

Conclusion

The study concluded that, the diarrheagenic *E. coli* isolates were shown to be resistant to the following antibiotics: Cefoperazone/Sulbactum (SCF), Norfloxacin (NOR), Ciprofloxacin (CIP), Septran/Co-Trimexazole (SXT), Chloramphenicol (C), Cefixime (CFM), Trimethoprim (W), Pipemidic acid (PIP), and Nalidixic acid (NA). Additionally, the results of the present investigation demonstrated that the medicine fosfomycin (FOS) is a viable option for the management of *E. coli*. The results of the study conclude antibacterial potential of the root and leaves of *L. cabulicum* against diarrheagenic *E. coli*. The difference in antibacterial potential among the different extracts revealed that extraction solvent affects the recovery of bioactive compounds from plant material. Ethanol extract from root and water extract from the leaves exhibited strong anti- *E. coli* potential than the other tested extracts. The results of the study also concluded that the root and leaves of *L. cabulicum* might contain bioactive compounds having strong antibacterial potential against MDR *E. coli,* and recommended for the isolation and recovery of these compounds for the development of natural therapies in the treatment of highly resistant pathogens.

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Chapter 04

Herbal Treatment Options for Salmonellosis in Poultry Flock

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ABSTRACT

One of the challenging issues especially in the poultry industry of developing countries is the rise in salmonella infections. Salmonella bacteria have a pathologic impact on the gastro-intestinal system of its host hence reducing their gut health. It is commonly known as "food poisoning". Reduction in gut health lowers the capability to absorb nutrients which ultimately leads to lower production and sub-optimal immune response. Factors like lack of hygiene practices and insufficient disease control measures lead to increased salmonellosis incidence that in turn increases the economic losses of poultry farmers. Besides affecting poultry, salmonellosis is also a serious health concern for public health and biosecurity. Being a serious concern for the researchers, salmonella was treated effectively with antibiotics in the past. Azithromycin was the drug of choice against this disease. However, since the rise in antibiotic resistance researchers have now turned their attention towards formulation of other medicinal alternatives that have less side effects and chances of antibiotic resistance development. In case of salmonella in poultry many herbal items have been used but some of them give very effective results for example Green tea, Ginger extracts, Onion peel extracts, Guava leaf extracts, and Essential oils.

KEYWORDS		
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INTRODUCTION

Over the recent several years, the poultry industry has grown tremendously and become an important sector of the livestock industry. This also brings a lot of hurdles to be faced by the poultry industry, especially antimicrobial resistance and colonization of pathogens. Salmonella is an important disease of poultry birds which also affects human health. Growth promoters in poultry are banned in several countries, essentially antibiotic growth promoters; this is due to the development of resistance in bacteria against antibiotics. Salmonella destroys the gut integrity in poultry birds leading to the loss in production, performance, and eventually death. This alarming situation led to the discovery of alternative ways to antibiotics in poultry industries such as probiotics and herbal medications. These herbal products are safe to use as they don't exhibit any side effects and also treat many infections (Bajpai et al., 2012). These herbal medications have been used in many countries for their beneficial effects on the health of birds. They don't exhibit any adverse side effects. Also the risk of antibiotic residual is no longer the concern of farmers as the herbal products don't have residual substances to be left in the body of birds. Herbal products are known to exhibit antioxidants actions, antimicrobial activities, and immunomodulatory functions. Herbal products stimulate feed consumption in birds so increase the production and performance of poultry birds (Karadas et al., 2014).

Salmonellosis

Salmonella, which causes systemic infections, is an intracellular bacterium that has the capability to significantly affect both farmers and consumers. It has the ability to cause infections that affect the health as well as the safety of the host (Orimaye et al., 2024). The prevalence of salmonellosis is significantly high and it has deleterious impacts on the production rate of commercial poultry. It also presents serious public health risks. Morphologically, salmonella is a rod-shaped, Gram-negative bacteria and is able to survive in both the presence and absence of oxygen. The pathogenicity of salmonella is very high, causing inflammation of the intestinal tract which results in gastroenteritis (Figure1). *Salmonella enterica*, sub-species *serovar typhimurium*, is the major cause of gastroenteritis in both humans and animals, the leading cause of acute gastroenteritis and bacteremia (Kim et al., 2013). At a young age, chicks are more prone to the infection of salmonella due to the weak immune system at this very young age (Wilson et al., 2016). The source of infections of salmonella in chicks includes hatchery and poultry houses. If a chick gets infected with salmonella, the bacteria enters the body and starts multiplication and making colonies in the intestinal tract. The infection occurs at a high rate at a young age (the starter phase) and then decreases over time. Salmonella can transfer to the human population through contaminated food for example meat and results in serious cases of food poisoning (Bajpai et al., 2012).

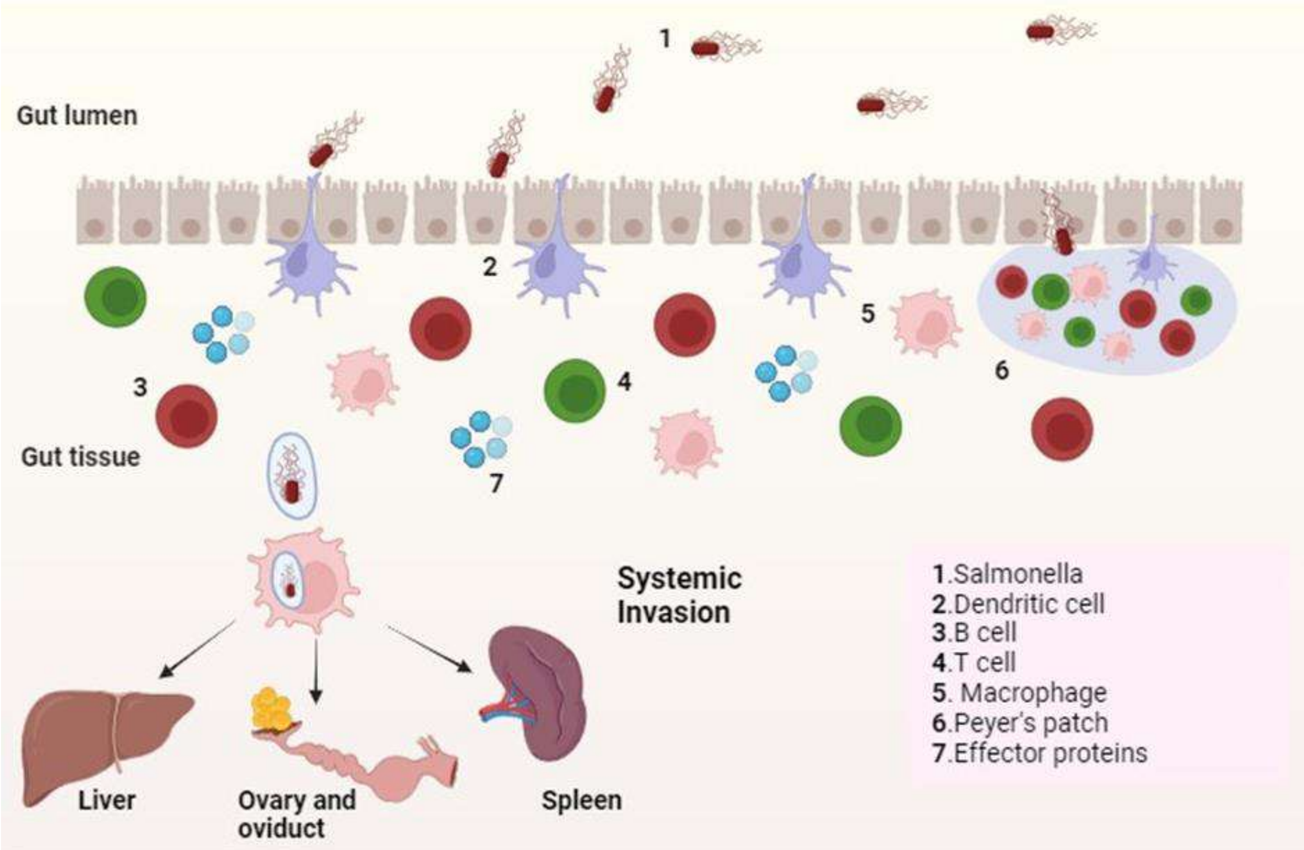

Fig. 1: Pathogenesis of *Salmonella* in poultry

Herbal Treatment Options

The escalation of resistance of antibiotics in bacteria is the result of excessive use of these antibiotics against microbes in poultry, especially meat-type, and livestock. This situation of antibiotic resistance in poultry and livestock leads to the urgent need for some alternatives of antibiotics (Kerek et al., 2023). Nature has gifted to humanity, a gift in the form of various plant-based antimicrobial substances (Fig. 2) which have many therapeutic benefits (Burt, 2004). There are potentially high sources of bioactive compounds of plant origin (Bajpai et al., 2008). It has been proved by both in vivo usage and in vitro studies that the bioactive compounds of plant origin can work against pathogenic actions of various types of bacteria, especially in controlling Salmonella infections in poultry to increase the production and performance of poultry (Ibrahim et al., 2021). The feed additives of plant origin have been used for their therapeutic capacities to enhance the production of poultry. The pharmacology properties of these plant-based products increase the production through stimulating feed consumption, enhancing the antioxidant properties, and preventing antibiotic resistance threats (Juskiewicz et al., 2011). Some other studies show that the use of plants derived products for example polyphenol and oils enhance the production of broilers in many ways including increased absorption of nutrients, improved antioxidant status, and immune response (Khan et al., 2012; Tehseen et al., 2016).

Green Tea

The use of herbal extracts in poultry enhances the production rate and decreases the rate of mortality (Khan, 2014). *Camellia sinensis* locally known as green tea is a natural herb with no toxic side effects. It has a wide variety of bioactive substances for example polyphenols, volatile oils, alkaloids, and polysaccharides (Banerjee and Chatterjee, 2015). Green tea contains high amounts of amino acids with L-theanine as the major element making up to 50% of its amino acid structure, this makes the nutritional value of green tea very high (Abd El-Hack et al., 2020). Catechins polyphenols are also a major component of green tea (Samynathan et al., 2016; Mohammadpour et al., 2021). The medical qualities attributed to green tea include antioxidant activity, antibacterial activity, and immunomodulatory activity which makes green tea a powerful tool against many poultry diseases (Angga et al., 2018). Green tea helps to control the level of cholesterol, especially the LDL cholesterol and decreases the level of lipoprotein lipase and the level of adipose triglyceride lipase. These functions are controlled by polyphenols, as they increase the reverse cholesterol transport. This function is done when polyphenol removes the cholesterol from peripheral tissues. This cholesterol is then transferred to the liver which lowers cholesterol uptake (Huang et al., 2013). Study shows that the leaf of green tea meal polyphenols shows antimicrobial activities against fungi, viruses, and bacteria in the intestine (Zhao et al., 2013). Green tea contains compounds that help in the growth and development of good microbes and inhibit the production of infectious microbes (Pérez-Burillo et al., 2021). This action ends in the low production of harmful microbes which in turn reduces the microbial competition and provides room for good microbes to thrive. *Camellia sinensis* (L.) is widely in use all around the world especially in China, Japan, and Taiwan. Green tea is one of the oldest beverages and is consumed all over the world. The classification of green tea is based on different aspects including the way of processing green tea leaves, the location of its location, and the type of soil in which green tea grows. During the fermentation process of green tea, the capacity of antioxidant activity is impacted. This is due to the increased production of catechins which is the result of catechins oxidation to aflavins (Hinojosa-Nogueira et al., 2021). According to the chemical composition of green tea, there are almost ten different types of compounds present in green tea which primarily include phenolic acids, and polyphenolic chemicals for example catechins, proteins, fats, and amino acids (Zhang et al., 2018). Green tea contains amino acids which include l-theanine, tyrosine, and tryptophan. The trace elements for example magnesium, chromium, manganese, calcium, copper, zinc, iron, selenium, sodium, cobalt, and nickel also present in green tea. Glucose, cellulose, and sucrose are the types of carbohydrates present in green tea (Ye et al., 2018).

Fig. 2: Various herbal remedies against *Salmonella*.

Ginger Extract

Zingiber officinale locally named Ginger is a semi-woody perennial plant belonging to the family *Zingiberaceae*. It is widely used as a spice as well as a medicinal plant. According to the chemical composition of ginger, its rhizomes contain carbohydrates, lipids, terpenes, and phenolic substances (Zhang et al., 2023). Ginger has been known as a medicinal agent as it contains different active biochemical substances which include gingerol, shogaols, gingerdiol, and gingerdione (George et al., 2015). Studies show that the administration of ginger root extracts in broiler chicks was found to be reducing the population of intestinal microbes specially Salmonella sp., Lactobacillus sp., and E. coli (Ofongo-Abule and Ohimain, 2015). This action provides the evidence of antibacterial activities of ginger root extracts, but there is also a risk to the good microbial population in the GIT, so it is suggested that the dosage should be critically considered. Ginger extracts are also widely used for its antioxidant potential and anti-inflammatory activities. Gas-chromatography-mass spectrometry technique shows the chemical composition of ginger, the main compounds found include zingiberene, curcumene, and sesquiphellandrene (Tao et al., 2009). In-vitro activity shows that ginger extracts decrease the peroxidation of tissue lipids and this is done by absorbing the free radicals for example superoxide, hydroxyl, and DPPH (Srinivasan, 2014). It is found that the oral administration of ginger oil for 30 days enhances the levels of glutathione reductase, glutathione, and superoxide dismutase. On the other hand ginger extracts were found to decrease the levels of phospholipids, total cholesterol, triglycerides, and cholesterol (VLDL or LDL) in the blood and aortic tissue (Al-Tahtawy et al., 2011). Ginger root extracts increase the antioxidant activity and boost the digestive enzyme in the birds. Ginger oil is widely used all over the world for medical activities (Shahrajabian et al., 2019).

Guava Leaf Extract

Guava (*Psidium guajava*) is well known for its high nutritional value and as a medicinal plant (Scholar, 2022). *Psidium guajava* is found all over the world and belongs to the family Myrtaceae. *P. guajava* is a phytotherapeutic plant used to manage different diseases in folk medicine for a long time and results are considered satisfactory. Different parts of the plant are used traditionally to treat different medical conditions, mostly malaria, cough, wounds, vomiting, ulcers, dysentery, gastroenteritis, and inflamed gums (Abdel-Hafez et al., 2015). Phytochemical analysis of *P. guajava* shows that this plant extract contains almost 20 compounds with tannins and P-sitosterol known to be the best elements. Leaf extracts of guava found to be very effective for antibacterial activity, especially against *Salmonella enterica, Serovars typhimurium*, *Staphylococcus. aureus*, *Escherichia coli*, *Bacillus subtilis*, and *Pseudomonas aeruginosa* (Mahfuzul Hoque et al., 2007). The chemical compounds found in guava leaves are glycosides, saponins, flavonoids, terpenoids, and phenol. Different studies show that the antibacterial activity of *P. guajava* is attributed to the bioactive compounds present in guava leaves (Adeyemi et al., 2022). Some other researchers show that the antimicrobial action of guava is due to the presence of phytochemical compounds in it which have been studied for their effect on bacteria (Biswas et al., 2013). A 5% concentration of guava leaf extracts is widely used against salmonella which inhibits the growth of salmonella. Guava is used for its natural potential against the pathogen and for control and management of the pathogen.

Onion Peel Extracts

Recent investigations show that onion peel can be used as a nutritional fiber and a source of bioactive compounds for livestock and also in food industries. Another amazing quality attributed to onion is that it is used as a source of biomolecules, a component of fertilizers made up of organic matter, and also used as a source of renewable energy (Stoica et al., 2023). Onion peel is found to contain a variety of chemicals that exhibit biological activities and used as pharmaceutical agents and also in the food industry. Phenolic compounds are present in onion, with higher volume in the outer as compared to the central layers. The main component of the phenolic chemicals is polyphenolic flavonoids (Pérez-Gregorio et al., 2014). A sun-induced chemical named quercetin formed by the deglucosidation of onion’s glycosides (Joković et al., 2024) is thought to be present in high amounts in the peel of onion. It. The antimicrobial activities of onion peel have been proven to be more effective against Gram-positive bacteria as compared to Gram-negative bacteria (Fredotović et al., 2021). Onion peel extracts have been studied and evaluated to check their activity to improve the health, productivity, performance, and growth of poultry (Olugbemi-Adesipe, 2019; Malematja et al., 2022). Onion peel extracts contain phytochemical substances that not only work against pathogenic bacteria but also improve the digestion and absorption of nutrients without affecting the total weight gain and feed intake of birds. Onion peel extracts have been used in the poultry industry as it does not have any adverse effects on the carcass yield of poultry meat (Kothari et al., 2019). Onion peel extracts have no negative effects on poultry production so they could be used as an alternative to antibiotics in poultry.

Essential Oils

Essential oils are naturally present non-toxic, volatile, and aromatic substances. They extract from a large variety of plants and different parts of plants and are known to have the ability to work as growth promoters, immunostimulants, antioxidants, antibacterial, antifungal, and antiparasitic in the poultry industry (Zhai et al., 2018). Essential oils have environment-friendly properties which are beneficial to use against the food borne microbes, especially *Salmonella*, *Campylobacter*, and *E. coli* O157:H7 (Burt, 2004; Johny et al., 2008; Nair et al., 2014; Nair et al., 2015; Nair et al., 2016a; Nair et al., 2016b). Some important essential oils have been drawn from different plants are discussed below. The extracts of *Cymbopogon citratus* locally named lemongrass can work as an antibacterial agent against some bacteria mostly *S. enterica* and *S. typhimurium*. Traditionally lemongrass is used as a flavoring agent in Asian cuisine (Singh et al., 2011). LGEO (lemongrass essential oil) which is extracted from the lemongrass (Tajidin et al., 2012) is standardized by the U. S. Food and

Drug Administration and is known as GRAS (generally recognized as safe). The bioactive compound of essential oil is present as a combination of isomeric forms for example geranial (α-citral) and neral (β-citral) whereas citral is the main bioactive component of essential oils (Tajidin et al., 2012). Other than citral, several other chemical compounds are also present in essential oils at a low concentration, for example, limonene, citronellal, b-myrcene, and gerniol (Schaneberg and Khan, 2002; Tajidin et al., 2012). The antimicrobial activities of LGEO against food-borne bacteria, especially Salmonella have been discussed in some old studies (Shin, 2005; Naik et al., 2010; Shah et al., 2011; Moore-Neibel et al., 2013). The combined action of citral and LGEO has been found to enhance the antibiotic sensitivity of streptomycin against *S. typhimurium* (Shin, 2005). Thyme and oregano-based essential oils are also used to administer in chickens which prevents the colonization of various species of Salmonella in the gastrointestinal tract (Johny et al., 2008). These essential oils are known to be used as a stimulant to feed intake in poultry which ultimately leads to weight gain (Bolukbasi et al., 2006; Cross et al., 2007; Khattak et al., 2014). The antibacterial activities of these essential oils improve the performance of poultry by maintaining beneficial gut microbes and inhibiting the growth of pathogenic bacteria. The antibacterial activities of essential oils are attributed to Carvacrol, thymol, eugenol, and cinnamaldehyde (Mathlouthi et al., 2009; Al-Shuwaili et al., 2015; Moukette et al., 2015). The antibacterial activity is done by destroying the genetic material, changing the permeability of the cell membrane, and disrupting the enzymatic system of bacteria (Hulin et al., 1998; Krishan and Narang, 2014). These oils stimulate feed intake and secretion of the enzymes of the digestive system in poultry birds (Bento et al., 2013), and immunomodulatory actions (Brenes and Roura, 2010; Tiihonen et al., 2010; Amerah et al., 2011; Hosseini et al., 2013; Karadas et al., 2014; Khattak et al., 2014). Cinnamaldehyde present in the bark of cinnamon plants is used for its antibacterial, antifungal, and anti-inflammatory activities (Johny et al., 2010). Cinnamaldehyde shows its antibacterial activities by different mechanics including change of membrane permeability and by stopping the consumption of glucose. 10mM of cinnamaldehyde is found to reduce the colonization of S. enteritidis. Daily feed supplementation of cinnamaldehyde in poultry chickens was found to decrease the colonization of cecal *S. enteritidis*.

Conclusion

Salmonellosis is a bacterial disease that mainly affects the digestive system in both poultry and humans. This disease not only affects birds but it may also be transmitted to humans through consumption of infested undercooked meat. Hence besides being disruptive for the poultry industry this disease is also a serious concern for the health of humans that come in regular contact with chicken and chicken products. The severity of this disease and recent increase in its incidence rate has raised an alarm among the researchers. Although it was easily controlled in the past by using antibiotics like azithromycin, the escalation of antibiotic resistance among bacteria has rendered this drug useless against Salmonella. Such trends call for development of alternative medicinal options to battle salmonella. Many of the alternative options are now being researched to develop commercial products that can be used to control salmonellosis with least side effects. For instance, herbal products like essential oils, ginger, guava leaf and onion peel extracts and green tea are some of the best options that have been reported to be substantially useful against the attack of Salmonella.

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Chapter 05

Herbal Remedies for Treating *E. coli* in Poultry Flock

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ABSTRACT

Due to the high consumption of poultry meat, poultry industry also gained major place in the economy of world. To enhance the rate of production of meat, many antibiotic feed additives are used in the feed and water of birds. But the increased use of antibiotics results in the resistance of antibiotics in the bacteria. To inhibit the emergence of resistance, many other products introduce to use as feed additives in bird. Plants and herbs are the potential source of naturally occurring compounds to use in poultry which possesses less side effects and in poultry and human as well. For the antibacterial, antiviral, anti-parasitic, and antioxidant activities of these herbs and spices, they are widely used in poultry to enhance the body weight and production rate. These plants also used for their therapeutic activities in the poultry against many bacterial and viral infections.

KEYWORDS
Poultry, Antibiotics, Feed additives, Herbs, Infection

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INTRODUCTION

Since the last four decades, the poultry industry has reached a milestone in production but there are still many hurdles in the way of achieving a high rate of production. The main problem includes high feed cost and improper use of antibiotics in birds (Kudoh et al., 1998; Alagbe et al., 2019). The indiscriminate use of antibiotics in poultry is a major health concern as the residue present in several end products present serious health issues in humans due to the resistance developed in bacteria against these antibiotics. These health concerns led to the ban on the use of antibiotic feed additives in poultry in 2006 by the European Union (Vicente et al., 2007). The most popular and potential alternative of antibiotic feed additives are phytobiotics, phytogenics and probiotics. These medicinal plants contain one or more beneficial bacteria or yeast which help in promoting gut health of the bird and also protect from the condition called as dysbiosis which probably results in stress, water deprivation, fasting infections which may result in disturbance of the normal gut microflora and number of infectious microorganisms increase (Vicente et al., 2007; Alagbe, 2020). Gut is considered as the most important organ as processes of digestion, absorption of nutrients, integrity of intestine, metabolism of nutrients and fermentation take place there (Al-Mashhadani, 2015). The exposure of the intestinal tract to the infectious agents such as *Escherichia coli*, *Clostridium*, *Pseudomonas*, *Blastomyces* and *Salmonella* result in imbalance of gut microflora, loss of productivity and immunosuppression (Kudoh et al., 1998).

E. coli Infections in Poultry

Avian pathogenic *Escherichia coli* (APEC) which is basically an extra-intestinal pathogenic *E. coli* (ExPEC) has the potential to cause local and systemic severe infections in chicken, ducks, turkeys, and many other poultry birds (Figure 1)

(Dho-Moulin and Fairbrother, 1999). APEC cause serious infections in poultry bird which collectively called as avian colibacillosis. In avian colibacillosis various systems of body faced serious infections for example in liver it cause perihepatitis, in air sacs it results in airsacculitis, also cause pericarditis, damage egg production by causing egg peritonitis, and various other infections such as salphingitis, coligranuloma, omphalitis, cellulitis, and osteomyelitis/arthritis (Dziva and Stevens, 2008). Swollen head syndrome in chickens and osteomyelitis complex in turkeys also caused by APEC (Guabiraba and Schouler, 2015).

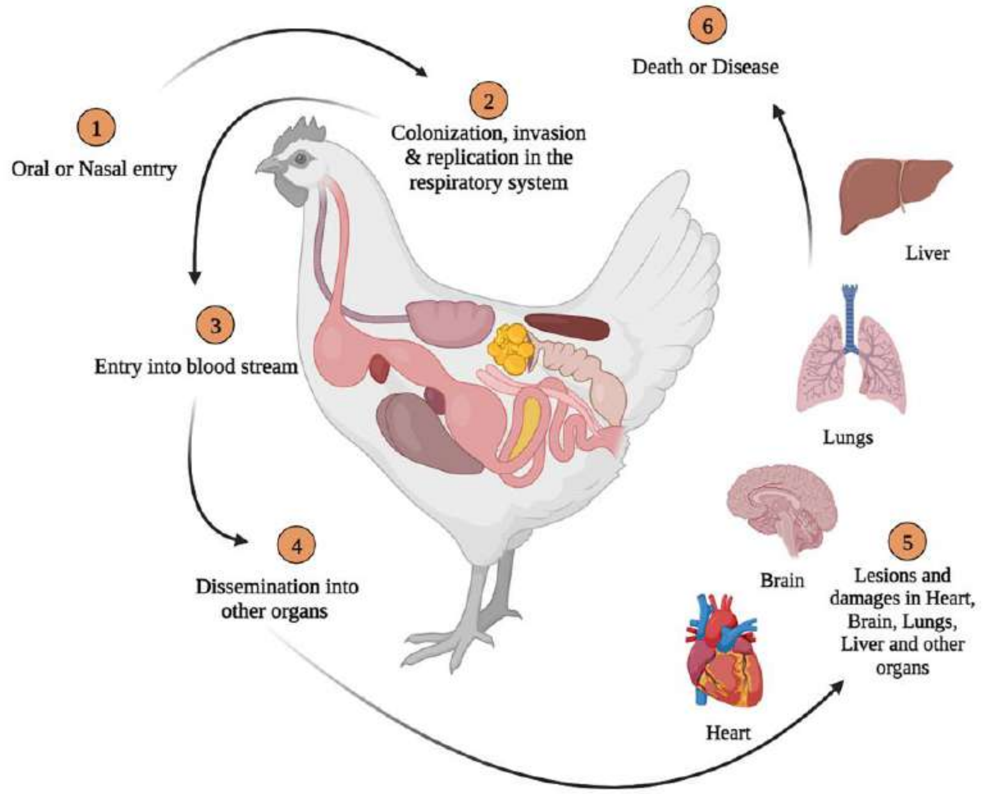

Fig. 1: Pathology of Avian Pathogenic *E. coli* (APEC)

The rate causes major harmful health outcomes in poultry due to colibacillosis include mortality (up to 20%) and morbidity, decrease in meat production (decrease in live weight 2%, 2.7% decrease in feed conversion ratio) and rate of egg production (up to 20%) decline in hatching rate, at slaughter high rate of condemnation of carcass (up to 43%) (Dho-Moulin and Fairbrother, 1999; Dziva and Stevens, 2008; Guabiraba and Schouler, 2015). While in young chickens the rate of mortality exceeds up to 53.3% (Mellata, 2013). Due to the high cost of treatment and preventive measures, the poultry industry faces hundreds of millions of dollars of losses due to APEC around the world (Ghunaim et al., 2014). The estimated loss due to APEC in broilers is $40 million which is only due to carcass condemnation in the United States (US) (de Brito et al., 2003). All types of poultry species raised in all types of production systems are under the threat of APEC (Dziva and Stevens, 2008). It is also noticed that APEC attacks (9.52% to 36.73%) all age groups of chickens (Lutful Kabir, 2010).

The age at which the attack of APEC is most prevalent in broilers is 4 and 6 weeks of age while in the layers the most susceptible age is throughout the grow and lay periods especially at the peak of egg production rate and late lay periods (Lutful Kabir, 2010). In the US it is noted that almost 30% poultry flocks are susceptible to APEC at any point of age (Johnson et al., 2008). A number of APEC serotypes causes colibacillosis in poultry especially in field outbreaks but most commonly found serotypes are O78, O2 and O1 which causes the majority of cases (80%) in poultry (Dho-Moulin and Fairbrother, 1999; Ghunaim et al., 2014). APEC causes systemic infections in poultry both as a primary pathogen or as a secondary pathogen to viral infections such as infectious bronchitis (IBV), Newcastle disease (NDV), avian influenza (AIV)) and Mycoplasma (*Mycoplasma gallisepticum* (MG)) infections, immunosuppressive disease, infectious bursal disease (IBD).

The age at which broiler chickens are at risk of getting APEC infections is at 4 and 6 weeks old but in case of layer, the chickens are more vulnerable at the peak of egg production and almost throughout the growth period (Dho-Moulin and Fairbrother, 1999). In the United States, it has been noticed that almost 30% of the population of poultry has been threatened by APEC at any time (Johnson et al., 2008). The three major serotypes used to cause almost 80% infection in birds are O78, O2 and O1 but many other serotypes have also been seen in field outbreaks (Dho-Moulin and Fairbrother, 1999; Ghunaim et al., 2014). APEC causes infection in poultry both as primary agent and secondary agent (Figure 2) (as a result of viral infections such as (infectious bronchitis (IBV), Newcastle disease (NDV), avian influenza (AIV)) and Mycoplasma (*Mycoplasma gallisepticum* (MG)) infections, immunosuppressive disease (infectious bursal disease (IBD)), and as a result of stress from overcrowding in poultry shed and high levels of ammonia as the pathogen can enters in the body of bird through oral and respiratory routes (Dho-Moulin and Fairbrother, 1999; Guabiraba and Schouler, 2015).

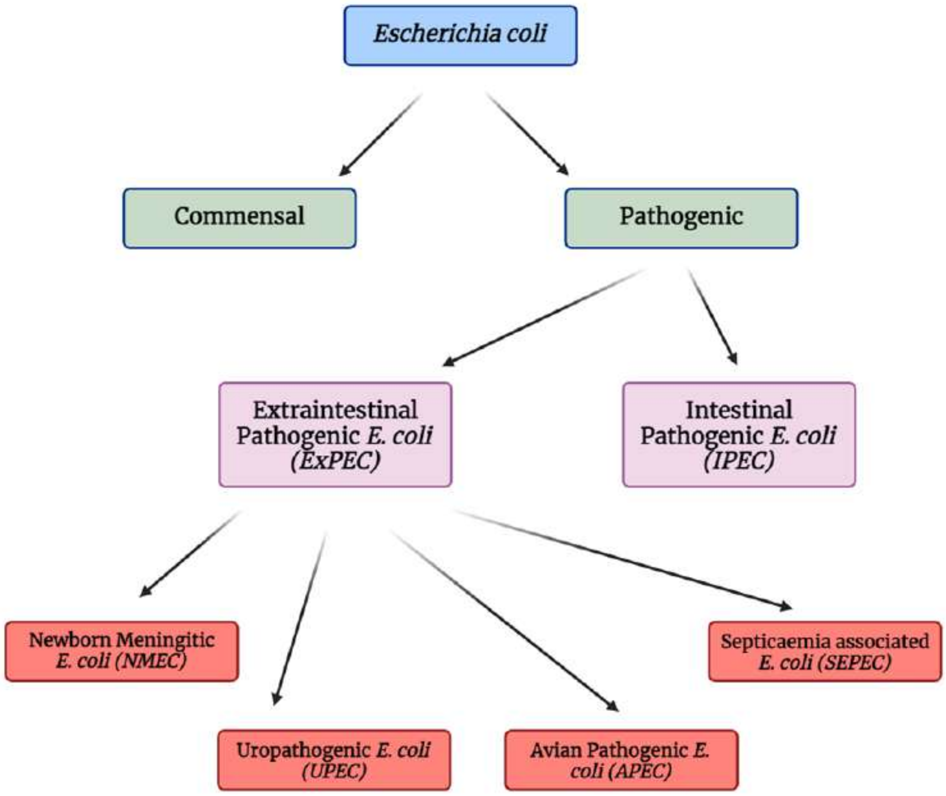

Fig. 2: Classification of *E. coli* based on origin and pathogenicity.

It has been seen that APEC didn't harm its host and colonize in the body of host at different places including intestinal and respiratory tracts but in the presence of any stress indicators for example production stress, immunosuppression or in any other infections (Dziva and Stevens, 2008; Collingwood et al., 2014). APEC enters in the body in the presence of any stress indicator and reaches in the intestinal or respiratory tract through the lacerations in the epithelial tissue of intestine and trachea through which it reaches the bloodstream and other internal organs of the host body (Dho-Moulin and Fairbrother, 1999; Dziva and Stevens, 2008; Guabiraba and Schouler, 2015). Contaminated feed and water are the major vectors of spreading infection in poultry birds and can be transferred to the other healthy birds through feco-oral and aerosol routes (Dho-Moulin and Fairbrother, 1999; Dziva and Stevens, 2008; Guabiraba and Schouler, 2015). Vertically, APEC transferred through contaminated eggs due to infected breeders (Dho-Moulin and Fairbrother, 1999; Dziva and Stevens, 2008; Guabiraba and Schouler, 2015). APEC acts as an opportunistic pathogen and remains in the intestinal and respiratory tract of the host without causing any infection but in the presence of any stressor such as immunosuppression, it causes infections (Dziva and Stevens, 2008; Collingwood et al., 2014).

APEC has many different virulence factors including adhesins, invasins, protectins, iron acquisition systems, and toxins to cause infection in the chickens (Dho-Moulin and Fairbrother, 1999; Guabiraba and Schouler, 2015). These virulence factors help APEC in various functions such as adhesion, invasion and evasion from the host different immune responses and also facilitate the proliferation, colonization and dissemination of APEC in different systems of host which result in serious infections in chickens (Dziva and Stevens, 2008; Collingwood et al., 2014). There are several other bacterial factors present for example secretion systems (type III and VI), quorum sensing systems, transcriptional regulators, two-component systems, and metabolism-associated genes also responsible for APEC infections in chickens (Palaniyandi et al., 2013; Ma et al., 2014; de Paiva et al., 2015; Jiang et al., 2015; Zhuge et al., 2016; Barbieri et al., 2017; Wang et al., 2017; Guerra et al., 2018; Li et al., 2020). To develop effective treatment methods and preventive measures, a detailed understanding of these factors will be very helpful.

Herbal Remedies for *E. coli* Infections of Poultry

Antibiotic-resistant bacteria are proliferating, endangering the safety of food products like chicken as well as people who use them. Numerous researches emphasize the antimicrobial qualities of medicinal plants, which are just as significant as those of current synthetic medications. The prospect is the driving force behind the growing interest in using medicinal herbs instead of conventional treatment for chickens (Table 1). Powdered Amla (*Phyllanthus emblica*) fruit contains tannin (Rose et al., 2018) has ability to destroy bacteria by their engulfing properties (Sai Ram et al., 2003). Consuming amla causes the gut's lactic acid bacteria to produce more lactic acid, which lowers the pH of the colon and keeps organisms from integrating into the intestinal mucosa, preventing harm to tissues from failed toxin synthesis (Dalal et al., 2018). Supplementing the broiler feed with *Salvia rosmarinus* can boost *Lactobacilli* numbers and lower *E. coli* levels (Norouzi et al., 2015). Likewise, another researcher (Al-Mashhadani, 2015) found as rise in Lactobacilli count had an impact on weight growth, supplementing with *Curcuma longa* (turmeric) reduced the viability of *E. coli* in the cecum. Lannaon (Lannaon,

2009) discovered, broiler chicks responded more positively to herbal mixtures of avocado leaves, guava, duhat, eucalyptus, or tam arind trees than to currently available medicines. Studies by Mapatac (Mapatac, 2015) revealed that giving broiler infusion of guava enhanced efficiency in addition to other vegetation, such as leaves of malunggay (*Moringa oleifera*) and avocado (*Persea americana*). Further research, yet, suggests that eating different avocado segments may have strong antimicrobial qualities.

Table 1: Effective antibacterial herbs against *E. coli* infection in poultry flock.

No.	Herb spp.	Botanical name	Effective part of plant	Effective against	References
1.	*Salvia rosmarinus*	Rosemary	Leaves	*E. coli*	(Norouzi et al., 2015)
2.	*Curcuma longa*	Turmeric	Rhizome	*E. coli*	(Al-Mashhadani, 2015)
3.	*Persea americana*	Avocado	Leaves and bark	*E. coli, S. aureus*	(Ogundare and Oladejo, 2014)
4.	*Persea americana*	Avocado	Fruit	*E. coli, S. aureus*	(Guzmán-Rodríguez et al., 2013)
5.	*Persea americana*	Avocado	Seed	*E. coli, S. aureus, S. agalactiae*	(Cardoso et al., 2016)
6.	*Psidium guajava*	Guava	Fruit	*E. coli, S. Typhimurium*	(Ibrahim et al., 2011)
7.	*Syzygium cumini*	Duhat	Stem	*B. amyloliquefaciens, S. aureus, E. coli, P. aeruginosa*	(Sharma, 2017)
8.	*Tamarindus indica*	Tamarind	Fruit	*E. coli, K. pneumoniae, S. paratyphi A., P. aeruginosa.*	(Daniyan and Muhammad, 2008)
9.	*Thymus vulgaris*	Thyme	Leaves	*E. coli, S. Typhimurium*	(Aktuğ and Karapinar, 1986; Marino et al., 1999)
10.	*Cinnamomum zeylanicum*	Cinnamon	Inner bark	*Klebsiella spp., E. coli, L. monocytogenes, and Bacillus spp.*	(Griggs and Jacob, 2005; Gupta et al., 2008; Abd El-Hack et al., 2020)
11.	*Allium sativum*	Garlic	Bulbs	*E. coli*	(Ziarlarimi et al., 2011)

Use of Herbal Extracts in Poultry

The extracts of leaves and stems work well in opposition to *Staphylococcus aureus* and *E. coli* because they include terpenoids, tannins, flavonoids, and saponins (Table 2) (Ogundare and Oladejo, 2014). Additionally, the fruit has a raised-phenolic component that is work well towards *Streptococcus agalactiae, S. aureus*, and *E. coli* (Cardoso et al., 2016), and the seed has defensin PaDef, that is powerful in killing these pathogens (Guzmán-Rodríguez et al., 2013; Cardoso et al., 2016). The aerial parts of duhat (*Syzygium cumini*) consist of bioactive compounds, like flavonoids, tannins, terpenoids, and alkaloids, which restrict different bacteria such as *Bacillus amyloliquefaciens*, also *S. aureus*, with *E. coli*, and *Pseudomonas aeruginosa* to grow further. Guava (*Psidium guajava*) also have the ability to limit the growth of *Salmonella Typhimurium* (Ibrahim et al., 2011) and *E. coli* (Sharma, 2017). The foliage of Eucalyptus (*Eucalyptus globulus L.*) are rich in naturally occurring compounds that reduce the activity of *Salmonella, Klebsiella spp., S. Streptococcus A., Proteus spp.*, and *S. aureus*. These components include tannins, flavonoids, volatile oils, and terpenoids (Sallam et al., 2009). The ripe fruit of the tamarind tree, Tamarindus indica, also includes bioactive substances that prevent the growth of *Salmonella paratyphi A, P. aeruginosa, Klebsiella pneumoniae,* and *E. coli*. These components include alkaloids, flavonoids, saponins, and tannins (Daniyan and Muhammad, 2008). Additionally, thyme inhibited the in situ development of *S. Typhimurium* (Aktuğ and Karapinar, 1986) and *E. coli* (Marino et al., 1999). Enhanced antibacterial qualities versus pathogenic bacteria such *Klebsiella spp., E. coli, Listeria monocytogenes*, and *Bacillus spp.* were seen in the vital oil of cinnamon (*Cinnamomum zeylanicum*) (Gupta et al., 2008; Abd El-Hack et al., 2020). Furthermore, cinnamon (*C. zeylanicum*) essential oil may have inherent antibacterial qualities in chickens, according to Griggs and Jacob (Griggs and Jacob, 2005). Furthermore, *Menthe spp.*, *Allium sativum*, and *Allium cepa* may all successfully stop E. coli from growing (Ziarlarimi et al., 2011).

Table 2: Various herb preparations that are effective against *E. coli* infection in poultry.

No.	Plant Spp.	Effective extract	Zone of inhibition (mm)	References
1.	*Achillea wilhelmsii*	Methanol	9	(Amjad et al., 2011)
2.	*Allium sativum*	Methanol	21.5	(Garba et al., 2013)
3.	*Artimesia scoparia*	Methanol	24	(Moghaddam and Sani, 2015)
4.	*Artimesia scoparia*	Essential oil	26	(Moghaddam and Sani, 2015)
5.	*Coriandrum sativum*	Ethyl acetate	7	(Keskin and Toroglu, 2011)
6.	*Coriandrum sativum*	Ethanol	14.5	(Shaheen et al., 2015)
7.	*Cuminum cyminum*	Methanol	8	(Keskin and Toroglu, 2011)
8.	*Withania coagulans*	Methanol	10	(Peerzade et al., 2018)

Cumin was shown to be greater in effectiveness against *E. coli* and *Enterobacter aerogens* than against other types of bacteria in a research that used the technique of disc diffusion to examine the antibacterial properties of cumin (Chaudhry and Tariq, 2008). Cassia angustifolia was found to be incredibly effective in opposition to methicillin-resistant *Staphylococcus aureus*, *Salmonella*, *E. coli*, and *Shigella shinga*, as well as *K. pneumoniae*. Bameri et al. (Bameri et al., 2013) demonstrated this effectiveness, which may have implications for the digestive system, where certain pathogenic bacteria rely on the binding of microbes to intestinal mucosal cells, a process that is strongly regulated by the hydrophobic surface characteristics of these microorganisms. According to Jamroz et al. (Jamroz et al., 2003), a combination of plant extraction decreased the number of *C. perfringens* and *E. coli* in intestinal materials in a way that was equivalent to the effects of the drug avilamycin. According to reports, the addition of a volatile oil (EO) blend including carvacrol, trans-cinnamaldehyde, and capsaicin at 49.5, 29.7, and 19.8 g/kg, each, significantly reduced the amount of *E. coli*. (Jamroz et al., 2005). According to Yasar et al. (Yasar et al., 2011), adding 1.5% of cumin to the diet dramatically lowered the counts of lactic acid bacteria, enterobacteriae, psychrophilic aerobic bacteria, and *E. coli*. Four herbs—cumin, peppermint, yarrow, and poley—as well as an antibiotic—flavomycin—were added to the feed of young chicken by Sharifi et al. (Sharifi et al., 2013). They discovered that the middle part of intestine Lactobacilli and Coliform bacterial populations remained unchanged after supplementation. Intestinal *Bifidobacterium* and *Clostridium* counts were lowered in broiler chicken feed upon the incorporation of flavomycin, peppermint, yarrow, and poley. There was no discernible effect of cumin on Bifidobacterium. Hosseinzadeh et al. (Hosseinzadeh et al., 2014) use different amount of coriander powder and its extract in the water amd feed of the bird and found no discernible impact on *Lactobacillus* bacteria. In contrast, the use of 1.5% coriander seed powder and 1250 ppm extract considerably decreased the *E. coli* count. Ten or one gram per kilogram was fed to meat birds' basal with black cumin seed and/or seed extraction. According to the findings, the addition inhibited the number of Coliform bacteria in the intestine's caecal region, improving health in conjunction with promoting development-related features (Erener et al., 2010). Additionally, the possible advantages of supplying a botanical cocktail containing coriander, cumin, black pepper, and turmeric included the capacity to reduce the overall *Coliform* count in the quail ileum (Khosravifar et al., 2014). Similar to what was previously said, several studies have shown that eating carwey, turmeric, and cumin inhibited the formation of *E. coli* and coliform and increased the health of the digestive tract, which in turn enhanced consumption and processing (Samarasinghe et al., 2003; Iacobellis et al., 2005).

Conclusion

Many plants contain some naturally occurring compounds in them which work as medicine for poultry birds to treat many bacterial, viral, antiparasitic and antifungal infections. These plants offer many advantages but major advantages of the use of these plant includes less side effects, harmless for use in birds, human and environment, decrease the risks of antimicrobial resistance and almost no residue present in chicken meat and eggs and their products for human consumption. Many plant species have been used as therapeutic agents in poultry and many are under research to find out their potential benefits on the health of poultry birds. Near future, many natural products with less risk of side effects will be used in birds to fight against diseases.

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Chapter 06

Homeopathic Medicine for Treating Various Diseases of Poultry

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ABSTRACT

Homeopathy word is derived from two Greek words “homoios” and “pathos” which means similar and suffering, respectively. It was created in 1796 by Samuel Hahnemann. This practice is based on 3 basic principles including similarity, individualization of cases and infinitesimal. It is equally effective in veterinary field as in humans. One of the basic principles which is ‘similia similibus curantur’ means let like to be treated by like. It is used in poultry to treat various bacterial, viral, parasitic diseases, nutritional deficiencies, stress and to enhance their production and growth. Homeopathic medicines have many advantages like they cannot cause disease, have no major side effects, small doses are sufficient, easy to be administered and are cheaper than others. They can be used along with the allopathic drugs or vaccines to eliminate their adverse effects or to enhance recovery. The routes of administration are internal or externally, optimum results are by internal administration. Commonly used homeopathic medicines in poultry are Mercuris solubilis, Nux vomica, Sulphur, Carbo vegetabilis, Veratrum Album, Belladonna, Kali, Kali sulphuricum, Thuja, Pulsatilla, Natrum sulphuricum, Natrum muriaticum, Ferrum phosphoricum, Calcarea phosphoricum, Bryonia, Sabadilla, Kali bichromicum, Allium cepa, Alfalfa, Santonin, Glonoine, Arnica montana, Aconite napellus, Antimonium tart, Cicuta, Echinacea, Hypericum, Vaccininum and Variolinum.

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INTRODUCTION

The world’s population is expanding at a greater rate and similar is the scenario with the demand for food to fulfill global nutritional needs (Tian et al., 2021). The food security principles are highly centered on the motive to provide safe, hygienic, and quality food to every human being on the globe at an affordable price. The poultry industry has shown a significant potential to meet the growing demands of the population while fulfilling the food security parameters (Kleyn and Ciacciariello, 2021). Although the poultry industry provides a promising future yet, modern poultry production practices must face a lot of issues due to the adoption of control shed systems as it makes the whole flock prone to a particular disease due to closed premises. There are a lot of bacterial, protozoal, and viral infections that poultry birds must come across during their lifespan (Wickramasuriya et al., 2022). The most prevalent conditions faced in the open backyard and closed control shed systems of poultry rearing are parasitism, bacterial diseases like CRD, salmonellosis, infectious coryza and viral diseases like avian influenza, Newcastle disease, infectious bursal disease (Gentile et al., 2023). Fighting these diseases is a big challenge for the poultry farmers although, there are a lot of treatment options including commercially available antimicrobial therapies, but these may fall prey to antimicrobial resistance. Similarly, the treatment of viral diseases is also a serious concern as currently antivirals are very costly and the industry relies on vaccines only. The use of antimicrobials for secondary infections and preventive purposes is also common, rendering poultry meat prone to antimicrobial residues which contributes to the transfer of antimicrobial resistance in the humans in one health preview (Endale et al., 2023). In such aspects besides the herbal medicines which may not provide a sustainable solution for enormous poultry production houses there lies another option referred to as homeopathic medicine.

History

The homeopathic medicine is a well-known alternative medicine that originated in Germany about 200 years ago (Cukaci et al., 2020). Its foundation lies in two unconventional theories: “like cures like” and “law of minimum dose”

(Nengovhela, 2022). These theories refer to the use of substances which may induce similar symptoms and signs of a particular disease in healthy individuals. Homeopathic medicines are manufactured based on a mixture of chemicals, animals, and botanical sources (Thakkar et al., 2020). This alternative medication field has gained much repute in recent years and is even being used by many veterinary physicians and surgeons around the globe (Prasad et al., 2021). Homeopathic medicines have shown promising results in treating various bacterial and parasitic diseases in food animals and experimental lab animal trials. Similarly, two medications: Fertsigo® and Ovosigo® have been found to improve the eggshell quality and nutritional profile in an experimental trial conducted on Japanese quails (de Souza Eberhart et al., 2021). The underlying study will encompass various important poultry diseases and their remedies which are currently being implied in veterinary facilities around the globe.

Homeopathy in Treating Protozoal Diseases

The parasitic and protozoal diseases play an important role in decline of the poultry industry throughout the world (Mohammed and Sunday, 2015). These diseases are highly pathogenic and cause severe economic losses including high mortality, decreased production and high medicine costs. Farmer is facing a lot of challenges due to such diseases.

Coccidiosis

Coccidiosis is one of the lethal diseases of poultry caused by various species of *Eimeria* parasite which belong to the phylum *Apicomplexa* and family *Eimeriidae* (Berto et al., 2011; Blake et al., 2020). The *Eimeria* parasite mainly affects the intestinal epithelium of birds (Fernando and McCraw, 1973). The severity of disease depends upon the age of bird, immunity, and environmental conditions (Hawley and Altizer, 2011). The characteristic clinical signs of coccidiosis include:

- Loose or watery diarrhea often with mucus or blood.
- Decreased feed intake ultimately led to poor FCR.
- Weight loss due to less feed intake and severe diarrhea.
- Loss of egg production.
- Blood in droppings visible as red streaks or a dark tarry consistency.
- Increase mortality rates due to severe disease.
- Dehydration with the signs of sunken eyes, dry skin and decreased skin elasticity (Mesa-Pineda et al., 2021)

Treatment

Limited availability of modern drugs has very high cost and it also produce antimicrobial resistance in infectious organism ultimately producing a lot of challenges in poultry industry. Medical plants can be used as antidiarrheal, antiparasitic and anti-inflammatory as well as stimulate immunity of birds enhancing their potential as an alternative remedy to commercial drugs. These medical plants include

Common Name	Secondary Bioactive Metabolite	Application
Cyamopsis tetragonoloba taub	Saponins	Reduce chance of coccidiosis in chicken
Vitis vinifera	Proanthocyanidin	Reduce coccidiosis via down regulation of oxidative stress
Phyllantus emblica	Tannins	Against coccidiosis
Curcuma longa	Curcumin	Reduce gut damage in birds
Olea europoea	Maslinic acid	Enhance anticoccidial index

Histomoniasis

Histomoniasis also known as "blackhead disease" is caused by Histomonas meleagridis belonging to phylum Parabasalia and family Dientamoebidae.

Histomoniasis affects chickens, turkeys and other poultry species as well. Signs and symptoms of this disease depend upon severity of infection, species of bird and organs infected. Signs of Histomoniasis include

- Watery foul-smelling diarrhea with greenish or yellowish tint.
- Poor appetite or complete loss of interest in food
- Swollen head and blue comb due to impaired blood circulation
- Pale comb and wattles due to less blood flow and anemia
- Increased mortality in severe disease

Treatment

There are few homeopathic remedies that have been traditionally used in poultry for various ailments including histomoniasis.

i **Arsenicum album** is a homeopathic remedy used in poultry for digestive disturbances such as diarrhea considered as supportive treatment for histomoniasis gastrointestinal issues.

ii **Carbo vegetabilis** is used to stimulate immunity and general weakness. It is used in histomoniasis where bird show signs of weakness and require support for their overall viability

iii **Nux vomica** is mainly used for diarrheal problems.

Ectoparasitic Mites

Ectoparasitic mites such as the Northern fowl mite Ornithonyssus sylviarum and red mite Dermanyssus gallinae cause infestation in poultry and ultimately affect health of birds. These mites are introduced into flock due to poor management.

Characteristic Signs

Signs of ectoparasitic mites include

- Anemia due to infestation of blood feeding mites
- Intense itching and feather pecking
- Decreased egg production due to anemia
- Restlessness and stress ultimately affect production of birds

Treatment

Few homeopathic remedies also used for treatment of ectoparasitic mites' infestation that include

i Psorinum is a homeopathic remedy used for mite infestation having effect on itching, skin eruptions and general discomfort

ii Arsenicum album used for signs of itching, restlessness and anxiety

Tapeworms

Etiology

Tapeworms including Raillietina spp. And Davainea spp. Infect the intestines of poultry which are ultimately affecting production of poultry.

Characteristic Signs

Tapeworms mainly affect chicken and Turkeys showing given signs of disease

- Watery droppings due to decreased normal bowel movements
- Poor growth due to less absorption of nutrients through intestine
- Less weight gains due to poor FCR
- Potbellied appearance of birds in severe infestation of tapeworms
- Reduced egg production

Treatment

i **Cina** is a homeopathic remedy that result in expelling of tapeworms from the body

ii **Teucrium marum verum** is also recommended for tapeworm infestation

Viral Diseases

Newcastle Disease

The Newcastle disease is a serious threat and an infectious and contagious disease of avian species all over the world (Suarez et al., 2020). It is commonly known as "Ranikhait disease" in Pakistan and India (Puro and Sen, 2022). It is caused by a virus Newcastle Disease Virus (NDV) (Ul-Rahman et al., 2022). It has caused losses at vast levels. These losses can be prevented by controlling these viral diseases. Many homoeopathic drugs have given beneficial results.

Clinical Signs and Symptoms

- Respiratory distress (sometimes birds make a whistling sound).
- Bright green diarrhea.
- Clear mucus discharge from the mouth.
- Loss of appetite.
- Nervous signs such as paralysis and convulsions.
- Sudden death (sometimes the only finding) (Kumaravel, 2020).

Infectious Bursal Disease

It is a lymphocytolytic disease of poultry chicken, commonly encountered in Pakistan due to a lack of adaptation to biosecurity and intensive farming (Schat, 2022). It causes immunosuppression in birds by affecting the defensive mechanism of poultry and damaging the bursa of fabricius (Orakpoghenor et al., 2020). The IBDV mainly divides into the B cells of the bursa of fabricius (Shah et al., 2021). The control of this disease is by vaccination and proper monitoring of the immune response (García et al., 2021).

Clinical Signs and Symptoms

- Inflammation of the cloaca
- Lesions in the cloacal bursa (bursa of Fabricius)
- Ruffled feathers
- Huddling (Orakpoghenor et al., 2021).

Fowl Pox

Fowl pox is a widespread disease of poultry which is present worldwide, reported in mild to severe form in poultry (Umar et al., 2021). It is present in all types of poultry, but chickens are mostly affected. Frequent cases of pigeon turkeys are also reported, commonly called chickenpox (Ahmed et al., 2022). It is caused by FWPV (Fowl pox virus) (Zhao et al., 2020), primarily in two forms cutaneous and diphtheria (Cui et al., 2023; Umar et al., 2021). The most severe form is the diphtheritic form in which necrotic proliferative lesions on gastrointestinal and respiratory tracts are observed (Shalaby et al., 2021), more deaths are reported in the diphtheritic than cutaneous form (Williams et al., 2021). It is of zoonotic importance as there are some cases of transfer of virus from chicken to human (Izhar, 2021). It is more often in fall and winter. It spreads to poultry by biting mosquitoes.

Clinical Signs and Symptoms

- Yellowish diphtheritic patches in the mouth and throat
- Eyelid swelling and eyes sealed shut or scabbed over
- Reduced water consumption (Kicepa et al., 2023).

Disease	Homeopathic treatment (Common name)	Homeopathic treatment (Scientific name)	Mode of action	References
Newcastle Disease	Pot marigold	Calendula officinalis	immunomodulation effect against different live viruses	(Riaz et al., 2021)
	Licorice and sweet wood	Glycyrrhiza glabra extract	leaves of Glycyrrhiza glabra have strong antiviral activity	(Riaz et al., 2021)
	Andrographis paniculata	Nilavembu extract	extracts have the ability to inhibit the Newcastle disease virus (NDV)	(Riaz et al., 2021)
Infectious bursal disease (Gumboro)	Pot marigold	Calendula officinalis	immunomodulation effect against live virus	(Jaime et al., 2020)
		Livol (herbal supplement)	increase post vaccination humoral immune response	(Jaime et al., 2020)
	Fructus mume (F. mume), an unripe fruit of Prunus mume (P. mume)	Plum (Prunus sp.)	Improve the immune response for chickens inoculated with infectious bursal disease virus (IBDV)	(Jaime et al., 2020)
	Black cumin	Nigella sativa	have an immunomodulatory effect through improvement of the immune system	(Jaime et al., 2020)
	Garlic, indian barberry,false daisy,mango	Allium sativum, berberislycium, Eclipta alba and Mangiferaindica	improved immunity against IBD and ND while enhancing growth performance	(Jaime et al., 2020)
Fowl pox	Monkshood, friar's hood, auld wife's huid and wolfsbane	Aconitum napellus	prophylactic effect	(Bukar et al., 2021)
	Neem	Azardirachta indica L.	Immunomodulatory and growth promoting	(Bukar et al., 2021)

Homeopathic Treatment of Bacterial diseases

Bumblefoot

Bumblefoot refers to any degenerative and inflammatory condition in foot of poultry (Miesle, 2021). Bumblefoot is also known as pododermatitis (Samour et al., 2021). It is characterized by erythema, ulceration, and swelling. The foot injury is primarily due to the overweight of the bird followed by secondary bacterial infections. Most common occurring secondary bacterial infections are *E. coli* and *Staphylococcus sp* (Manohar et al., 2020). The predisposing factors include wet, hard, or soiled bedding, and overweight. We can avoid bumblefoot by changing the bedding material from wood shavings to wheat straw. The treatment of bumblefoot includes using Arnica mixed with the warm water and given to the birds. Sometimes, in the complicated cases when pus is present in the foot Silica and Hepar sulph are given and Calendula can be given externally (Greenacre, 2021).

Fowl Cholera

Fowl cholera is a contagious disease affecting wild and domesticated birds (Izhar, 2021). The etiological agent of fowl cholera is *Pasteurella multocida* (Saha et al., 2021). The subspecies of *P. multocida* includes *gallicida, multocida*, and *septica*. Main infection site of *P. multocida* is the respiratory tract. It also has the ability to survive in the gastrointestinal tract. When birds get infected with fowl cholera, a large number of sudden deaths are seen in the flock. According to recent studies, fowl cholera has been treated with *Citrus limon* (a fruit from Rutaceae family). Juice from the fruit has been extracted mixed with water and given to the birds through the water supply. Other natural products used for the treatment of fowl cholera include Neem, Shiferaw, and Shinfae. (El-Saadony et al., 2022).

Prolapse of Cloaca

It is also named as vent prolapse in which cloaca protrudes from its normal position (Lima et al., 2023). During egg laying, the lowest portion of the reproductive tract turns outside for a short duration of time, resulting in laying clean eggs. But sometimes it may not contract back after the laying which causes prolapse. When other birds notice the moist and shiny texture of soft tissue, they start picking the prolapsed area resulting in severe injury to the hen (Ussery, 2022). It will lead to severe blood loss and possible removal of cloaca and fallopian tubes.

Factors Responsible for Prolapse

1- Inaccurate management before egg production.
2- Nutritional deficiencies in feed.
3- Poor development of skeleton during pre- laying.
4- Heavy weight breeds are more prone to prolapse.
5- The presence of a large amount of fat around reproductive organs.
6- Unbalanced feed ration.
7- Feed deficient with calcium causes muscle weakness and makes the cloaca harder to retract back into the body.
8- Hens which lay double yolked eggs are more susceptible.
9- Excessive lighting (King and Hopper, 2024).

Treatment

Immediately isolate the bird and wash the prolapsed area with medicated spray. Carefully push back after lubricating the area. To prevent the prolapse from occurring again, Kali phos works very effectively. For 100 birds, Kali phos 30 @25ml can be given to stop mortality and help in complete recovery (Uluocak, 2023).

Prolapse of the Uterus

Prolapse of uterus is similar to cloacal prolapse (Chourasia et al., 2023). The Uterus protrudes from its normal position and does not retract back after laying egg. It is more common in white leghorn breed. The mortality is high due to excessive bleeding. The prevention is through improved management practices. The homeopathy works very effectively in treating prolapse (Sheeba et al.).

Factors Responsible for Uterine Prolapse

Similar factors are responsible for cloacal prolapse like excessive lighting, inaccurate management, poor skeletal development, various nutritional deficiencies, unbalanced feed, weak muscles and double yoked eggs etc. (Doumouchtsis et al., 2023).

Treatment

Manually push back the prolapsed area after lubrication. The following combination works effectively in prolapse:
1- Kali mur 30 @ 5ml
2- Ferrum phos 30 @5ml
3- Calc fluor 30 @5ml
4- Helonias 200 @5ml (Madrewar, 2003).

Sunstroke in Poultry

Birds will always suffer losses in the summer since their bodies' ability to withstand the heat is not fully matured (Nawaz et al., 2021). These losses will increase if the birds have no protection from the heat or sunburn. The mortality rate in young and broiler chicks is greater. In homoeopathic medicine, the following drugs at equal doses are helpful as both preventative and therapeutic measures
Natrum mur 6 100ml
Calcarea carb 6 100ml
Glonoine 30 100ml (Madrewar, 2003).
A mixture of all these can be mixed in 80 liters of water that is sufficient for 800 birds.

The sunstroke is caused by an imbalance in the quantity of heat energy that an animal produces and the net amount of energy that flows from its body to its surroundings. Variations in the combinations of environmental elements, including movement, humidity, sunlight, and thermal irradiation, may be the sources of this imbalance. It is essential for the wellbeing and production of poultry to regulate the environmental conditions (Hafez and Attia, 2020). The heat stress is a significant environmental stressor that chickens face. A reduced development, lowered egg output, decreased egg quality, and decreased safety are just a few of the negative effects of heat stress on broiler and laying hens.

Stress in Poultry Birds

Stress is a reaction to negative stimuli and is hard to characterize and understand due to its imprecise perception (Arnaldo et al., 2022). The SELYE states that "stress is the body's nonspecific response to any demand." Stressor (Appelbaum, 1984), on the other hand, is defined as "any agent that produces stress at any time," meaning that stress is an animal organism's biological response to a stimulation that upsets its homeostasis, or normal physiological equilibrium. Stress in poultry may result from various factors, including transportation, vaccination, deworming, and debeaking. Homoeopathic remedies are just as affordable and potent as other medications that farmers take on a regular basis (Patwardhan, 2005). These work well for treating sunstroke.

Arnica Montana plus Five phos (Madrewar, 2003). This is given 15ml in 5 liters for 100 birds given for the 3 days morning only.

Growth and Production

Poultry birds can convert feed into food products quickly, efficiently, and with relatively low environmental impact (Costantini et al., 2021). As we know, poultry birds are very fast-growing birds being used to meet the meat requirements for human consumption. The high rate of productivity of poultry birds results in relatively high nutrient requirements. The required dietary nutrients for poultry are 38 in appropriate concentrations and balance. These requirements demand that the nutrients be in a highly bioavailable form. Consequently, various feedstuffs should be adjusted based on the bioavailability of nutrients. Different nutrients are required in balanced concentration by the poultry birds for proper growth and development. These nutrients include water, minerals, vitamins, and amino acids. Water is one of the essential nutrients. Different factors influence water intake, including environmental temperature, relative humidity, salt, protein levels in the diet, and birds' productivity. Water deprivation for ≥12 hours have a negative effect on the growth of young poultry (Özlü et al., 2020). Poultry, like all animals, synthesizes proteins that contain 20 L-amino acids. The poultry birds lack certain enzymes, due to which they are unable to synthesize particular amino acids (Nte and Gunn, 2021). Different vitamins are required by poultry birds for proper growth and development, and these vitamins are subject to degradation over time. This process is accelerated by moisture, oxygen, trace minerals, light, and heat. Mostly, phosphorus in feedstuffs of plant origin is present in the form of phytate and is not absorbed efficiently by poultry. Consequently, it is critical that only the available phosphorus (digestible) and not the total phosphorus levels be considered. The appropriate calcium nutrition depends on the ratio of calcium to available phosphorus. For growing poultry, this ratio should not alter substantially from 2:1 (Matuszewski et al., 2020).

Alfalfa is very suitable for poultry birds, which have nearly all the required nutrients. Alfalfa contains flavonoids, saponins, dietary fiber, minerals, vitamins, organic acids, and polysaccharides (Barszcz et al., 2022). The above-mentioned bioactive substances have a wide range of bioactivities such as antioxidant, anti-cancerous, anti-inflammatory, and enhancing immunity function. Hence, the alfalfa flavonoids are being used as an additive added to animal feed to enhance the antioxidant activity of serum and liver, meat quality, growth, and production performance. Alfalfa contains flavonoids, which are a group of polyphenol compounds with a C6-C3-C6 carbon skeleton (Chen et al., 2020). Flavonoids are powerful antioxidants based on their polyhydroxyl structures (Shen et al., 2022).

Conclusion

Homeopathic or herbal medicine has been proven very effective against treating various diseases of poultry birds including bacterial, viral, parasitic, metabolic and environmental problems. A variety of herbal medicines is available in the market, and it has been in use for many decades. Efficacy of homeopathic drugs is far greater than any synthetic drug with high safety index. We can use homeopathic medicine without any hesitation for treatment and prevention of poultry diseases. In this chapter we conclude that the natural remedies i.e., commonly used homeopathic drugs are very effective against multiple parasitic, viral, and bacterial diseases of poultry birds. Homeopathic medicine is also used to treat various diseases of the birds which are caused by environmental factors. The naturally occurring parts of the plants including roots, stems, leaves and flowers can be used to synthesize the homeopathic medicine. Homeopathic medicine can be also used for the growth of the birds and increase their production which will ultimately be beneficial for economic growth.

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Chapter 07

Homeopathic Medicines for Treating Various Diseases of Bovine

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ABSTRACT

Homeopathy is a substitutive and a different approach to medicine founded on the idea that natural elements, when processed carefully and usually in very little doses, cure diseases and maintain health. It is derived from two Greek words and is used worldwide. Despite its vast distribution, it is still considered controversial in some areas. Oral use of medicines has more beneficial and early effects as compared to external use. Nosodes, sarcodes, plants and minerals are the common sources of these medicines. Belladonna, calcarea phos, five phos, cicuta virosa, stramonium and nux vomica are the common homeopathic medicines. Calcarea phos found to be very effective in the treatment of parturient paresis. Five phos are largely used to accommodate mineral deficiencies in animals. Cicuta virosa treats the nervous form of ketosis in an effective way. Stramonium is used to control fits and convulsions. Nux vomica has a wonderful effect in the treatment of bloat. Mercurius. Solubilis is highly recommended for pustules and blisters. It has a vast future because it is cheaper and easily available. It covers a lot of diseases in single treatment and has long term effects and has a potential to prevent future illness.

KEYWORDS
Homeopathy, Homeopathic treatment, Bovines

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INTRODUCTION

Homeopathy is derived from 2 Greek words 'homoios' meaning 'similar or same' and 'pathos' meaning 'suffering' (Kozat, 2022). The word 'homeopathy' was first used in history in 1807. Basically, homeopathy is the idea of 'let like be cured by like'. In 1796, Samuel Christian Friedrich Hahnemann, a germen physician used this concept of treating like by like. The concept of homeopathic medicine became popular in the 19th century and in the 20th century it became the most popular idea. In the early 21st century, homeopathy became known to the most parts of the world. But in many parts of the world, homeopathy is considered controversial due to the use of more diluted medicines. There exists a concept that homeopathic medicine has a placebo effect, but many trials, research, and meta-analysis have proved that homeopathy does not have placebo effects. The placebo refers to a dummy treatment which does not have any actual effect but appears to improve a patient's health (van Lennep et al., 2021). According to some researchers, use of homeopathic medicine is equally effective in humans and in animals (small, large, and pet animals). Despite the long controversial history of homeopathy, it has been proven effective in every aspect. Many institutes are currently working on homeopathic medicine. Homeopathy is now worldwide distributed. But there is a lot more to reveal about homeopathy.

Administration of Homeopathic Drugs

The homeopathic drugs can be used both externally and internally (Nicol, 2021). For better results, these also should be taken orally, ideally 15 to 30 minutes before or after the feeding schedule.

Internal use:

The following varieties of homoeopathic drugs are available for internal use:

1- Potentiated dilutions

Vehicles such as disks, globules, or pellets that can be soaked in the dilutions and stored in marked bottles are used to dispense potentized dilutions (O'Connor, 2024). The globules can be given to sick animals as food or as a drink. To ensure that the medications' potency lasts for months or even years, keep them away from heat sources and light. The medication is absorbed when the medicated globules are applied directly to the tongue and dissolve in saliva. It is not required to take a homoeopathic medication orally. The ability of homoeopathic medications to be absorbed by the tongue or palate gives them an edge over allopathic medications (Jain, 2022). Although it may seem laborious at first, with some practice, the attendants will become skilled at administration.

2- Mother Tinctures

Ten drops of tincture should be combined with clean, cold water and poured into bottles to saturate large animals, such as horses and cattle (Madrewar, 2003) Before using the bottle on other animals, it should be thoroughly cleaned. Dogs, pigs, sheep, and goats are among the small animals that require five drops of tinctures.

3- Triturated Pills or Powder

Triturates or pellets can be fed to animals in combination with feed or applied dry to their tongues (Ubhe and Gedam, 2020). For large animals, the dosage rate of the powders is two grains; for small animals, it is one grain.

External use

Very few ointments and lotions are made with homoeopathic medicines. To make lotions for external use, combine half a glass of pure water with one scoop of mother tincture.

1- *Rhus toxicodendron*

With rheumatism, it is very beneficial for sprains and injuries to tendons, ligaments, membranes and joints (Kearns, 2021).

2-*Arnica Montana*

Beneficial for blows, falls, contusions, and other mechanical injuries. When applied promptly to bruising-related stiffness, swellings, and discomfort, it helps to stop more tissue damage. Its use on surgical wounds has shown to be quite beneficial. Areas that have been bruised are cleaned using a cloth dipped in lotion or lint (Madrewar, 2003). Merely covering the injury with a desiccated cloth will stop the medication from vanishing. For bruising, contusions, collar galls, or other external inflammatory conditions caused by repeated blows or friction, arnica lotion works well. Be careful not to apply this on freshly cut surfaces.

3-Calendula Officinalis

It helps stabs, cuts, and wounds when granulation healing is required since the tissue is ripped (Singh et al., 2022). Additionally, it stops bleeding and eases excruciating pain from accidents.

Sources of Homeopathic Medications

1- Animal sources: *Naja tripudians, Lachesis* and *Coccus spp.* (A'Grade, 2022).
2- Minerals: It includes organic and inorganic substances, metals, minerals, iron, phosphorus and sulphur etc.
3- Plant sources: *Calendula, Arnica, Bryonia, Aconite napellus* etc.
4- Imponderabilia
5- Sarcodes: Specific secretions and tissues from healthy animals are utilized such as sheep thyroid extract (Thyroidinum) and internal suprarenal gland secretion (Adrenalin).
6- Nosodes: Pathological products, viruses, bacilli, and human or animal sources can all provide nosodes (Combrink-Potter, 2020).

Homeopathy in the Treatment of Metabolic Diseases

1- Parturient Paresis

Parturient paresis, also known as hypocalcemia or milk fever, is a metabolic disease of dairy cattle which commonly occur at the time of parturition (Bzuneh et al., 2020). Hypocalcemia will occur which causes afebrile, acute to per acute, flaccid paralysis and circulation collapse in cows. It also occurs after parturition.

Etiology

Dairy cattle are at great risk for milk fever when attained their highest productivity (Bzuneh et al., 2020). Gradual increase in calcium excretion (10- 30g per day) takes place which imbalances calcium homeostasis. As a result, concentration of calcium in the blood falls below the normal range (8.5mg/dL). Cases in the late lactational period are also seen. Hyperexcitability of the nervous system leads to decreased contraction of muscle and ultimately paresis occurs. Milk fever can occur at any age but Guernsey and Jersey breeds are more susceptible (Madrewar, 2003).

Symptoms

Milk fever has three apparent stages:

1- Stage 1

Cows are in a standing position but unable to eat and move. Hyperexcitability can be seen. Stiffness of flanks and triceps may occur. Shaking of head and ear twitching may also be seen. Restlessness occurs and animals fall easily. If proper treatment is not provided in stage one then it progresses towards the second stage (Daresjö, 2020).

2- Stage 2

Also termed as the stage of sternal recumbency. Animals are unable to stand. Dry muzzle, extremities become cold and subnormal rectal temperature are the typical signs. Tachycardia and paralysis of smooth muscle occur. Animals are unable to urinate and constipation can also be seen (Daresjö, 2020).

3- Stage 3

This stage is also termed as phase of coma or paralysis. The muscles become extremely flaccid. There is a sharp increase in the heart rate (above 120bpm) and animals may have severe bloat. At this stage, animals survive only for a few hours if left untreated (Daresjö, 2020).

Treatment

Subcutaneous and intravenous administration of calcium can be used for successful recovery in most of the cases (Ibrahim and Kirmani, 2021). The homeopathic drugs work very effectively to prevent the danger of relapse and avoid complexities of the nervous system. These drugs provide complete prevention of disease near parturition.

1- Calcarea phos 1M: One dose two times a day for 3-5 days is recommended. It is a tribasic pellet used in acute cases of milk fever.
2- Magnesium phosphoricum 30: One dose with a gap of half an hour for three days is given to compensate the deficiency of magnesium.
3- Belladonna 1M: One dose with the gap of an hour for three doses is given. It contains anticholinergic alkaloids which are used to reduce the excitement of animals.
4- Stramonium 200: One dose with the gap of an hour is recommended when nervous signs start to appear.
5- *Cuprum metallicum*: It is used to reduce muscular cramps and helps in recovery.
6- *Nux vomica* 30: If an animal is facing indigestion after the recovery, then nux vomica is given.
7- Bryonia 30: Recommended when chest symptoms start to appear.
8- Five phos 30: To accommodate the mineral deficiencies, a weekly dose of five phos 30 can be given to retain minerals.

2- Ketosis

Ketosis is a common metabolic disease of cattle (Zhang and Ametaj, 2020). It is an early lactational disease marked by hypoglycaemia, ketonuria, ketonaemia, decrease in milk production and reduced feed intake. It occurs rarely in late gestation.

Etiology

The exact cause of ketosis is not completely understood. In the early lactation, fat mobilization occurs due to negative energy balance and high glucose demand being produced due to milk synthesis (Lei and Simões, 2021). As a result, the glucose concentration decreases while the non-esterified fatty acids in the serum increases. Ultimately ketosis develops.

Types of Ketosis

Type I Ketosis

This type of ketosis occurs for 4-6 weeks after parturition. During this time, animal has achieved its peak milk production (Lei and Simões, 2021).

Type II Ketosis

This type of ketosis occurs 1-2 weeks after parturition. It may be linked with the fatty liver (Zhang and Ametaj, 2020).

Clinical Signs

Ketosis occurs in two clinical forms:

Nervous Form

Nervous ketosis is typically manifested by nervous dysfunction which includes incoordination, abnormal licking, pica, aggression and typical head shaking (Manzoor et al., 2021).

Digestive Form

Inappetence is the typical sign of digestive ketosis. Lethargy, reduced milk production and tucked up abdomen are seen in stalled animals. Animals become dehydrated and afebrile. Ruminal motility is absent or variable. Grinding of teeth may be observed. Manure becomes dry. In rare cases, no clinical signs may be found on examination (Huizenga, 2021).

Treatment

1- *Cicuta virosa* 30: One dose with the gap of two hours for the total 4 doses is given and works effectively in nervous form.
2- Aconitum 12: One dose with a gap of one hour for the total 3 doses is given. In the early stages of nervous form, it provides relief to the animal.
3- Five phos+Alfalfa 30: 5 globules of this combination thrice a day gives good results in both nervous and digestive forms.
4- Stramonium 200: One dose with a gap of an hour is suggested to control convulsions and fits.
5- *Nux vomica* 1M: Daily dose will retain normal digestion and treatment will continue for 5 days. Usually administered after Lycopodium.
6- Opium 200: 2 doses with a gap of 2 hours will relieve depression in animals.
7- Lycopodium 1M: Daily dose proves to be a good remedy for eliminating digestive signs. It exerts a tonic effect on liver, retains glucose level in the blood and regulates glucose function (Ghosh et al., 2021).

Homeopathy in the Treatment of Bacterial Diseases

1- Mastitis

It is inflammation of the mammary gland characterized by swelling, pain, heat and induration of the udder (Qureshi et al., 2023). Different physical, chemical and pathological changes occur in the gland which in return causes changes in the milk. These alterations include blood clots, changes in milk colour and increase in leuckocytes. The organisms which are responsible for mastitis are called mastitogens. Their classification is as follows:

1- Environmental mastitogens: *Streptococcus fecalis, Streptococcus uberis, E. Coli, Klebsiella species* etc. (Nathawat et al., 2020)
2- Contagious mastitogens: *Mycoplasma bovis, Staphylococcus aureus, Pasturella* species etc.
3- Endogenous mastitogens: *Mycobacterium tuberculosis, Mycobacterium bovis, Leptospira* species.
4- Opportunistic mastitogens: *Staphylococcus epidermidis, Staphylococcus hyicus* (Emrobowansan and Hosua, 2022).

Clinical Signs

Symptoms can occur in three forms:

1- Acute form: It suddenly occurs after parturition. Colour and consistency of milk suddenly changes after parturition.
2- Subacute form: These are generally caused by *Staphylococcus* species. Changes in the colour and consistency are persistent, but inflammation is mild.
3- Chronic form: In chronic form, teat fibrosis occurs, and milk secretion is reduced. Fever is absent and there will be recurrent attacks (Cobirka et al., 2020).

Treatment

1- *Apis mellifica* 30: One dose with a gap of 3 hours for the total 4 doses is recommended. This drug is given when oedema of udder is suspected in heifers.
2- Bryonia Alba 30: One dose with a gap of half an hour for the total 4 doses is recommended when udder becomes indurated and hard, showing symptoms of pain. While in chronic form, teat fibrosis occurs, and this drug will be continued for one month.
3- *Bellis perenis* 30: One dose thrice a day for 4 doses is given when teats become deeply injured.
4- Aconite 30: One dose with the gap of half an hour for a total of 6 doses is given. Highly recommended in acute cases when cows are affected by cold or dry winds.
5- Arnica 30: One dose thrice a day for a total of 3 doses is highly recommended when blood appears in milk after injury.
6- Belladonna 1M: One dose with the gap of an hour for a total of 4 doses helps to prevent mastitis which develops after parturition.
7- Ipecac 30: It is also recommended in udder bleeding when milk has a pinkish ting.
8- Hepar sulphuris: Helps to prevent mastitis caused by *Corynebacterium pyogenes*. It works effectively by draining out pus from udder.
9- Silica 200: It is also indicated in chronic mastitis especially in those cases where abscesses develop.
10- Phytolacca 30: Recommended when small clots start to appear, and milk becomes curdled.
11- *Urtica urens* 6: Indicated when plaques appear in the perineal region.
12- Sulphur 30+ carboveg 30: Highly recommended in both acute and chronic form. Especially in those cases when milk has a yellow ting (Morgans, 2020).

2- Tetanus

The causative agent of tetanus is *Clostridium tetani* (Popoff, 2020). It is an anaerobic bacterium which produces neurotoxins in the body. Bacteria enter into the body through deep punctured wounds. However, disease occurs rarely in cattle. Neurotoxins will be produced in anaerobic condition which is taken up by the motor neurons and travel to spinal cord, ultimately producing signs of tetanus.

Clinical Signs

The incubation period varies among the species. The stiffness of hind limb, neck and masseter muscles occur (Šoštarić et al., 2022). Head muscles become seized leading to lockjaw. Hyperesthesia and spasm become evident. In the initial stages, prolapse of the third eyelid occurs and in later stages, the animal will feel difficulty in swallowing and there is a sudden increase in respiration. Spasms develop which affect intercoastal muscles, diaphragm and larynx leading to pulmonary insufficiency. The autonomic nervous system will be greatly leading to hypertension, tachycardia and cardiac arrhythmias (Popoff, 2020).

Treatment

Apart from the administration of various antibiotics and antitoxins, following homeopathic drugs can be given:

- *Ledum palustre* 30: One dose with the gap of one hour for a total of 5 days can be given in case of deep wounds which have become cyanotic.
- Hypericum 1M: In the case of deep punctured wounds, one dose with the gap of one hour for a total of 5 doses is given.
- Strychninum 200: It can be given to relieve muscle rigidity.
- Colchinum 200: It can be given in combination with *Nux vomica* to relieve bloat.
- Cuprum met 1M: It is used to relieve spasms and cramps when wounds become deep.
- *Nux vomica* 1M: It is used when digestive symptoms appear such as bloat (Van Hao et al., 2021).

3- Anthrax

It is a non-contagious disease caused by spore forming bacteria *Bacillus anthracis* (Apriliana et al., 2021). It is characterized by septicemia and sudden death. Splenomegaly, incomplete rigor mortis and dark tarry blood are the important postmortem findings. The rectal temperature raised up to 105-108 °F.

Treatment

Anthrax has three forms: Peracute, acute and chronic.

- Arsenic 1M: Give good results in peracute form.
- Lachesis: Recommended when eyes colour change and blood appears in manure.
- Echinacea: Give good results in the third stage of disease.

Homeopathy in the Treatment of Viral Diseases

1- Foot and Mouth Disease

FMD is a highly contagious and transmissible disease of cloven-footed animals. The causative agent of FMD is *Aphthovirus* belongs to family *Picornaviridae*. As the name indicates, it is the disease of food and mouth and commonly found in buffalo, cattle, sheep and goat in Pakistan. There are 7 serotypes of this virus which are: A, O, C, Asia-1, SAT 1, SAT 2 and SAT 3. It is present worldwide and characterized by formation of vesicles in the feet, teats, mouth and muzzle. Virus is transmitted by direct contact and various secretions and excretions of animals (Azeem et al., 2020).

Symptoms

After getting entry into the body, the virus replicates in the mucosa of larynx and pharynx and distributed throughout the body by the lymphatic system. The incubation period depends on the serotype, environment, host and route of entry. Initially, fever develops followed by vesicle formation in the feet, teats, tongue, dental pad, hard palate, lips, coronary band and muzzle of infected animals. Lameness, restlessness, grinding of teeth, shaking of head and reduction in milk productivity are the initial symptoms. Rupture of vesicles leads to secondary bacterial infection, which then develops into deep ulcers. Mastitis commonly develops due to vesicles in infected teats. Hoof may fall off in extreme complicated cases. Bloody saliva, bad breath, swollen face, purging and secondary bacterial infections ultimately lead to death (Yi et al., 2022).

Treatment

1- *Rhus toxicodendron* 30: This drug is recommended in pain, mouth redness and lameness of foot.
2- Arsenicum 30: Recommended for the onset of disease.
3- Ferrum phos 30: Give support to animals in febrile condition.
4- *Natrum muriaticum* 30: Given when animals become weak and dehydrated due to salivation and high temperature.
5- *Mercurius solubilis* 30: Highly recommended in extreme conditions like bloody discharges, deep ulcers and blisters etc.
6- Five phos 30+ Alfalfa 30: It helps in recovery and restores normal production.
7- Borax 30: Recommended when stomatitis develops (Wang et al., 2020).

2-Blue Tongue

Blue tongue, also known as muzzle disease, is a non-contagious and insect born viral disease that occurs rarely in cattle (Rivera et al., 2021). The causative agent of BTV is *Orbivirus* belongs to the family *Reoviridae*. 29 serotypes of BTV have been identified and are present worldwide.

Clinical Signs

Clinical signs occur rarely in cattle and limited to oral vesicles, stiffness, salivation, lacrimation, hyperesthesia and dermatitis. Abortion may occur and malformations can lead to porencephaly. Postmortem leisons include edematous and ulcerated skin and ulcers in mouth. There is no specific treatment and main prevention is through the control of vectors (Vinomack et al., 2020).

Treatment:

1- Natrum mur 30: One dose with the gap of an hour for the total 5 doses is recommended when there is persistent salivation.
2- Aconitum 30: Recommended in early stages of disease.
3- Nitric acid 30: One dose thrice a day is given when vesicle formation occurs at the opening of mouth and nostrils and gives a pungent smell.
4- *Mercurius corrosivus* 30: It is indicated in dysentery and bloody saliva.
5- *Mercurius solubilis* 30: One dose with the gap of half an hour for a total 6 doses is indicated when vesicles form in the buccal cavity.
6- Arsenic alb 30: Recommended in all types of cases especially when tongue become purple due to swelling.
7- Calendula lotion: Indicated for the vesicles of hoof.
8- Borax 30: Indicated in mouth bleeding.
9- *Rhus toxicodendron* 30: Recommended to reduce lameness and inflammation of hooves (Bumbarov et al., 2020).

Homeopathy in the Treatment of Protozoal Diseases

1- Anaplasmosis

1- Phosphoricum 1M: One dose daily is recommended. It prevents the destruction of liver cells.
2- *Crotalus horridus* 1M: One dose with a gap of two hours is given in acute condition.
3- Trinitrotoluene 30: One dose with the gap of 3 hours for the total 4 doses is given in anemic conditions and to increase heart rate.
4- Phytolacca 30: One dose daily is recommended to restore normal functions in the body.
5- China 30: One dose two times a day will help to regain the strength of the body (Atif et al., 2021).

Quick Prescription for Common Diseases

Disease	Prescription	Description	References
Abscess	Hepar sulph	Abscess that commonly develops in various body sections	(Ghosh et al., 2024)
	Rhus tox	Parotid gland abscess	
	Calcarea sulph	Abscess close to rectum	
Anemia	Nux vomica	Anemia due to haemorrhages	(Pandharkar and Thote, 2021)
	Crotalus	For Addison's anemia	
	Arnica	Anemia due to haemorrhages	
	Ferrum met	When an animal becomes pale due to fever	
Bites	Cedron	Snake bite	(Sunderraj, 2023)
	Lach	Dog bite	
	Urtica U	Bee sting	
	Natrum mur	Insect bite	
	Ledum	Scorpian bite	
	Hypericum	Cat, dog and rodent bite	
Cough	Belladonna	For dry cough and sore throat	(Akbar and Akbar, 2020)
	Drosera	For hollow, deep and chronic cough	
	Iodium	For tracheal cough and laryngeal cough	
	Kali phos	Cough due to irritation	
Fever	Sulphur	Fever due to viral infection	(Wrotek et al., 2020)
	Merc sol	Which occurs after vaccination	
	Echinacea	Which occurs after septic shock	
	Kali phos	Which occurs due to nervous shock	

2- Babesiosis

1- Millefolium 30: One dose three times a day is recommended to compensate the severe blood loss.
2- F*icus religiosa* 6: One dose three times a day is given. It is an anti- haemorrhagic agent use to cure respiratory symptoms.
3- China officinalis 6: One dose three times a day is given in anemic conditions to restore strength.
4- Cantharis 30: It is used to relieve the pain while defecation.
5- Phosphoricum 1M: It is used to control haemorrhages and especially used in those cases when jaundice is present.

6- Crotalus horridus 200: It also controls haemorrhages and prevent hemolysis of RBCs.
7- Belladonna 30: It is recommended when colour of urine changes to yellowish red.
8- Pulsatilla 30: It is recommended when colour of urine becomes dark.
9- Aconite 30 + Ipecacuanha 30: Give good results in combination to cure babesiosis (Renard and Ben Mamoun, 2021).

3- Toxoplasmosis

1- Cuprum 1M: It is used to relieve rigidity and muscle cramps.
2- Aconitum 12: Give good results in early stages of disease.
3- *Lathyrus satius* 200: It is used to overcome nervous signs such as paralysis and ataxia.
4- Conium: This drug is recommended when symptoms like incoordinated movements occur.
5- Stramonium 30: Recommended in convulsions and muscle twitching.
6- Belladonna: It is used to control hyper excitability in animals.
7- Strychninum 200: It is recommended in chorea-like conditions.
8- Phosphoricum 1M: It is recommended in pneumonia and other respiratory diseases which occur during the course of disease (Casoy et al., 2020).

Conclusion

There is growing interest in the application of homoeopathy as a supplemental or alternative to traditional veterinary care for the treatment of various diseases of bovines. Homeopathic medicine provides customized treatment to patients based on their distinctive signs and symptoms. Increased cooperation between conventional medical professionals and homoeopathic practitioners, resulting in integrated treatment modalities. Holistic approach of homeopathic drugs not only treats the symptoms but also the basic cause of the disease. Using homoeopathic treatments to treat both physical and mental health issues, such as stress, anxiety, and depression. Non-toxic behaviour of homeopathic medicines treats the animals in safe zone. Treating not the reported disease but also prevents the occurrence of other diseases in animals with long time effects. Use of homeopathic medicine also reduces the use of modern antibiotics and chemicals and promotes sustainable farming practices. Homeopathy has a vast future because it is cheaper and conventional and easily available in every country of the world. Digital platforms are being used more frequently for consultations, medication prescriptions, and educational resource access. In short, it is important for the veterinarian and farmers to use homeopathic remedies because it covers a lot of diseases in single treatment and animals become healthy for a long time because of its potential to prevent the future illness and having complete ingredients in required amount.

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Chapter 08

Use of Botanicals for Prevention and Treatment of different Poultry Diseases

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ABSTRACT

Poultry diseases are a major global public health concern, affecting millions of individuals globally. This research explores the potential impacts of plants and their bioactive compounds, frequently employed in treating different chicken illnesses. The medicinal properties of natural herbs depend on their bioactive compounds extracted from raw plants, leading to distinct effects on the body. The poultry industry faces substantial financial losses due to the emergence of drug resistance in many harmful parasites and bacteria, worsened by limited access to efficient treatments and their expensive nature. This necessitates the development of new sources for medications to overcome therapeutic deficiencies. Ecologically sustainable feed supplements have proven to be excellent substitutes for antibiotic growth promoters (AGP) in broilers. Utilizing natural substances with medicinal qualities is an age-old practice that is gaining more recognition. Around 20,000 species of higher plants are used worldwide for medicinal purposes, although traditional medicine does not have a complete understanding of their efficacy and safety. This study investigates the use of medicinal herbs for parasitic disorders in chickens, analyzing existing information and pinpointing research areas that may be explored to harness herbal medicines for this specific application. Herbal medications provide crucial components for identifying poultry diseases and creating phyto-pharmaceuticals to manage parasite infestations.

KEYWORDS
Poultry, Botanicals, Essential Oils, Antimicrobial

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INTRODUCTION

In this chapter, we delve into the fascinating world of botanicals and their role in the prevention and treatment of various poultry diseases.

Pakistan is an agricultural country located in the subtropical region of the world. As such, livestock is essential for the basis of agriculture. Poultry is highly valued in this nation's livestock industry, so poultry has a significant impact on the national economy. Exporting chicken eggs and meats contributes substantially to the country's foreign exchange earnings. Poultry are domesticated birds raised for meat, eggs, and feathers, such as chickens, turkeys, guinea fowls, ducks, and other species like pigeons. Chickens constitute over 90% of the global chicken population and are the most important poultry species worldwide. Poultry farming is becoming increasingly important globally, especially in Asia. Poultry farming in Asian countries has the potential to offer economic advantages such as enhanced nutrition, increased income for farmers, job possibilities, a steady grain market, and an affordable source of protein.

Poultry farming can be a viable occupation for unemployed young people, landless farmers, impoverished individuals, divorced women, and children to increase their family's earnings. Poultry eggs and meats are high in protein content. Poultry meats are nutritious, tasty, and contain less fat. Poultry farming is vital for the survival of rural communities in Pakistan. Farmers raise hens to meet family food needs and earn additional income. However, avian breeding is impeded by many diseases. Underprivileged communities lacking modern veterinary facilities experience substantial disease burdens and rely on traditional remedies to cure livestock infections. We study the medicinal plants used to treat chicken diseases in Pakistan and worldwide.

Farmers may find it difficult to get or afford traditional drugs or immunizations for preserving their flocks' health. Impoverished farmers turn to unconventional remedies since they do not have access to conventional treatments or vaccinations. Conventional poultry disease treatments are designed for large-scale commercial farms with numerous birds, but small-scale poultry farmers handle tiny flocks of birds at different stages of growth. The flocks may comprise multiple species. Rural farmers claim that ethno-veterinary approaches are effective, but additional research is required to confirm their assertions.

Mechanism of Action of Botanicals

Plants possess antibacterial characteristics that are primarily generated during secondary metabolism. Plant-based antimicrobial drugs have significant therapeutic potential by effectively carrying out their function without the common adverse effects of synthetic medications. The antimicrobial mechanisms of phytobiotics are not completely understood. Proposed mechanisms include disrupting pathogen cellular membranes, altering cell surface hydrophobicity and virulence, stimulating the immune system (including lymphocytes, macrophages, and NK cells), and shielding intestinal cells.

The inherent value and functional use of plant extracts including garlic, cinnamon, tulsi, and ginger etc. are well known. Plants frequently contain bioactive compounds that are less harmful and more environmentally friendly. They have shown antibacterial activity against methicillin-resistant Staphylococcus aureus (MRSA) and various other bacteria such as Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Proteus mirabilis, Brevibacterium ammoniagenes, Streptococcus mutans, and Propionibacterium acnes. Although there is growing worldwide attention towards plant-based antimicrobials, numerous plants are not fully utilized in addressing antibiotic-resistant bacteria. Botanicals, or phytobiotics, consist of primary and secondary plant components. Protein, fat, and carbohydrates are the primary nutrients, accompanied by secondary elements such as essential oils, bitter chemicals, colourants and phenolic compounds.

Essential Oil Used in Disease Control

Essential oils are commonly used as phytobiotics because of their antibacterial and growth-promoting properties. Essential oils are derived from fragrant plants, herbs, or spices using solvent or distillation methods. Essential oils containing multiple active components often serve to shield plants from insect and bacterial damage. Each component may have distinct mechanisms, but they collaborate synergistically. The effectiveness of essential oils is dictated by their chemical makeup. Thymol and carvacrol exhibit similar antibacterial capabilities, but their mechanisms of action differ due to changes in the position of the hydroxyl group. Limonene and p-cymene have distinct alkyl group locations and antibacterial properties. Assessing the effectiveness of essential oils is challenging because of variables such as extraction method, geographic location, plant genetics, harvest time, and storage period. Out of 3,000 essential oils, 300 are crucial for commercial use in various industries such as pharmaceuticals, agriculture, food, hygiene, cosmetics, and perfumes, as stated. Essential oils (EOs) are being increasingly utilized in the food industry and by animal producers due to their antioxidant, anti-inflammatory, antimicrobial, coccidio-static, anti-helminthic, and antiviral properties, as confirmed by different researchers. Carvacrol, thymol, and eugenol extracted from clove oil are effective antibacterial agents against several harmful microorganisms. Oils are being studied as potential additives to enhance food microbiology. Essential oils are increasingly being used in both conventional and organic poultry feed to enhance gastrointestinal health. Enhancing the stability of gut flora enhances the absorption of meals. Essential oils improve nutrition absorption by enhancing the activity of digestive enzymes like trypsin and amylase. Furthermore, active components increase intestinal mucus production, which helps to avoid bacterial adhesion.

Botanical Characteristics

A-Antimicrobial Characteristic

Many plant extracts include chemical components with anti-inflammatory, antimicrobial (Hammer et al., 1999), antioxidant (Hashemi and SR, 2010), and anthelmintic properties. Proteins, peptides, oligosaccharides, fatty acids, vitamins, and micro-minerals make up the majority of plant extracts. Plant extracts are multifunctional and their active secondary plant metabolites are mostly classified as flavonoids and isoprene derivatives (Tajodini et al., 2015). They engage in a variety of activities. Their chemical and biological variety is influenced by various elements such as the agricultural area, climatic circumstances, vegetation phase, genetic alterations, and others.

B- Sensory Characteristics

Essential oils possess antioxidant capabilities because of their redox features, chemical makeup, and the presence of phenolic groups. Certain botanicals can influence the sensory characteristics of the meat. Research indicates that fragrant plants like rosemary, oregano, and sage, together with spices such as cinnamon, can decrease the oxidation of oils and fatty acids. Precooked and ready-to-eat poultry products are prone to oxidative degradation due to their high polyunsaturated fatty acid content. Research has shown a reduction in lipid metabolism and cholesterol levels. Research has discovered that limonene plays a role in cholesterol production. Research has shown that Thymol, carvacrol, and β-ionone control non-sterol molecules. Lipid oxidation happens during meat processing, cooking, and refrigerated storage, impacting food quality by leading to a change in color, smell, and taste, and reducing the shelf life. Research suggests that herbs like rosemary, tea catechins, and essential oils can aid in preserving raw and precooked chicken when refrigerated. Poultry nutritionists study the antioxidant capabilities of several plants and essential oils to enhance meat quality.

C- Antioxidants

There have also been reports of hypo cholesterolemic effects and lipid metabolism,documented limonene's function in the production of cholesterol (Qureshi et al., 1988). According to reports from other authors, non-sterol products are regulated by thymol, carvacrol, and β-ionone (Case et al., 1995). Processing, cooking, and refrigerated storage of meat all involve lipid oxidation, which reduces the shelf life and results in the loss of desired colour, flavour, and odour in food products. According to (Brenes and Roura, 2010), the presence of phenolic groups, along with their chemical structure and redox characteristics, are primarily responsible for the antioxidant activity of EOs. Extensive research has been conducted on the potential benefits of aromatic plants like rosemary, oregano, sage, and spices like cinnamon in delaying the process of lipid peroxidation in oils and fatty acids. Poultry items that are precooked and ready to eat are especially vulnerable to oxidative degradation due to their high polyunsaturated fatty acid concentration. It has been seen those herbs like rosemary, tea catechins, and essential oils help to stabilize both raw and cooked chicken flesh while it is refrigerated. The antioxidant qualities of several plants and essential oils are also of interest to poultry nutritionists as they may enhance the quality of meat. The antioxidant activities of grape seed and grape pomace concentrate as free radical scavengers have made them seem like potential supplements (Viveros et al., 2011). Nevertheless, a few of these herbs may have an impact on the meat's flavor. Grape seed and grape pomace concentrate are recommended as useful additives because of their antioxidant properties in neutralizing free radicals.

Impact on the Digestive Process

Plant-based treatments are referred to as phytobiotics or botanical medicine. Medicinal plant components consist of flowers, fruits, roots, leaves, seeds, bark, berries, and complete plants. Phytobiotic feed additives are plant-derived components incorporated into animal feed to enhance performance. Phytobiotics can enhance the efficiency and quality of broiler and layer chickens by decreasing gut microbe populations through various mechanisms such as antimicrobial properties, promoting mucous secretion, preventing bacterial adhesion to cell membranes, altering gut bacterial populations, stimulating digestive secretions, improving nutrient absorption, and offering antioxidant, anti-inflammatory, and immune modulatory effects.

Key Botanicals and Their Function in Managing Certain Poultry Diseases

Garlic

Garlic, scientifically known as Allium sativum, is a perennial plant with bulbous flowers belonging to the amarylidaceae family and originating from Central Asia. It is stated that both cooked and raw garlic offer various health advantages (Kovarovič et al., 2019). Garlic was widely utilized by ancient Chinese, Egyptians, Greeks, Babylonians, Hindus, and Romans. Garlic has various functional qualities, including sulfur-containing chemicals, essential oils, and polyphenol compounds. Rats given 5 mL/kg of garlic oil daily for three months showed reduced toxicity and oxidative stress caused by NaNO2 (Hassan et al., 2010). This unusual spice includes the allicin precursors L-gamma-Glutamyl-(S)-Allyl-Cysteine and ACSO, as well as the lipid-soluble sulfur compounds di-2-propenyl disulfide and diallyltrisulfide. Garlic has antioxidant and antimicrobial properties. Propyl propane thiosulfonate (PTS-O) generated from garlic is effective in eradicating Salmonella typhimurium, Escherichia coli, and Campylobacter jejuni in diets with concentrations of 45, 90, and 135 mg/kg, respectively. Thiosulfinate and allicin in garlic may possess antibacterial effects (Curtis et al., 2004). These compounds contribute to the scent, fragrance, and biological properties of garlic. Garlic extracts containing phenolics (0.05-0.98 mg gallic acid equivalents/g) and flavonoid aglycones (4.16-6.99 µg quercetin equivalents/g) demonstrate antioxidant and chemo-preventive effects in response to chemically produced oxidative stress in a manner that depends on the dosage. Garlic's antimicrobial and antioxidant properties could stimulate growth. Garlic essential oil, a potent antioxidant, decreases TBARS levels and hinders DPPH-free radicals in grilled breast muscles. It has been discovered that garlic increased HDL levels and reduced cholesterol and triglycerides in grilled hens (Rusli et al., 2022).

Jir/Bootae

Jir/Bootae (Artemisia scoparia) is classified under the Asteraceae family, Artemisia genus, and scoparia species Waldstand Kit. The Asteraceae family comprises a multitude of plant species. This plant is cultivated in many regions worldwide, including Asia and Europe. Mint oil comprises sesquiterpenes, oxygenized sesquiterpenes, cis-arteannuic alcohol (25.9%), β-caryophyllene (5.5%), β-maaliene (6.3%), β-farnesene, caryophyllene oxide (4.4%), and 2-phenylbenzaldehyde (3.5%).Additional chemicals include artemisia ketone, eugenol, germacrene-D, capillin, transpinocarveol, verbenone, and 1,8-cineole (Goel et al., 2007). Artemisia scoparia has the ability to produce antibacterial chemicals. The annual plant includes bioactive chemicals with antibacterial, antifungal, anti-leishmanial, and anticancer properties. It has been found that its use inhibits the development and production of Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, and Mycobacterium. Studies conducted in a laboratory setting show that compounds from Jir have antioxidant properties by scavenging free radicals (Bhowmick et al., 2020).

Cumin

Cumin is scientifically referred to as Cuminum cyminum L. Belonging to the family Apiaceae, this slender, fragrant plant is an annual plant that completes its life cycle in one year and contains two seed leaves. Natural herbal remedies and derivatives are known to promote growth (Granados-Chinchilla, 2017). The seeds are used to enhance the flavor of foods.

Cumin is preferred by both human and animal nutritionists owing to its many medical properties (Shafiee et al., 2020). Broilers given a basic diet supplemented with 0.75% cumin showed increased immunological response, enhanced growth, and lower cholesterol levels. Cumin includes many significant compounds, including pyrazines, cuminaldehyde (4-isopropylbenzaldehyde), 2-methoxy-3-methylpyrazine, 2-methoxy-3-secbutylpyrazine, carvone-limonene, and linalool (Kaur and Sharma, 2012). Cumin seeds include phytochemicals that have antioxidant, carminative, and anti-flatulent properties. Cumin's active substance promotes gastrointestinal motility and enzyme synthesis(Platel and Srinivasan, 1996). Spices are thought to help digestion by increasing the activity of digestive enzymes.

Fennel

Fennel, scientifically named Foeniculum vulgare, is a biennial plant that possesses medicinal and aromatic characteristics. It is a member of the Apiaceae family and is frequently seen in Central Europe and the Mediterranean region (Foroughi et al., 2016). This plant has demonstrated efficacy in treating respiratory and gastrointestinal disorders because of its antibacterial qualities. Fennel extract exhibited strong antibacterial activities against respiratory tract infections in comparison to broad-spectrum medicines. Furthermore, they contain volatile scent molecules as fenchone, estragole, and trans-anethole. Phyto-constituents primarily include glycosides, phenolic compounds, and phenols. The fennel seed has 42.3% carbs, 18.5% fiber, 13.4% minerals, 93.7% dry matter, 9.5% protein, and 10% fat. Fennel is high in B vitamins and minerals. Fennel extracts in water and ethanol at a concentration of 100 mg/mL have substantial antioxidant properties, including reducing power, hydrogen peroxide scavenging, metal chelating activity, superoxide anion radical scavenging, and free radical scavenging. The pharmacological properties of fennel fruit are mostly derived from its essential oils. The primary component, trans-anethole, ranged from 81.63% to 87.85%. Fennel contains phytochemicals include phenols, phenolic glycosides, and flavonoids (Kwon et al., 2002). Fennel has high antibacterial effects owing to components such as coumarin and phenyl propanoid derivatives.

Coriander

Coriander (Coriandrum sativum) belongs to the Apiaceae/Umbelliferae family, with the genus Coriandrum L. and the species sativum. The herb dhanya has beneficial medicinal effects and has been used in various locations for a long time. Coriander's bioactive components have anti-inflammatory, hypoglycemic, and hypocholesterolemic properties. Coriander contains phytochemicals such as flavonoids, essential oils, sterols, isocaumarins, fatty acids, coriandrones, and phenolic components such caffeic acid, protocatechinic acid, and glycitin. Coriander essential oil contains geranylacetate (4%), geraniol (1.9%), alpha-pinene (10.5%), gamma-terpinene (9%), linalool (67.75%), and camphor (3%). In vitro research have shown that coriander essential oil has antibacterial capabilities against microorganisms. Kovarovič et al. (2019) found that Subtilis, Stenotropomonas maltophilia, and Penicillium expansum have antioxidant activity with 51.05% radical scavenging. Furthermore, it enhanced liver function, blood-related signs, and digestion. In 2014, Hosseinzadeh and colleagues studied the impact of incorporating 750, 1000, or 1250 ppm coriander extract into drinking water, or 1.5%, 2.0%, or 2.5% coriander powder into grilled meals over a period of 42 days (Hosseinzadeh et al., 2014). All therapies greatly reduced E. coli levels in the ileum, but had no impact on Lactobacillus. Coriander extract in water increased humoral immunity against Newcastle, infectious bursal disease, and infectious bronchitis vaccines, suggesting its potential as an antibiotic in grill diets.

Oregano

Oregano, technically known as Origanum vulgare L., is a fragrant plant prevalent across the Mediterranean and Asia. Oregano is a popular folk remedy and culinary plant. It is a helpful component in chicken feed that promotes bird development and strengthens the immune system (Young et al., 2003). Oregano is a fragrant plant with a high concentration of strong chemical components.Oregano essential oil (OEO) comprises Thymol (15.9%), Z-sabinene hydrate (13.4%), and -terpinene (10.6%), along with p-cymene (8.6%), linalyl acetate (7.2%), sabinene (6.5%), carvacrol methyl ether (5.6%), and carvacrol (3.1%) (Simirgiotis et al., 2020). Oregano meal has essential oils strong in antioxidants such as carvacrol and thymol. Oregano is beneficial due to its antibacterial, anti-inflammatory, and antioxidant qualities. Oregano essential oil has been shown to be effective in eliminating plant-damaging bacteria and fungus according to studies. Origanum vulgar extract, containing antioxidant and phytophenolic components, enhanced hepatic activity in grilled chicken when added at a concentration of 50 ml per litre of water (Alagawany et al., 2018). Oregano essential oil at 600 and 1200 mg/kg in chicken feed increased growth and inhibited caecal Eimeria coli. A combination of OEO with carvacrol and thymol reduced subclinical Necrotic Enteritis in broiler chickens by changing host inflammatory responses and improving intestinal barrier function. It is proposed that a 100-400 ppm OEO preservative might replace synthetic antioxidants in chicken meat. Adding 5% oregano powder had no influence on the production of grilled chicken or cell-mediated immunity. To increase antioxidant qualities, add 0.05% OEO to broiler chicken diets. Oregano oil is a suitable substitute for chemical BBQ enhancers. On day 28, administering 200 mg/kg of OEO enhanced globulin levels in laying hens, presumably altering the inflammatory response and raising blood immune globulins and proteins. A diet rich in oregano (3 g/kg) enhanced egg lipid profiles and reduced the incidence of cardiovascular disease in chicken egg consumers (Migliorini et al., 2019). Oregano extracts in chicken diets may improve feed intake, digestion, productivity, illness prevention, and cost effectiveness. Oregano's antioxidant and antibacterial qualities may be useful as a phytobiotic feed supplement for chickens.

Sinna

Sinna, also known as Senna alexandrina Mill. or Cassia angustifolia, is an important medicinal plant in Indian, Chinese, and Arabic civilizations (El-Morsy, 2013). Senna leaves and pods have long been used as a stimulating laxative. The chemical components of leaf and pod walls may include 2-5% anthra quinone derivatives and similar dianthrone glycosides in dry matter. Sinna contains many chemical components, including flavones, β-Sitosterol, mucin, essential oil, tartaric acid, tannin compounds, mucilage, and resin (Singh et al., 2013). The dehydrated medication is largely composed of sennosides A and B, with trace levels of other chemicals. Sennosides have poor absorption in the small intestine. However, bacterial flora in the colon convert anthraquinones into active anthrones, which stimulate bowel motions by increasing peristalsis. The antibacterial activity of ethyl acetate, chloroform, n-hexane, and methanolic extracts from Cassia angustifolia leaves was tested by disc diffusion against five Gram-positive bacteria, eight Gram-negative bacteria, and three fungi. The methanol extract had minor antibacterial activity, but the chloroform and n-hexane fractions had moderate to poor efficiency against various infections when compared to Kanamycin. El-Morsy (2013) tested the antibacterial activity of Senna alexandrina leaf extracts (water, acetone, dichloromethane, hexane, and methanol) against gram-positive and gram-negative bacteria, fungus, and yeast in a laboratory environment. Various activities were observed, with the acetone extract demonstrating the greatest activity and the water extract having the lowest.

Neem tree

Azadirachta indica, also known as Neem, is a plant belonging to the Meliaceae family. It is used to prevent Newcastle disease and is frequently found in Pakistan. Neem has specific chemical and physical properties that can fight against this deadly virus. A study was undertaken in 2015 at Agricultural University, Faisalabad, to evaluate the antiviral activities of Neem bark extract. For in-vitro assessment, spot assay and micro-hemagglutinin test were utilized, whereas in-ovo evaluation entailed injecting the extract into 11-day-old embryonated eggs. The data show that Neem is directly correlated with antiviral activity in reducing ND.

Thyme

Thyme, scientifically known as Thymus vulgaris L., is a medicinal herb belonging to the Lamiaceae family and is commonly utilized globally. It is frequently used in human cooking to enhance a specific taste. Due to its antioxidant, antibacterial, and therapeutic qualities, it is frequently utilized in livestock farms as a substitute for antibiotics to enhance animal productivity and health. Dry thyme essential oil contains a blend of mono terpenes, primarily thymol and carvacrol. Thyme contains phenolics such as bi phenylics and flavonoids, which have been shown to have antioxidant properties and be good to birds. Phenolic components in essential oils increased catalase activity, leading to the detoxification of hydrogen peroxide and the conversion of lipid hydro peroxides into innocuous compounds. Thyme extracts are suggested for use in laying farms to enhance egg quality, particularly by improving the fatty acid composition in the yolk.

Ginger

Zingiber officinale, usually known as ginger roots, contain significant levels of volatile oils, gingerols, and zingerone, making them popular therapeutic plants worldwide. Ginger roots enhance digestive enzymes and antioxidant activities in birds. Adding 5000 mg/kg of ginger powder to grilled meals enhanced antioxidant capacity and blood metabolites. Quails fed a diet supplemented with ginger at a concentration of 125 mg/kg showed the best feed conversion ratio, body weight, and humoral immunity. In addition, including ginger enhanced the lipid profile in blood serum and elevated the bird's antioxidant status. Combining bee propolis at a concentration of 500 mg/kg with ginger powder at 125 mg/kg enhanced growth performance and health in chicken. Adding ginger powder at a rate of 10-15 g/kg to the meals of laying hens improved their laying performance and enhanced their serum antioxidant levels. Adding 2.5 and 5 g/kg of ginger to the grill breeder's diet enhanced male reproductive function, such as semen ejaculate volume, sperm concentration per ejaculate, live sperms, and viability.

Aloe vera

Aloe vera's antibacterial, anticoccidial, and immunomodulatory characteristics can improve gut health and function. Studies are needed to understand the mechanism of action, effective forms, and dosage levels of Aloe vera for its proper utilization in the chicken sector, both in feed and drinking water. Aloe vera shows promise in improving growth performance in meat type birds, but its impact on egg output and quality in commercial laying hens remains unexplored. The advantages of incorporating Aloe vera into broiler feeds depend on various aspects such as dosage, diet composition, broiler genetics, application method (powder, gel, ethanolic or aqueous extract, and polysaccharide generated from gel), and other relevant variables.

Turmeric

Turmeric, scientifically named Curcuma longa L. (Zingiberaceae), is a tropical plant that is widely used and grown for its therapeutic properties. Turmeric powder is fed to grill chickens in poor nations like Pakistan in order to prevent coccidiosis (Abbas et al., 2010). Curcumin, a phenolic molecule that is the major ingredient in turmeric, has been demonstrated to have immunomodulatory, anti-inflammatory, and antioxidant qualities (Allen et al., 1997). In an experiment, 1% curcumin supplementation to the meal had an anticoccidial effect on hens infected with E. maxima and E. tenella species. When E.

maxima was the only target, better weight gain, lower lesion scores, and oocyst numbers were seen. Only E. maxima-infected and curcumin-treated birds showed a considerable drop in plasma $NO2^{-}$ and $NO3^{-}$, which may account for the variation in anticoccidial activity observed for the two Eimeria species. Subsequently, showed that food supplementation with 3% C. longa powder was successful in treating a mild E. tenella infection. Curcumin, or C. longa, is thought to work by inducing oxidative stress to inhibit coccidia (Abbas et al., 2010).

Licorce

The manufacture of various medicinal substances for subsequent usage in the poultry industry may involve the extraction of G. glabra, which could have a significant impact. Bioactive substances found in licorice, such as glycyrrhizin and flavonoids, have pharmacological and therapeutic uses. It has been discovered that the licorice extract exhibits immunogenic and antioxidant properties. These properties may enhance the growth performance, feed efficiency, carcass characteristics, and blood biochemical indices of the poultry birds as well as serve as a potential treatment for respiratory, digestive, and immune issues in poultry. The addition of LE up to 0.4 g/L to chicken drinking water improved the lipid profile, immunological response, and antioxidant indices in addition to increasing feed consumption. It has been discovered that supplementing laying hens' diets with 50 _g/mL of LE has some positive effects on their cellular immunity. G. glabra extract exhibited strong antiviral activity against NDV at a dosage of 300 _g/mL. Additional research is required to determine the advantages of adding licorice herbs to poultry feed and to investigate other characteristics of this medicinal plant that may improve chicken health and productivity.

Below given Table 1 summarizes various plants with potential anticoccidial properties, highlighting their common names, active compounds, and proposed mode of action against coccidiosis in poultry (Jamil et al., 2022).

Table 1: Plants with Potential Anticoccidial Properties

Plant (Scientific Name)	Active Compounds	Potential Mode of Action
Camellia sinensis Kuntze (Green tea)	Polyphenolic compounds	May inactivate enzymes needed for coccidian reproduction
Pinus radiate D. Don (Pine bark)	Tannins	May be effective against specific Eimeria species
Cyamopsis tetragonoloba Taub (Guar bean)	Saponins	May damage the protective outer layer of coccidian oocysts
Berberis lycium Royle (Barberry root bark)	Berberine	May inhibit the development of coccidian parasites
Olea europaea L. (Olive tree)	Maslinic acid	May improve the effectiveness of other anticoccidial treatments
Quisqualis indica L. (Rangoon creeper)	Gallic acid and ellagic acid	May reduce tissue damage and parasite production
Morinda lucida Benth. (Brimsstone tree)	Alkaloids, anthraquinones, anthraquinols	May decrease the number of coccidian oocysts produced
Artemisia afra Jacq. (African wormwood)	Flavonoids, terpenes, coumarins, phenolic acids	May reduce parasite numbers, improve feed intake, and lessen tissue damage
Echinacea purpurea Moench (Coneflower)	Echinolone, chlorogenic acid	May stimulate the immune system to fight coccidiosis
Curcuma longa L. (Turmeric rhizome)	Curcumin	May inhibit parasite development and reduce gut damage
Aloe vera (L.) Burm. f. (Aloe vera)	Acemannan sugars, anthraquinones	May lessen intestinal damage caused by coccidiosis
Phyllanthus emblica L. (Emblic fruits)	Tannins	Potential anticoccidial effects require further investigation
Moringa oleifera Lam. (Drumstick tree)	Flavanols, rutin, glycosides	May decrease parasite numbers and improve weight gain

Various Poultry Diseases and Their Management with Botanicals

Parasitic Diseases

Ethnoveterinary medicine is the source of the application of herbal remedies for the management and treatment of gastrointestinal parasites. Herbal remedies have long been used to treat parasitism, and these medicinal herbs are being utilized today in many parts of the globe to cure parasites (Practices, 1994). Almost each parasite infection in cattle and poultry can be treated with a variety of medicinal plants and their extracts in ethnoveterinary medicine, which is inspired by ancient methods. It has been reported that animals and birds with parasitic gastrointestinal diseases can be treated with seeds from plants including onion, garlic, and mint.

In many parts of the world, gastrointestinal nematodes and other infections have been treated with the well-known therapeutic qualities of the Azadirachta indica tree, also known as neem (Subapriya and Nagini, 2005). Additionally, data demonstrating the great anthelmintic efficacy of anti-helminth species of N. sativa extract in poultry (Aseel chicken). The strong anthelmintic efficacy of N. sativa extract against helminth species that infect poultry (Aseel chicken) has also been identified. Thymoquinone is one of the bioactive substances present in N. sativa seeds and oils, and it has been noted to be a significant phytochemical anthelmintic.

Furthermore, N. sativa's other bioactive ingredients, which enhance nutritional status and host immunity, may possibly be responsible for its anthelmintic effect.

Coccidiosis

Drug-resistant species have emerged due to the improper usage and excessive use of anti coccidial medications, and their presence in poultry products can be harmful to humans. Anti coccidial drugs typically necessitate a seven-day withdrawal period before being sold commercially. Concerns about drug residues contaminating poultry and posing a risk to people have led to legislation limiting medication administration until the animals are slaughtered. Discontinuing the medicine could leave the bird susceptible to sickness due to a lack of acquired protective immunity from the anti-coccidial drugs. Contaminated eggs in the litter could lead to serious sickness. Therefore, it is necessary to implement effective avian coccidiosis management strategies. Various botanical supplements and herbal treatments have demonstrated efficacy against protozoa, arthropods, and helminths.

Viral Diseases

Newcastle Disease

Various medicinal plants possess potent antiviral and immune-enhancing properties against Newcastle Disease (ND), a significant ailment in the chicken sector. These plants could serve as alternatives to commonly used synthetic medications, which pose risks such as drug resistance in local pathogen populations and drug residues in poultry. This could be a method to enable chicken farming with reduced dependence on chemical prophylactics. It is suggested that active components from medicinal plants proven to improve immunity and provide therapeutic effects in poultry should be extracted and made available for practical usage in feed.

Decoction procedures were utilized to extract the components of A. annua and their impact was assessed in chicken embryos to determine the suppression of NDV (Liu Yali et al., 2009). The extracts inhibited the proliferation of NDV in chicken embryos, as shown by the results.

Adenovirus

Numerous diseases in humans and animals are caused by adenoviruses, or Ads (Whickam, 2000). A persistent, asymptomatic infection is created by the intermittent shedding of Ads (Garnett et al., 2002). Adenoviruses cause gastroenteritis and conjunctivitis, respectively, by infecting the lining of the stomach and eyes. In addition, they produce additional symptoms by colonizing the mucous membranes of the urinary and respiratory systems (Aslam et al., 2014). Green tea catechins block adenovirus proteases, which are involved in cancer spread. Green tea and EGCG in particular are effectively absorbed by the cells and prevent one or more of the late stages of viral infection against adenovirus. According to, green tea and its separated catechins have antiviral activity against the fowl adenovirus type-4 when tested in vitro in cell culture and in vivo against an IBH-HPS virus challenge in broiler chickens (Aslam et al., 2014).

Avian Infectious Bronchitis Virus (IBV)

Infectious bronchitis virus in birds (IBV) is one kind of virus belonging to the genus Gammacoronavirus. IBV emerged as the first coronavirus in 1931 found in chickens and was regarded as a very important pathogenic virus in animals. Regardless of vaccination, avian coronavirus IBV is now an important economic disease of domestic chicken, resulting in large production losses and death. Numerous studies have documented global outbreaks of IBV in chickens and other animals, which are marked by high rates of illness and death as well as subpar egg and meat output (Parvin et al., 2021). Live attenuated vaccines are now widely utilized to prevent and manage infectious brain disease. However, vaccine effectiveness is being seriously undermined by the increased genetic diversity of viruses and the appearance of new strains.

An evaluation of several plant extracts was carried out, and Mentha piperita, Desmodium canadense, and Thymus vulgaris all shown antiviral activity against IBV both pre- and post-infection (Lelešius et al., 2019). Saint John's Wort, or Hypericum perforatum L, has been extensively researched for its pharmacological properties and biochemical makeup (Zhou and Lai, 2008).

The antiviral properties of H. perforatum extracts, including hypericin (HY), quercetin, pseudohypericin, and quercitrin, were evaluated against IBV. It was shown that an increase in type I interferon via the MDA5 signaling route and a decrease in the mRNA expression of pro-inflammatory cytokines [tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)] via the nuclear factor kappa B (NF-κB) signaling pathway.

Avian Influenza Virus (AIV)

Another significant virus that is a member of the Orthomyxoviridae family and causes enormous losses for the poultry industry worldwide is the avian influenza virus (AIV) (Parvin et al., 2018). This pathogen possesses an single-stranded RNA that is eight segments negative and encodes around 11 proteins (Liu Yali et al., 2009). Furthermore, AIV is classified into subtypes according to the surface proteins hemagglutinin (HA) and neuraminidase (NA), which are in charge of viral attachment and release, respectively.

In this sense, Rumex extract enhanced with polyphenols.
Acetosa inhibits the replication of AIV by reducing the viral particles' ability to adhere to target cells (Derksen et al., 2014).

Water extract of Psoraleae semen (WPS) has a promising function as a new anti-influenza agent due to its antiviral properties. Choi evaluated the inhibitory impact of the virus employing 100µg/ml in WPS in a thorough investigation using RAW 264.7 and MDCK cells (Choi et al., 2016). It has been shown that WPS functions as an immunomodulator and influenza HA and NA inhibitor.

Moreover, they proposed that WPS's ability to interrupt infection via the type I IFN-mediated signaling pathway involving RAW 264.7 cells make it a viable candidate as an antiviral therapeutic drug. Similar results have been documented, whereby WPS's anti-influenza properties directly limit the mediation of HA and NA.

Bacterial Infections

The use of antibiotics subtherapeutically to treat enteric and other illnesses in chicken has raised concerns, which has led to a rise in interest in effective and alternative treatments with antibacterial qualities.

Since the beginning of time, plants have been a valuable source of vital substances for medicine and therapy. It examined the antibacterial activity of Curcuma aromatica and Curcuma longa rhizome extracts against enteric infections in chicken as well as the presence of significant phytochemicals (Patil et al., 2019). Extracts of C. longa and C. aromatica were shown to contain phytochemicals of pharmaceutical importance, such as alkaloids, flavonoids, terpenoids, steroids, saponins, phenols, glucosides, etc. Escherichia coli and Salmonella entertidis were both effectively inhibited by C. aromatica extracts.On the other hand, C. longa extracts against E. coli alone demonstrated a zone of inhibition (Anjusha and Gangaprasad, 2014).

This work offers important new information about the therapeutic use of Curcuma spp. against enteric poultry diseases, indicating its potential as a substitute for antibiotics and pave the path for additional application in chicken feed for efficient production.

Future and Potential of Plant-Based Ingredients in Organic Poultry Farming

Studying how herbal medicine works can help determine safe and effective dosages, proper storage methods, and ways to enhance its benefits. Advances in genomics, proteomics, metabolomics, bioinformatics, and chemo informatics can boost medicine detection and effectiveness. It is crucial to have cooperation between traditional medicine experts and well-established government and private research institutions. Biotechnological advancements can offer an efficient screening system for natural medicinal plant components. Herbal extracts can be kept for a long shelf life, turned into tablets, teas, and infusions, freeze-dried, or utilized to enhance dishes. Patents for indigenous knowledge should be utilized to incentivize stakeholders to collaborate and develop economically feasible herbal product models. Medicinal plants need to be collected and kept in a sustainable manner. Policies should restrict the removal of medicinal plants from natural habitats such as forests and instead promote community-based nurseries to conserve plant supply. When screening medicinal plants for anthelmintic activity, utilize both in vitro and in vivo models. It is crucial to do controlled trials when utilizing ethno veterinary data to verify if medicinal plants enhance parasite resistance. Observe the performance and conduct of hosts that have been parasitized. Track immunological reactions, host well-being, and performance consistently during research. Monitor the effectiveness of deworming agents in various environments as they may differ depending on the plant material present. Identify the active components. Determine bioavailability and devise methodologies. Studying pertinent literature is essential for gaining insight into the utilization of tropical medicinal plants in temperate environments. Conventional medicine is readily accessible in temperate countries, leading to its reduced obscurity (Gulzar and Ullah, 2023).

Distribution Mechanisms

One significant problem with certain essential oils is their decreased antibacterial effectiveness in animal feed because of their volatility and poor solubility. Phytobiotics can be given in feed or water, depending on the product’s composition. Using ground leaves instead of extracts may decrease effectiveness. Plant extracts are more potent than pulverised leaves because they contain higher concentrations of active compounds. Extraction costs have increased because of the rising demand for chemicals and the need for a large quantity of plants to provide an adequate supply. Novel methods of distribution are being investigated to transport phytobiotics to the animal intestines for maximum effectiveness. Research has shown that lecithin, extensively utilized in various applications, boosts the antibacterial effects of carvacrol and eugenol against both gram-positive and gram-negative infections.

Microencapsulation is a commonly studied technique used to enhance the antibacterial properties of isolated chemicals against E. Escherichia coli O157:H7 with Listeria. Listeria monocytogenes is prolonged in its antibacterial action by microencapsulation of coated essential oils, delaying absorption. Current research on essential oil encapsulation mainly involves micrometric capsules to shield active compounds from environmental factors such as oxygen, light, moisture, and pH. Microencapsulated additives offer benefits like improved palatability and reduced strong odours, leading to consistent feed intake.

Conclusion

Phytogenics and probiotics can stabilize the intestinal environment, promote the growth of Lactobacilli, and reduce harmful organisms. Additionally, utilizing medicinal herbs is both safer and more cost-effective. It could also help bridge the gap between food safety and production and reduce mortality in animals. The primary expense in chicken production is the nutrients found in the feed. To improve nutrient absorption, several additions are commonly employed. Feed additives are growth-promoting substances added to chicken feed in specific amounts without causing substantial changes in composition. The prohibition of AGPs in the poultry sector in many nations led to the exploration of substitute sources. Using herbs has numerous advantages compared to antibiotics. Utilizing botanicals as feed supplements in poultry are valuable for optimizing performance and enhancing poultry health.The majority of the herbs tested in poultry demonstrated positive effects on production while having no detrimental effects on bird health or bird products. Phytochemicals have therapeutic advantages owing to their antiviral, antioxidant, anti-inflammatory, immunological modulatory, antibacterial, and antifungal properties. Thus, they may be used as botanical alternatives in poultry nutrition. Herbal therapy can effectively treat and manage various parasitic illnesses and is utilized in the development of phytopharmaceuticals for drug identification. According to the World Health Organisation, more than 80% of individuals rely on plants for treating common ailments. Despite the abundance of traditional medicinal resources, there has been limited initiative to endorse and understand its application in medical settings. The Drug Regulatory Authority of Pakistan (DRAP) is currently registering nutraceuticals and herbal products, such as Bio dewormer created by specialists from the University of Agriculture Faisalabad. These products utilize native plants with anti-parasitic qualities.

Future Perspectives

Currently, there is ongoing research on various herbal preparations used in poultry feeding to determine their potential benefits in improving health and performance. These investigations focus on areas such as feed intake, feed conversion, body weight, weight gain, growth performance, feed conversion ratio, gizzard function, gut development, nutrient digestibility, digestibility of organic matter and crude protein, gut microflora, and metabolizable energy content of feed mixture.These properties may include antibacterial, antiparasitic, or antioxidant effects. For instance, certain businesses in Austria are currently engaged in the following fields:

- Delacon for phytogenic feed additives
- Indian Herbs GmbH
- Biomin AG for feed additives

Clinical trials involving the feeding of herbal additions to various fowl, such as broilers, turkeys, and laying hens, are being conducted. PRATU (Poultry Research and Teaching Unit) is an organization based in Australia that provides financial support for research projects in several areas of poultry science, including nutrition and physiology, health and welfare, disease, productivity, and environment. Research groups engaged in similar work can be found globally, including in Germany, the United Kingdom, Poland, Finland, Spain, The Netherlands, Turkey, China, Taiwan, India, Pakistan, Ukraine, Lithuania, United States, Canada, Australia, and Brazil. These groups are affiliated with universities, institutes, and businesses.

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Chapter 09

Botanical Elixirs and Ancient Wisdom against Rinderpest in Buffalo

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ABSTRACT

Rinderpest, sometimes referred to as bovine plague, is a contagious viral illness that mostly affects animals with cloven hooves, such as cattle and buffalo. Famine and poverty are widespread over the continent due to a terrible sickness that affects cattle. It is a viral illness that affects cattle and other ruminants, both domestic and wild. It is characterized by high morbidity and mortality rates, fever, and erosive stomatitis. Animals having the virus can effectively contact susceptible animals to spread rinderpest. The World Organization for Animal Health and the UN Food and Agriculture Organization declared the worldwide elimination of rinderpest in 2011 the greatest veterinary accomplishment of our time and just the second disease to be eradicated culminating centuries of veterinary progress. If the virus were to unintentionally or deliberately escape from high-containment storage facilities, rinderpest would still need to be reported to the OIE, and sufficient surveillance mechanisms would need to be kept in place to guarantee the early identification of clinical cases.

KEYWORDS Botanica,l Elixirs, Ancient Wisdom, Rinderpest in Buffalo	Received: 22-May-2024 Revised: 12-Jul-2024 Accepted: 07-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

A member of the Paramyxoviridae family of morbilliviruses, which is the cause of rinderpest, often known as the cattle plague (Schmitz et al., 2024). Both the Peste des petits virus (PPR) and the measles virus are closely related to the rinderpest virus, which mostly affects ungulates, both domestic and wild. Viruses belonging to the family Paramyxoviridae, genus Morbillivirus, are significant pathogens that cause acute, life-threatening illnesses in animals. The host specificity of other related viruses remains unclear and is primarily determined by the genera to which they were initially linked (Hinds et al., 2024). These include the canine distemper virus, which affects several other carnivore families and has been linked to epidemics in African lions and pinnipeds, the phocid distemper virus, the cetacean morbillivirus, the measles virus in humans, and the recently identified felid morbillivirus (Libbey et al., 2023). In addition to causing high rates of morbidity and mortality from oral and gastrointestinal tract ulceration, diarrhea, dysentery, dehydration, protein loss, and immunosuppression from lymphocyte depletion, reinfection in cattle and buffaloes is characterized by fever with ocular and nasal discharges. Rinderpest (RP) epidemics devastated three continents for centuries, killing millions of cattle, buffalo, yaks, and other species (Aslam and Alkheraije, 2023). In the late 1800s and early 1900s, RP destroyed between 80% and 90% of Africa's cattle, or hundreds of millions of animals, and severely damaged livestock in Asia, the Middle East, and Europe (Kroon, 2024). This destruction caused widespread malnutrition and famine, as well as the incapacitating incapacity of hundreds of villages, to use draft animals for farming work (Cobbing, 2024). Worldwide, people have been promoting health and wellness with botanical elixirs for ages. The practice of spagyrics, which was founded in the early 1500s by the Swiss physician Paracelsus, entails the alchemical processing of plants and herbs into elixirs (Seger, 2022). For thousands of years, people have used herbal and botanical items to either prevent or treat illnesses. Botanical medicine has recognized the contributions of Asian and Native American cultures worldwide (Bhattacharjee et al., 2024). Less than 300 herbs and botanicals are routinely utilized in Western medicine, although an estimated 30,000 or more have been investigated for their potential medical benefits. Plants are probably naturally used to treat or prevent illness (Ahmed et al., 2024). In a world devoid of prescribed drugs, people looked around them to discover remedies for illnesses (Nwanaji-Enwerem et al., 2024). The works of Hesiod and Hippocrates, who detailed the use of herbs in the fourth century B.C., provide documentation of the benefits of herbs as early as the eighth century B.C. The first professional organization dedicated to the study of botanical medicine was the National Institute of Medical Herbalists, which was founded in 1864. All civilizations and ethnic groups have utilized plants medicinally for a very long time to promote human health (Li et al., 2024). It is the most ancient type of medicine that humans are aware of (Finch and Burstein 2024). The FDA's guidance on botanical drug products states that herbal items meant for therapeutic, preventive, mitigating, or diagnostic purposes are considered drugs (Faqi, 2024). A botanical product may be controlled as a medication or as a food supplement, depending on the situation, if its goal is to alter the composition or operation of the human body.

An elixir is a sweet beverage that is ingested internally and used medicinally to treat illnesses (Ungerer, 2024). An elixir is a pharmacological preparation that has at least one active component that is meant to be consumed orally (Barik and Dhar, 2024). The FDA defines a botanical medicine product as one that is made of vegetable materials, which can include plant materials, algae, macroscopic fungi, or combinations of these; it is meant to be used in the identification, treatment, mitigation, or prevention of human disease. Botanical medication products can be found in various forms such as tea, powder, pill, capsule, elixir, topical, injectable, and more.

Ancient Wisdom in Veterinary Practices

Plant-based medicines have been used since the prehistoric era, which dates to 4000–5000 BC (Barrett et al., 2024). Approximately 80% of the developing world still depends on plants for treatment, despite the modern period (Bell et al., 2024). It is interesting to remember that more than 50% of the medications used in clinical practice today have plant origins. The ancient Ayurveda, sometimes known as the science of life, included veterinary practices (Scanlan, 2024). Cattle were valued belongings and sacred creatures during the Vedic era (c. 1500–500 BCE), and early animal clinics and sanctuaries were devoted to them.

Early treatises also addressed the Asian elephant, which was valued for its mobility and military prowess, although many species had well-developed treatment techniques (Collins, 2024). The emperor Ashoka the Great funded the first Ayurvedic veterinary facilities during this period when veterinary activities were funded by the state. Ashoka's purported spiritual motive stemmed from the idea that dharma practice connected animal and human welfare (Bilimoria and Rayner, 2024). As a result, early veterinarian and medical practice was linked to spiritual beliefs and holy rites in a sacred society, where institutional veterinary activity originated. Via Buddhist writings, Ayurvedic notions about physiology, health, and illness made their way from India to China, where they were subsequently connected to local conceptions of human and animal bodies in the setting of religion (Geisshuesler, 2024). In the ancient Arab and Mediterranean countries, medical and veterinary procedures were initially associated with religious rites. Secular medicine based on natural notions of health and disease also arose, even if religion and rituals remained important in medical treatments (Shaikh et al., 2024). As early as 130 BCE, regular hote-doctors were described in ancient Greek treatises, with "Metrodoros" being named among them.

Veterinarius and mulomedicus were the titles of animal healer professionals in the Roman Empire (Jones and Koolmees, 2022). The term "veterinarian" was used by the Roman scholar Publiush Vegetius Renatus (c. 385 CE) in his writings; Arabic scholars translated this to "bitar" or "baytar," signifying an animal surgeon (particularly a horse surgeon). Based on the revered notion that humans and animals are interconnected, Islamic medicine, both human and veterinary, rose to prominence as the most developed model globally for centuries (Riordan and Flood, 2024). Ibn Akhī Hizām, commander and stable master under caliph Al-Mu 'tadid (r. 892–902), made significant contributions to veterinary medicine. Kitāb al-Furūsiyya wa 'l-Baytara (Book of Horsemanship and Hippiatry) is a work authored by him. Later, in his Kitāb al-Baitara (c. 1209), Ahmad ibn al-Hasan included camel, horse, cattle, and sheep medicine. Tenth-century Hippiatrica was a key medieval source for the dissemination of veterinary knowledge (Bouras-Vallianatos, 2024).

Understanding Rinderpest in Buffalo

Native to Asia, buffaloes (Bubalus bubalis) were then introduced to Africa, Europe, Oceania, and finally the American continent, where they are now found in the United States, Argentina, and Brazil (Martínez-Burnes et al., 2024). The buffalo population has increased and is now widespread throughout the American continent. The world's population was estimated by the FAO to be 206.6 million in 2018 (Kumar et al., 2024). With an estimated 208,098,759 heads, and 77 nations with buffalo herds (Minervino et al., 2020). Worldwide, the fastest-growing buffalo production systems are found in Latin America (Eyasmin and Ghosh, 2024). An RNA virus belonging to the family Paramyxoviridae and genus Morbillivirus is the cause of rinderpest (Alemu, 2024). Its virulent variants can cause up to 77% of morbidity and mortality in India, while mild strains can also cause varied levels of illness and death (Zhu et al., 2024). Sheep, goats, cattle, water buffalo, and wild animals are all impacted. It poses no risk to the public's health and does not affect humans (Ayejoto and Egbueri, 2024). The vulnerability of buffalo varies; species from the Far East seem to be particularly vulnerable, while Egyptian and Turkish buffalo seem to be rather resistant (Wankar et al., 2024). Indian buffaloes are three times more vulnerable than cattle, which may be because certain viral strains are host-specific (Khan et al., 2024). This virus is never reported in Australia, New Zealand, and America. Both direct and indirect contact with secretions, urine, feces, vaginal discharge, and milk can spread the virus (Shekhar, 2024). The upper or lower respiratory tract's epithelium is the primary target of attack. Buffaloes have an incubation period of 3–7 days, though this might vary depending on the individual's natural resistance (Chauhan et al., 2024). Buffaloes with rinderpest exhibit fever (40–42 ◦C), depression, anorexia, decreased rumination, rough coats, and elevated heart and respiratory rates. Within two to three days, there is anorexia, necrosis, erosion of the oral mucosa, and congestion of the mucous membranes together with acute mucopurulent tearing and copious salivation (Pepper, 2024).

Thereafter, there is widespread hemorrhagic diarrhea accompanied by mucous and necrotic material. Within seven to twelve days, severe tenesmus, hypothermia, decubitus, weakness, breathing difficulties in the abdomen, dehydration, and even mortality are possible (Jatav et al., 2024). There have been reports of an unusual form even with nerve symptoms and miscarriage in young and neonatal animals, as well as a per acute form (Calado et al., 2024). Latent infections increase vulnerability to other infectious agents due to the lymphotropic impact of the virus. Hemorrhages, necrosis, erosions of the mouth, gut, and respiratory tract, as well as lymphadenomegaly with edema, dehydration, and emaciation, are the typical lesions (Chang et al., 2024).

Traditional Remedies for Rinderpest

Acute and highly contagious, rinderpest is a viral illness that affects cattle, tamed buffalo, and certain wildlife species (Odetokun et al., 2024). One of the deadliest diseases affecting cattle is classical rinderpest, which can seriously harm unsuspecting herds (Yadav et al., 2024). Rinderpest epidemics were common across Eurasia in the past. In the beginning, 90% of the cattle in sub-Saharan Africa perished. Populations of wild buffalo, giraffes, and wildebeest were wiped out (Kock, 2023). A third of the human population in Ethiopia and two-thirds of the Maasai tribe in Tanzania perished from mass famine brought on by the loss of plow animals, herds, and hunting (Mniga, 2024). Thickets developed in grasslands as a result of the decrease in the number of grazing animals (Gxasheka and Dlamini, 2024). These thickets served as tsetse fly breeding grounds, which led to a human sleeping sickness outbreak (Gachoki, 2005). Others believe that this disease is the worst natural disaster to ever strike Africa. On the other hand, it must be taken into account while making a differential diagnosis for erosive and ulcerative illnesses across the past, rinderpest was found across Asia, Africa, and Europe (Singh et al., 2024). There have never been rinderpest epidemics in the Americas or Oceania (Toor et al., 2024). Sanitary prophylaxis should be undertaken, with isolation or sacrifice of sick and in-contact animals, destruction and careful disposal of carcasses and infectious debris, and protection of unaffected regions, since there was no specific treatment available only supportive care for diarrhea and fluid loss. The same preventative measures that are used in nations where foot-and-mouth disease is listed as an alien illness also apply to free countries (Oda et al., 2024). The attenuated virus strain vaccination is utilized in places deemed epizootic; it delays immunity but remains effective for life, and it can be re-administered in areas of concern. Historically, vaccination campaigns have resulted in a global drop in rinderpest prevalence. Heat-stable recombinant vaccines are also advised by the OIE (Fanelli et al., 2024). The 1980s saw the launch of the Global Rinderpest Eradication Program (GREP) (Jain, 2023). The Food and Agriculture Organization of the United Nations (FAO), in partnership with the World Organization for Animal Health (WOAH) and significant contributors like the European Commission, launched the GREP in 1992. Over time, the program gradually decreased the number of nations affected by the illness; the most recent outbreak occurred in Kenya in 2001 (Abboud et al., 2024). In 2011, rinderpest was officially declared eradicated worldwide, marking the first instance of an animal disease being eradicated in human history (Mashinagu et al., 2024). Animals infected with rinderpest that recovered have gained immunity for life (Bhagwat and Gurav, 2024).

Modern Applications of Botanical Elixirs

The last several decades have seen a sharp increase in interest in the use of traditional herbal medicines as a sort of life-giving elixir (Sørensen, 2024). This interest can be attributed to scientific evidence supporting the therapeutic efficacy and patient-friendliness of traditional medicines (Zhang et al., 2024). Because Chinese and Indian medical systems have access to more traditional knowledge than those of other nations, there has been a preference for using those (Liu et al., 2024). With its abundant biodiversity and longstanding reputation in the medical community, India has the potential to make a significant contribution to the global system that sustains life (Landrigan et al., 2024). Several species of medicinal plants have been used for millennia to treat 80% of human ailments worldwide (Nenungwi et al., 2024). Even though traditional herbs are still used extensively throughout the world, the current study looks into the possibility of some species having novel Ayurvedic and pharmacological uses (Uthara, 2024). Numerous studies show that natural remedies, with their antibacterial, anti-inflammatory, and antioxidant qualities, are essential for treating a wide range of illnesses. Differentiated mechanisms from a variety of herbal plants efficiently fight bacteria, providing a useful remedy for patients who are resistant to antibiotics (Nasrollahian et al., 2024). According to in-vitro research, the herbal chemical complex not only shows promise in treatment but also offers benefits including decreased toxicity and a decreased chance of resistance developing (Chaudhary et al., 2024). Phytochemicals, which include a variety of compounds such as tannin, tocopherol, quinine, quercetin, and alkaloids, have been shown to have substantial promise in treating patients' ailments. Botanical elixirs have a wide range of purposes in modern times, from sports nutrition and detoxification to cleansing cosmetics and skin care products to functional drinks (Toor et al., 2023). Herbs such as fennel, ginger, and peppermint can be added to botanical elixirs to help buffalo's digestive systems function better. By addressing problems like gas, bloating, or indigestion, these herbs can enhance digestive health in general. Throughout the world, the use of herbal plant-based remedies has increased during pandemics like COVID-19, Zika, Ebola, etc (Tulsawani et al., 2024). The history of this practice begins with the Egyptians, who were the first to use plants as medicine. The Greeks and Romans carried on this tradition and recorded it in a book called Pharmacopoeias. Traditional plant-based remedies are still trusted in our cultures and nations today. Furthermore, plant-based therapies are becoming more and more common in modern medicine. At the moment, scientists are focusing their attention on researching and finding new compounds derived from plants that can successfully control diseases that currently exist.

Integrating Ancient Wisdom with Modern Veterinary Medicine

Traditional veterinary medicine has been known to humans since prehistoric times (Gao et al., 2024). The days of dismissing ethnoveterinary medicine and all other forms of ethnic knowledge as superstition, witchcraft, or myth are long gone. There is no denying the importance of ethnoveterinary medicine in the evolution of livestock (Solazzo et al., 2024). The practice of ethnoveterinary medicine has frequently trailed behind that of modern veterinary care, in part because it was carried out covertly and the data was concealed in the gray literature. Currently a sizable body of published material, including an annotated bibliography that abstracts over 1200 papers (Paul et al., 2024). Over time, ethnoveterinary knowledge (EVK) has gained recognition on a global scale. This knowledge is kept in the same way as it is passed down through practice, in the form of artifacts passed down from mother to daughter or father to son, or it is haphazardly documented in book (Rogers-Stokes et al., 2024). According to Wynn (2001), conventional medicine as it exists today is unquestionably the earliest kind of medicine and most likely developed at the same time as human evolution (Vaneechoutte et al., 2024). Records from the past show that animal treatment dates back more than 14,000 years. As animals were being domesticated, veterinary medicine developed expressly to address their health. Over the years, simple traditional remedies have gradually changed in almost every nation on Earth (Van der Vliet, 2024). While veterinary medicine is an ancient field, its recognition and subsequent appreciation in scientific and academic circles is relatively recent. Its significance was only brought to light in the mid-1970s and began to gain traction in the early 1980s. This time frame can be fairly and rightly considered a revolution in the field of ethnoveterinary medicine today (Padalino et al., 2024). Some of these essential traditional health practices were abandoned without thought when modern medicine arrived and ethnocentric interactions persisted (Inman, 2024). It wasn't until the turn of the 20th century that it became apparent that some essential traditional health information had been forgotten and needed to be recovered. However, the realization did not receive the serious attention it deserved until the Western world's researchers, scholars, planners, and developers came to terms with the fact that ethnoveterinary medicine is just as important as orthodox medicine and that the two can work in tandem to create a sustainable system for the delivery of livestock health care toward the end of the 20th and the beginning of the 21st centuries. To ignore ethnoveterinary medicine in the current evolution would be a greater loss of human history (Shekhawat and Baher 2024).

Conclusion

In the end, nations themselves must take action if rinderpest is to remain free to spread around the globe. Due to deficiencies in national veterinary services in many regions of the world, certain nations would be more equipped than others to deal with a rinderpest outbreak. Since rinderpest is still a risk, it will be crucial that veterinary education and training programs, especially for government veterinarians, keep veterinary professionals aware of the disease's clinical and pathological manifestations and that OIE Reference Laboratories can conduct diagnostic tests on suspected cases. Additionally, nations and foreign donors must keep up their investments in bolstering national veterinary services' capacity to combat any dangers to animal health. Support for the framework's implementation will be required to preserve global freedom. It will be crucial to persuade donors of the mid-to-long-term necessity for such investment because rinderpest post-eradication efforts are funded by extramural funds given by donors, as they fall outside the purview of the OIE and FAO's primary mandates. It is challenging to envision an endpoint in 2016, given that official reports to the OIE state that RVCM is stored in 22 facilities across 21 countries worldwide, and that five facilities in four countries have been approved as rinderpest holding facilities (with several other countries considering putting their institutes forward for approval). Will the world community consent to destroying any rinderpest material and virus stocks left? Will the virus be kept in a minimum number of facilities that have been approved? And what figure is that going to be? How will the risks associated with synthetic biology be reduced, even if destruction is accomplished? In the upcoming years, the international community will need to give these questions careful thought. In the twenty-first century, a "one health" approach to illness is being emphasized a lot; the rinderpest eradication procedure was possibly the first coordinated effort that might be considered a success story of this strategy. The fields of veterinary medicine and wildlife ecology both made contributions, which were combined with socio-ecological methods of diagnosing illnesses and providing care.

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Chapter 10

Role of Barley in Maternal Health

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ABSTRACT

Barley is a cereal of the Poaceae family and it is produced and consumed widely across the world. It is a multipurpose crop that is cultivated for human use as well as for animal feed and in terms of production it is the fourth most produced grain. Barley consists mainly of carbohydrates, protein, low fat, and micronutrients such as vitamin E, potassium, magnesium, and antioxidants, especially polyphenols. Moreover, barley's functional properties relate to the various phytochemicals found in it including flavonoids, sterols, folates, phenolic acids, and lignans as well as β-glucan. These are known to improve various health aspects and prevent the incidence and progression of chronic diseases. Barley also plays an important role in maternal health as it is a galactagogue that improves milk supply in lactating women, maintains blood glucose levels and reduces insulin resistance in gestational diabetes, prevents obesity during gestation and is used in its management, and its antioxidative potential to reduce oxidative stress prevent pregnancy complications and adverse pregnancy outcomes including preeclampsia.

KEYWORDS		
Barley, Maternal health, Galactagogue, Gestational diabetes, Obesity, Oxidative stress, Preeclampsia.	Received: 16-May-2024 Revised: 29-Jul-2024 Accepted: 05-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Barley is a cereal of the Poaceae family and it is produced and consumed widely in Asia, Africa and semi-arid regions although it is also produced in Europe, Australia and America (Hussain et al., 2021). It is a multipurpose crop that is cultivated for human use as well as for animal feed and in terms of production it is the fourth most produced grain; this also owes to the fact that it adapts to various environmental conditions, it has an early maturation and has a lower need for water and nitrogen fertilizers to give a high yield (Idehen et al., 2017; Ruggeri et al., 2022).

Its resilient nature allows it to be cultivated in various climatic zones including the Arctic and Mediterranean countries. In Tibet it is grown at high altitudes where it adapts to low temperatures (Meng et al., 2023). Therefore, its ability to adapt to unfavorable conditions allows it to be used widely in areas where other cereals are not produced (Idehen et al., 2017; Ruggeri et al., 2022).

Furthermore, Barley varieties vary in their genetic composition and can be categorized as winter or spring variety, two-rowed or six-rowed, and naked (hulless) or covered (having the outer inedible husk intact). The naked variety is richer in soluble fiber, protein, and antioxidants than the covered variety thus it has a greater nutritional value and potential for food production (Lukinac and Jukić, 2022). In addition, the various colors of different barley varieties relate to their flavonoid content found in the seed (Meng et al., 2023).

Barley consists mainly of carbohydrates, protein, low fat, and micronutrients such as vitamin E, potassium, magnesium, and antioxidants, especially polyphenols. Starch content in barley is about 68%, protein is up to 17%, non-starch polysaccharide β-glucan ranges from 4-9%, (4%–9%), and total dietary fiber ranges from 11-34% with 3-20% of it being soluble dietary fiber (Hussain et al., 2021).

Moreover, barley's functional properties relate to the various phytochemicals found in it including flavonoids, sterols, folates, phenolic acids, and lignans. These are known to improve various health aspects including growth, development, and reproduction, and boost immunity (Hussain et al., 2021). Barley is also a cereal rich in the bioactive component β-glucan, which confers functional and health benefits such as lowering cholesterol and antihyperglycemic effects (Koren et al., 2021).

Furthermore, barley's health-promoting properties also relate to its high resistant starch, and tocol content. With resistant starch working to promote intestinal health, regulate blood sugar and cholesterol and tocols working to reduce serum cholesterol. In addition, among cereals, barley has the lowest glycemic index and the greatest amount of soluble fiber glucans as well as the greatest antioxidant potential (Raj et al., 2023).

Studies have also found that whole grain barley consumption has been linked to a reduced risk of chronic diseases such as cancer, cardiovascular disease, and diabetes. Consumption of wholegrain barley as a part of a balanced diet also has a preventive effect against obesity. Furthermore, barley grass has been found to be an important functional food as it has shown to have antihyperglycemic, antihypertensive, antihyperlipidemic, anticarcinogenic, antioxidative, anti-inflammatory, and antidepressant effects, improves sleep, cognition, and digestion (Zeng et al., 2018).

As a versatile grain, barley has many applications in food and barley-containing foods are termed functional foods as they are nutritious and play a role in promoting health and preventing disease. Thus various cereal products including bread, pasta, biscuits, muffins, malted beverages are produced using barley (Lukinac and Jukić, 2022). Different types of barley are used in the production of different food products for instance, pearl barley has use in soups, malted barley is used to produce brewed beverages, milk-based beverages, and syrups, and milled barley is used in the production of infant foods, bread, and cookies.

Furthermore, Malted barley is the primary form used for human consumption and malting has three steps. These include steeping to elevate the moisture content in the grain, followed by regulated germination to produce green malt that undergoes kilning in the last step. Moreover, it has been found that germination and kilning of the grain alter the texture, flavor, taste, and nutritional value of the grain (Koren et al., 2021).

The purpose of this chapter is to further explore the health-promoting effects of barley, owing to its nutrient composition and bioactive components, particularly its role in promoting maternal health and wellbeing.

Galactagogue

Lactogenesis in humans begins due to a rise in prolactin levels post-delivery, but the amount of milk produced depends of the frequency and duration of breastfeeding and pumping during the first few weeks of lactation. Delayed or inadequate milk production and a reduced milk supply are a challenge that is especially faced in preterm deliveries and this related to lower prolactin levels in mothers who give birth before term.

Animal studies found that β-glucan in barley promote milk production by improving prolactin levels. Moreover, a study involving human mothers with inadequate milk supply also found that the consumption of a barley malt-based product for 14 days improved milk supply (Wesolowska et al., 2021).

Further investigation was conducted in mothers of premature infants with low milk supply and it also found that barley malt-based product functions as a galactagogue. The group of mothers given the galactagogue composition were found to produce 30% more milk thus this barley malt-based product was found to be a lactation stimulant and its use was found to be a safe way to increase the mothers' milk supply. The study concluded that the barley malt-based galactagogue formula was safe to be given during the lactation period and in the first two weeks of lactation it greatly increased milk production. The galactagogue effect was widely associated with the glucan content of barley malt and it was also found that the malting process of barley releases bioactive components that have the potential to elevate milk production.

Moreover, in many cultures barley is used by mothers to increase their milk supply and although allergy to barley is rare mothers with celiac disease are advised to avoid it (Wesolowska et al., 2021; National Institute of Child Health and Human Development, 2024).

In addition, barley is also used to produce nonalcoholic beer which is beneficial against inflammatory diseases, respiratory issues, and diarrhea and is also used to initiate and enhance breastfeeding. A study also found it to increase serum prolactin in lactating mothers thus concluding that the phytochemicals other than alcohol are responsible for the lactation-stimulating effects of beer. Another trial found that supplementation of lactating mothers' diet with nonalcoholic beer increased the antioxidant content of breast milk as well as the amount of coenzyme Q_{10} in breast milk (Javan et al., 2017; Monte-Guedes et al., 2018).

Gestational Diabetes

Gestational diabetes (GDM) is a kind of diabetes mellitus (DM) that is considered as a pregnancy complication in which hyperglycemia occurs in pregnant women who previously did not have diabetes and this usually resolves postpartum. GDM occurs when maternal beta cells cannot maintain the insulin balance required during pregnancy. There are adverse consequences of GDM for the mother and infant. These include a greater risk of maternal and infant heart disease and type 2 DM, macrosomia, and premature birth (Nakshine et al., 2023).

Moreover, a high triglyceride-glucose index during early pregnancy presents a greater risk of GDM and studies have found that supplementing with dietary fiber, before 20 weeks of gestation, can prevent GDM as well as preterm delivery in women with an elevated triglyceride-glucose index as dietary fiber plays a role in metabolizing glucose and lipids (Cao et al., 2023).

Furthermore, women who were overweight or obese prior to pregnancy are at greater risk of GDM as obesity in linked to elevated inflammatory markers which lead to insulin resistance and GDM. A study also confirmed that a greater intake of dietary fiber for these women may also prevent insulin resistance leading to GDM, preterm delivery, glucose intolerance, and excess weight gain during pregnancy; women supplementing dietary fiber in their diet were found to have lower fasting plasma glucose levels and HbA1c levels thus showing better tolerance to glucose post intervention (Zhang et al., 2022).

In addition, β-glucan has been found to reduce blood sugar in diabetics by promoting delayed gastric emptying, decreasing appetite, and promoting the activation of signaling pathways. Moreover, whole grain consumption is associated with a reduced risk of type 2 diabetes and whole grains and fiber have antidiabetic properties through promotion of various mechanisms such as energy depletion. In pregnancy, 25-35g/day of fiber is recommended and wholegrains can provide a majority of it especially barley which is rich in fiber. High fiber intake was also found to improve blood sugar levels as well as reduces hyperinsulinemia in diabetics (Barati et al., 2021).

Furthermore, β-glucan from barley grains has been found to reduce post-prandial blood glucose levels after the consumption of a meal high in carbohydrates and intake of ≥ 6 g/day β-glucan for at least 4 weeks significantly affects post-prandial blood glucose levels. The consensus of most studies in humans is that at least 4g of β-glucan is required for every 30g of available carbohydrates to significantly reduce glucose levels post meals. β-glucan reduces blood glucose by interacting with enzymes on the intestinal brush border as well as interacting with nutrient transporters to inhibit the intestinal uptake of glucose (Malunga et al., 2021; Lante et al., 2023).

Obesity

Pregnant women who are obese before pregnancy or those who become obese during gestation present a lipotoxic environment in the placenta with elevated pro-inflammatory cytokine levels thus leading to various complications in the mother and infant. Obesity is a risk factor for preeclampsia, GDM, delivery complications, insulin resistance, anemia, and inflammation in the newborn (Jiménez-Osorio et al., 2023).

Moreover, studies have found that women who are obese are less insulin sensitive than women of normal weight thus the risk of GDM is higher in these women along with hypertension during gestation, macrosomia, and cesarean deliveries (Kim and Ayabe, 2023).

Obesity is also a challenge for fertility as it leads to problems in conception and also increases the risk of miscarriages and stillbirth as well as maternal death. Moreover, an excess gain of weight during gestation and weight retention post birth further increase difficulties conceiving in the future as well as elevate the risk in pregnancies that may result (Langley-Evans et al., 2022).

Barley promotes satiety and reports found that consuming barley before lunch led to feeling less hunger than consuming wheat and rice-based products. The satiety-promoting effect of barley relates to its high fiber and β-glucan content which regulate appetite, and delay gastric emptying and absorption. Whole-grain barley is also known to prevent insulin resistance, hyperlipidemia, and obesity. Due to its high viscosity and interactions with nutrient transporters, it slows the digestion and absorption of glucose and leads to the feeling of early satiety.

Moreover, dietary fibers undergo fermentation in the large intestines to produce short-chain fatty acids that promote satiety by increasing the satiety hormones which increase energy expenditure and fat oxidation while preventing fat accumulation. In addition, other phytochemicals in barley also prevent obesity including coumaric acid and ferulic acid which are the major anti-obesity agents in hulled barley extracts and prevent fat accumulation in mice and rats (Gong, 2019).

Other studies have also found that an increase in dietary fiber consumption promotes satiety by increasing the food volume in the stomach while lowering the meal's calorie density and ultimately leading to weight loss (Zhang et al., 2022). Furthermore, barley foods are rich in fiber, are nutrient-dense, and promote satiety thus making them appropriate choices for weight maintenance diets. Evidence also suggests that these foods are associated with lower body weight, adiposity, and waist circumference owing to their β-glucan content (Mathews et al., 2021).

In addition, foods with a low glycemic index are used to manage obesity and barley is one such cereal that lowers blood sugar and lipid levels. Barley is rich in fiber β-glucan, and bioactive components that have antioxidant effects to reduce inflammation, lower serum cholesterol, and reduce the absorption of glucose into the bloodstream thus making barley appropriate for obesity management (Gong et al., 2019; Sharma et al., 2022).

Antioxidative Potential to Prevent Adverse Pregnancy Outcomes

Oxidative stress in the body due to the increased production of free radicals increases the risk of chronic diseases as well as pregnancy complications. Certain dietary crops can scavenge these free radicals and reduce oxidative stress. In barley, β-glucan and phenolic compounds have antioxidative potential against various chronic conditions (Desta et al., 2024).

Flavanoids in barley are potent antioxidants against cancer, allergies and inflammation. Moreover, tocols or vitamin E are also found in barley which are protective against neurodegenerative conditions and heart disease, as well as in lower serum cholesterol levels and reduce platelet aggregation (Abebaw, 2021).

Oxidative stress plays an important role in the incidence of GDM and obesity as it leads to insulin resistance, reduced glucose tolerance and impaired β-cell function. The phytochemicals in barley work to prevent the incidence and advancement of these diseases especially phenolic acids, tocols, flavonoids, and phytosterols which are potent antioxidants. In addition, a study using methanolic extracts from various grains found barley to have the highest antioxidant potential compared to wheat, oat, and rye. This antioxidant potential reduces the inflammatory markers, particularly in adipose tissues, that are an important feature in obesity and diabetes (Idehen et al., 2017).

Another study isolated the flavonoids lutonarin and saponarin from barley grass and found that saponarin is a strong antioxidant that can prevent the incidence of oxidative damage in various inflammatory conditions, heart disease, and cancer (Zeng et al., 2018).

Oxidative stress is linked to chronic inflammation and various diseases that include reproductive disorders and pregnancy complications. During gestation oxidative stress normally increases as the placenta produces increased amounts of free radicals but these are usually neutralized by antioxidant levels. On the other hand, when these levels are not balanced the oxidative stress can lead to harmful effects for the mother and fetus and conditions such as preeclampsia, GDM, and hypertension during pregnancy can occur which greatly increase the risk of mortality in the mother and child (Phoswa and Khaliq, 2021).

Preeclampsia (PE) is a pregnancy complication in which hypertension occurs accompanied by proteinuria and this appears in after the first trimester of pregnancy. This condition may be accompanied by comorbid conditions such as edema, eclampsia, and hepatic alterations for the mother, and intrauterine growth restriction and low birth weight, premature birth, and stillbirth for the fetus. Preeclampsia is a result of oxidative stress causing oxidative damage in the placenta resulting in an increase in inflammatory factors and vasoactive compounds which leads to impaired endothelial function that is presented as increased constriction and inflammation of vessels. Therefore, oxidative stress plays a vital role in the etiology of preeclampsia (Aouache et al., 2018).

Preeclampsia and hypertension during gestation both present reduced placental perfusion which leads to hypoxia in the placenta that causes maternal inflammation. In the case of preeclampsia this inflammation affects kidneys and results in proteinuria. As for GDM, oxidative stress leads to hyperinsulinemia during gestation leading to an increase in lipid peroxidation factors which also prevent the release of antioxidants thus free radicals increase and prevent glucose utilization by body tissues (Phoswa and Khaliq, 2021).

In addition, oxidative stress is also associated with polycystic ovary syndrome, endometriosis, and infertility in women. Studies on pregnant women and laboratory animals have also found that oxidative stress in the placenta can transcend to distal tissues and cause oxidative damage resulting in complications and abnormalities in gestation. These include brain damage, retinopathy, and birth defects in the fetus and nausea, vomiting, damage to placental DNA as well as the above mentioned conditions (Grzeszczak et al., 2023).

Neural tube defects, cleft palate, and brain and cardiac defects in the fetus are some common adverse pregnancy outcomes and these are strongly associated with folate deficiency. Folate is another potent antioxidant and barley is a cereal rich in folate, which is found mainly in the outer layers of the kernel. Moreover, pearled barley flour has been found to provide a higher folate content. Foods such as pasta, and biscuits made from this flour are a means of providing increased folate content compared to unfortified products. These products play an important role in improving folate status in mothers and reducing the risk on congenital abnormalities and cardio-cerebral diseases (Ruggeri et al., 2022).

Furthermore, magnesium is another important antioxidative micronutrient involved in metabolic functions and its deficiency also contributes to diabetes and hypertension as well are neurodegenerative conditions. Women are more prone to magnesium deficiency as estrogen promotes the uptake of magnesium by tissues thus hormonal changes in women can affect magnesium status. Moreover, during gestation magnesium requirements increase due to increased fetal needs and renal output, and changes in tissue distribution. According to recent research, low magnesium levels during gestation are associated with pregnancy complications such as preeclampsia and intrauterine growth restriction in the fetus (Orlova et al., 2021).

Magnesium also plays an important role in glucose regulation and insulin signaling and insulin also regulates the accumulation of magnesium in cells. Low serum levels of magnesium are often associated with increased insulin resistance in diabetics and GDM is also observed with hypomagnesemia where total magnesium levels are low (Qu et al., 2022).

Moreover, barley is a rich source of magnesium with some varieties providing >600mg/kg magnesium (Hussain et al., 2021). Furthermore, one study found barley varieties to have Mg (546-643) mg/kg and it was the third most abundant macromineral in barley after potassium and calcium (Tilahun et al., 2022).

Conclusion

Barley is an important cereal that is widely consumed across the globe and beyond its nutritional benefits it also acts as a functional food to promote health and prevent disease. Its functional properties relate to its nutritional value and the phytochemicals found in it which work to regulate blood glucose, reduce serum cholesterol, reduce insulin resistance and inflammation, and prevent the incidence and progression of various chronic diseases. Moreover, barley is also important for maternal health as it improves milk supply, is effective against gestational diabetes and obesity and prevents pregnancy complications and adverse pregnancy outcomes such as preeclampsia, neural tube defects, cleft palate, cardiac and brain defects, premature birth and stillbirth. However, further research is required to further understand the precise role of barley and its components in promoting maternal and fetal health and preventing complications during pregnancy and birth as well determining the exact amount required to achieve these benefits.

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Chapter 11

Botanical Alchemy: Ancient Remedies in Modern Healing

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ABSTRACT

Plants have always been essential to the health and welfare of humans. Botanical knowledge has shaped our concept of healing from the oldest civilizations to current medicine through the decades. Recently, there has been a revival of interest in botanical alchemy, the ancient practice of using plants' therapeutic potential, as people look for more natural and holistic health care methods. Botanical alchemy is based on the idea that plants have natural therapeutic properties that may be extracted and used for a variety of medical conditions. Strong medicines were made from plant materials by ancient healers using a range of methods, including fermentation, distillation, and extraction. Skin illnesses, respiratory infections, and digestive problems were among the many ailments for which these medicines were often used to cure. Many of the traditional applications of herbal treatments have been confirmed by current scientific investigations. According to these studies, several plants have active ingredients that have antioxidant, antiviral, and antibacterial qualities. Because it provides natural alternatives to traditional therapies, botanical alchemy has grown in importance as a tool for integrative and complementary medicine. Plant alchemy has remained to be a popular method that has recently gained a resurgence as a useful instrument for complementary medicine. Botanical alchemy is a comprehensive approach to treat a wide range of illnesses by exploiting the therapeutic qualities of plants.

KEYWORDS
Remedies, Plants, Botanical alchemy

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INTRODUCTION

People have been using different plants and their various parts as medicine for thousands of years. Throughout history, people have employed plant-based ingredients, such as food portions or botanical portions and powders, to treat and prevent illness, with differing degrees of effectiveness. Archeological evidence points to even older usage of medicinal herbs, and written records about them go back at least 5000 years to the Sumerians (Pan et al., 2014). When Friedrich Bayer and Co. brought the synthetic acetyl salicylic acid (aspirin) to the human use in 1897, the long-standing, close relationship between plants and human health started to break down. Salicylic acid, the active component of willow bark, has a safer synthetic equivalent in aspirin, which was separately discovered by people in the old and new world as a treatment for fever and pain (Raskin et al., 2002). In a more traditional sense, Herbal Medicine (HM) refers to the use of plants, plant parts, their water or solvent extracts, essential oils, gums, resins, exudates, or other form of advanced products made from plant parts, therapeutically to provide proactive support of various physiological systems (Al-Attar and Shawush, 2014). According to the World Health Organization (WHO), non-conventional medicine is used for primary healthcare by over 70-80% of the world's population, especially in poor nations (Bordogna, 2011).

The use of these chemicals is not usually permitted by regulatory bodies that oversee safety and efficacy protocols, and several published studies highlight the poor quality of phytomedicinal product manufacturing, distribution, and prescription practices. Approximately 25% of medications prescribed globally are derived from plants, with 121 active plant chemicals currently in use. Of the 252 medicines from the WHO lists as basic and necessary, just 11% from it are derived solely from plants, and a significant portion are synthetic medications made from natural precursors. Digoxin from *Digitalis* spp. quinine and quinidine from *Cinchona* spp., vincristine and vinblastine from *Catharanthus roseus*, atropine from *Atropa belladonna*, and morphine and codeine from Papaver and somniferum are a few examples of significant medications derived from plants (Rates, 2001). Indian subcontinent has a rich, colorful, and varied cultural past. The concept of health and healing is important to this culture and heritage. As a result, all ethnic groups across the various ecosystems have access to a vast area of information about health and healing. Unfortunately, for the last several centuries, mainstream culture has had a greater effect on this body of knowledge, diluting the importance of regional health customs. To preserve local health customs, it is critical to quickly implement efficient recording and evaluation systems; otherwise, this magnificent people's health culture would be gone forever (Agrawal et al., 2006). Indian region is popular as "botanical garden of the world" as it is perhaps the world's biggest grower of therapeutic plants. More than 3000 plants are officially recognized as having therapeutic use in India. Around 6000 plants are thought to be used in traditional, folk, and HM in India; this amount is thought to cover around 75% of the third world nations' medical requirements (Rajasekharan and Ganeshan, 2002). Over 7800 pharmaceutical production facilities are thought to exist in Indian region, and these facilities are thought to use roughly 2000 tons of herbs in a year (Ramakrishnappa, 2003). India is home to three of the ten herbal medications that are most often sold in developed nations: *Allium sativum, Aloe arbedensis*, and *Panax* sp. formulations. Approximately 7000 medicine companies, either with or without standardization, produce traditional medicines (Dubey et al., 2004).

In a world where the conversation about healing is often dominated by contemporary medicine, there is a deep respect for the age-old knowledge found in the field of botanical alchemy. Ever since the beginning of human history, people have had a close connection with plants because they have realized how profoundly they can heal illnesses and promote life. Botanical alchemy, which is based on the fusion of THM and spirituality, is evidence of humanity's continuous pursuit of overall health (Balick and Cox, 2020). Botanical alchemy reveals an array of treatments, customs, and ceremonies that have withstood the test of time by drawing on the knowledge of civilizations that span continents and eras. Through experimentation, intuition, and investigation, people were able to determine the therapeutic qualities of plants. These traditional healers discovered the powerful properties of plants and used them to treat the body, the mind, and the spirit (Hoffmann, 2003). Botanical alchemy became a fundamental aspect of human health via the precise formulations of Ayurveda, the complex plant wisdom of European folk traditions, or the shamanic activities of indigenous civilizations (Frawley and Lad, 1994). Botanical alchemy remains popular in today's healthcare environment, appealing to those who are looking for holistic therapy and natural solutions. Ancient knowledge finds echo in contemporary study as scientists dive further into the molecular complexity of plant medicine, verifying the effectiveness of botanical medicines for a wide range of maladies. The therapeutic capacity of plants crosses cultural barriers, providing a gentle but deep route toward balance and repair. Examples of these traits include the relaxing benefits of chamomile and the effective anti-inflammatory capabilities of turmeric (Nunez, 2024).

HM is the study of pharmacognosy, and the holistic concepts of conventional treatment systems are all included in the multidisciplinary field of botanical alchemy. Utilizing the accumulated knowledge of various cultures and historical eras, it centers on the investigation and application of plants for medicinal purposes. Recognizing the significant influence of botanical treatments on general well-being, this holistic approach to healing emphasizes the interdependence of mind, body, and spirit. Botanical alchemy has its origins in the cultivation of plants for their symbolic and medicinal qualities in ancient civilizations including Egypt, Mesopotamia, China, and India. The herbal lore and therapeutic techniques of these ancient societies can be understood through literature such as the Indian Ayurvedic scriptures and the Egyptian Ebers Papyrus. Dioscorides and Hippocrates' writings, which represent the Greek herbal traditions, add much more botanical information to the library of knowledge (Barnes, 2001; Šavikin et al., 2013).

Different parts of different plants in different forms such as pills, capsules, gel, cream and oils are used to cure different diseases and heal. For example, Alo vera leaves have acemannan, arctigenin, ankit, arctiin, etc active ingredients used as anticancer, antiviral, antidiabetic, and anti-inflammatory (Sun et al., 2014). *Caesalpinia sappan* has brazilin and sappanchalcone in its roots that act as active ingredients as anti-allergic, antibacterial, anti-inflammatory, and viral neuraminidase inhibitors. It is used for edema, pain treatment and improvement of blood circulation (Zhao et al., 2014). *Rhodiola imbricate* has active ingredients in rhizomes used as anti-cancer, anti-oxidative, immunomodulatory agent (Senthilkumar et al., 2014).

The evolution of botany alchemy was significantly influenced by alchemy as it was conducted in medieval Europe. In addition to investigating the therapeutic qualities of plants and minerals, alchemists aimed to transform base metals into gold, establishing the foundation for contemporary pharmacology. Alchemical and herbal knowledge were combined by experts like Nicholas Culpeper, the author of the seminal herbal treatise "The Complete Herbal," and Paracelsus, with his "The Doctrine of Signatures." Using both sophisticated scientific techniques and age-old knowledge, botanical alchemy is still evolving in the current era. Native Americans have a rich history of using plants in their medicinal practices. This has been documented by ethnobotanists such as Wade Davis and Richard Evans Schultes, who have brought attention to the cultural importance of plants. Pharmaceutical pharmacology, the scientific study of natural products derived from plants and other living things, sheds light on the pharmacological characteristics and mode of action of herbal treatments (Kumar and Kumar, 2009). An all-encompassing approach to health, traditional Chinese medicine (TCM) has been practiced for thousands of years. It places a special focus on herbal compositions and energy concepts. To bring the body's equilibrium and harmony back, Ayurveda, an age-old Indian medical tradition, uses herbal and botanical concoctions. As a reflection of the close bond that exists between indigenous peoples and their natural surroundings, traditional healing traditions from Africa, the Americas, and Oceania also make use of locally accessible plants for medicinal and spiritual purposes. More overtrade and migration have made it easier for people to share plant knowledge across borders, which has enhanced cultural plant repertoires and promoted the blending of traditional medical practices (Šavikin et al., 2013). Several different industries employ Herbal Medicinal Products (HMPs). These are globally significant, fast-expanding, interdisciplinary industries that fall into several categories as shown in Fig. 1.

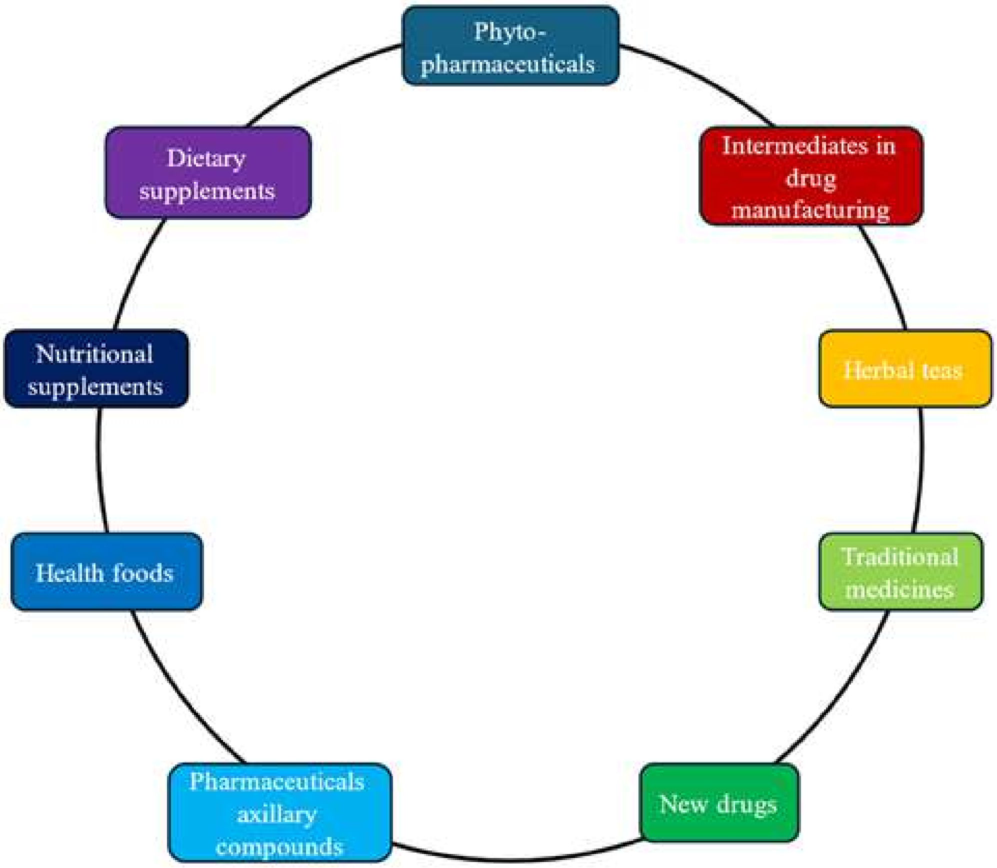

Fig. 1: Industrial use of HMPs

2. Historical Context of Herbalism and Traditional Medicine

The WHO reported almost 30 years earlier that in several nations, traditional practitioners and birth attendants care for 80% or more of the residents living in rural areas (Bannerman et al., 1983; Kayne, 2009). According to recent and realistic updates "traditional medicine is utilized frequently by the majority of the population in most developing countries" (WHO, 2008). Towards understanding the role of traditional medicine in modern era, following information need attention.

- In poor nations, the majority of people practice traditional medicine, while very few regularly have access to reliable contemporary medical care (Bodeker, 2001).
- Between 30 and 50 % of all medications used in China are made from traditional herbal medicine (THM) (Kayne, 2009).
- The Mexican government is constructing regional health facilities, which will be occupied by traditional healers who will also be trained in illness detection. Traditional midwives (parteras), herbalists (herbalistos), bone-setters (hueseros), and spiritual healers (curanderos or prayers) are among the practitioners (Kayne, 2009).
- Using herbal remedies at home is the first line of therapy for 60% of children in Ghana, Mali, Nigeria, and Zambia who have a high fever due to by malarial parasite infection (Kayne, 2009).
- Using knowledge that extends back as far as 1000 BC, an estimated 250,000 traditional healers in South Africa provide treatment to almost 80% of the black population (Edinburg, 1998; Kayne, 2009).

According to WHO estimates, traditional birth attendants help with most deliveries in some African nations. Traditional medicine is used in some Latin American, Asian, and African nations to deal with basic healthcare requirements. Up to 80% of people in Africa get their primary care from traditional medicine practitioners. More than one-third of people living in underdeveloped nations do not have access to basic medications (Kayne, 2009).

The consumption of botanical material for medical reasons, including entire plants, roots, bark, leaves, flowers, berries, or seeds, is referred to as THM, or "phytomedicine" (Organization, 2005). Archaeological evidence indicating human usage of HM going back to the Neanderthal era has long history of HM utilization outside of traditional medicine. Pollen from modern HMs, such as yarrow (*Achillea millefolium L.*, Asteraceae), chamomile (*Matricaria recutita L.*, Asteraceae), centaury (*Centaurium erythraea* Rafn., Gentianaceae), mallow species (Malvaceae), and ephedra species (Ephedraceae), has been found during dug-outs at Neanderthal sites (65,000 years old) at the Shanidar Caves in northern Iraq (Solecki, 1971). This finding suggests that these plants were used in ancient rituals or for medicinal use Hardy et al. (2012) discovered traces of yarrow and chamomile on the molars of five Neanderthal individuals from the El Sidrón site in northern Spain, which dates around 50,000 years ago (Hardy et al., 2012). Leach et al. (1996) reported a noteworthy discovery in Texas, whereby plant pollen of yarrow and chamomile were found alongside ephedra and coltsfoot (Leach et al., 1996). According to Applequist and Moerman, (2011) yarrow is well known for its ability to treat a wide range of ailments, and these varieties continue to be utilized in HM by many nations (Applequist and Moerman, 2011).

Throughout history, HM has been widely used on a worldwide scale. In Mesopotamia, Asia, Africa, the Americas, and Australasia, pre-Christian periods laid the groundwork for significant modern HM systems. For instance, many of the significant botanical remedies used in Ayurvedic treatment have their roots in the Rig-Veda, a compilation of holy Hindi scriptures that dates back thousands of years (Saboo et al., 2014). Written records of the use of herbal remedies by Shan Hai Jing or Shi Jing date back to around 1000–500 B.C. in Chinese Herbal Medicine (CHM) (Pan et al., 2014).

Wintergreen which includes salicin, a painkiller that Hippocrates, around 400 B.C., recorded his observation as "willow leaf brew eases the pain of childbirth" (Walker et al., 2018). Sources of some common HM present in the world are given in Table 1. In contrast to Europe, the use of HM did not become less common in Asia throughout the first century A.D. In actuality, the Chinese Manual of Materia Medica (Shennong Ben Cao Jing), which describes over 252 HMs, was produced in the first century A.D. during the Han Dynasty in TCM (Yang, 1998). Compendium of Materia Medica (Ben Cao Gang Mu), a later book created during the Ming Dynasty (1368–1644), is regarded as one of the most important Materia Medica ever documented. It was put together over 27 years ago by Li Shizhen, who was also a pharmacologist and herbalist. 12,000 plants and herbal remedies were included in this compendium (Hoizey and Hoizey, 1993; Selin, 2013). China's medical industry flourished throughout the Ming Dynasty (1368–1644), and medicinal exchanges occurred between China, Korea, Japan, and even Europe (Hinrichs and Barnes, 2013).

Table 1: Sources of some common HM (Lubbe and Verpoorte, 2011).

Product	Botanical Name	Wild/cultivated	Origin
Asian ginseng root	*Panax ginseng*	Cultivated	China
American ginseng root	*Panax quinquefolius*	Wild	USA
Buchu leaf	*Agathosma betulina*	Cultivated	South Africa
American ginseng root	*Panax quinquefolius*	Cultivated	USA (Wisconsin) Minnesota. Canada
Saffron style and stigma	*Crocus sativa*	Cultivated	Kashmir
Shatavari root	*Asparagus racemosus*	Wild/cultivated	India
Goldenseal rhizome	*Hydrastis canadensis*	Wild	USA
Costus root	*Saussurea costus*	Wild	India
Bilberry fruit	*Vaccinium myrtillus*	Wild	Bosnia Herzegovina, Croatia, Poland
Andrographis herb	*Andrographis paniculata*	Wild/cultivated	India
Schisandra fruit	*Schisandra chinensis*	Wild	China (North)
Goldenseal rhizome	*Hydrastis canadensis*	Cultivated	Wisconsin
Narrow-leaved coneflower root (Echinacea)	*Echinacea angustifolia*	Wild/cultivated	USA

Prehistoric periods on the subcontinent are where the application of HM in Indian Ayurvedic treatment began (Svoboda, 1992). In India, Ayurveda thrived during the Middle Ages, and during this time, several significant medicinal texts were created, most notably by Sushruta and Charaka. The Charaka Samhita was created by Acharya Charak. This was essentially a pharmacopeia, which is still important in Ayurvedic treatment. More than 100,000 plants and plant derivatives are listed, along with their characteristics and uses (Manojkumar, 2013; Sendker and Sheridan, 2017). While the use of HM by humans has expanded throughout time, it's important to remember that other primates, including chimpanzees (*Pan troglodytes*), also utilize medicinal plants as a kind of self-medication for illnesses and diseases (Huffman, 2003). It has also been shown that birds use the insecticidal properties of plants like Nicotiana to lessen the amount of ectoparasites they eat (Suárez-Rodríguez et al., 2013).

Numerous traditional and age-old herbal remedies have produced significant contemporary medicinal substances whose main bioactive components have been identified and defined. These include drugs like aspirin, whose precursor, salicin, is produced from willow (Salix species) and was first used more than 2,000 years ago as an analgesic (Smith et al., 2014). After aspirin was originally synthesized 110 years ago, Bayer registered its trademark under the Berlin Imperial Office in 1899. Vinblastine, vincristine, vindesine, and vinorelbine are examples of current anti-mitotic and anti-microtubule vinca alkaloids that are developed from the Catharanthus roseus (L.) G. Don (Apocynaceae) periwinkle plant found in Madagascar (Moudi et al., 2013). Asia, Africa, and Central America have traditionally used this plant as a traditional medicine to treat diabetes (Ong et al., 2011; Patel et al., 2012). It has historically been used topically to treat malaria and diabetes in CHM, as well as wasp stings in Ayurvedic medicine (Nejat et al., 2015). Among the Amaryllidaceae, snowdrops (Galanthus elwesii Hook and Galanthus woronowii Losinsk) are an intriguing example of a medicinal chemical discovered via traditional medicine. They create galanthamine, a cholinesterase inhibitor that is being utilized in clinical settings to treat Alzheimer's disease and mild to severe vascular dementia (Olin and Schneider, 2002).

Evidence-Based Medicine

HMs are becoming more and more popular, and they may be added to preventive medications and healthy diets. Furthermore, according to Chauhan et al. (2013) and Wachtel-Galor and Benzie (2012), they are becoming more and more prevalent in functional foods, nutraceuticals, and natural health products (Chauhan et al., 2013; Wachtel-Galor and Benzie, 2012). They may be made into pills, capsules, teas, tinctures, lotions, oils, and liquids, among many other forms of processing and formulation. The need for unprocessed medicinal plants and their mixtures is a significant and expanding global market (Chauhan et al., 2013).

Alo vera

5000 years ago alo vera and its products are used by Romans, Egyptians, and Indigenous peoples of Africa, America, and Asia for the treatment of ulcers, burns, and surgical wounds (Garcia-Orue et al., 2017). Some natural bioactive compounds such as oleic acid, phytol, glycosides, pyrocatechol, acemannan, and saponins are present in aloe vera (Salehi et al., 2018). It has better antimicrobial effects on Gram-positive bacteria as compared to Gram-negative bacteria (Lawrence et al., 2009). Acemannan, saponins, and anthraquinone have known antimicrobial activities (Martínez-Romero et al., 2006). Aloe vera's main mucopolysaccharide, or mesoglycan, acemannan, is a strong macrophage and T-cell activator that also triggers the transcription of proinflammatory mRNAs, such as IL-1α, IL-1β, IL-6, TNF-α, PGE2, and nitrous oxide (Ali et al., 2014).

Arctium lappa

Burdock, or *Arctium lappa*, is a perennial plant that is extensively grown (Lin et al., 2002). In North America, Europe, and Asia, *arctium lappa* is utilized for treating skin diseases such as acne, rashes, and boils as well as sore throats (Chan et al., 2011). Research findings indicate that *Arctium lappa* has many beneficial qualities, including anti-inflammatory (De Almeida et al., 2013), antidiabetic (Ahangarpour et al., 2017), antibacterial (Pereira et al., 2005), antiviral (Dias et al., 2017), anticancer (Sun et al., 2014), and hepatoprotective (de Souza Predes et al., 2014). *Arctium lappa* root extract has been demonstrated to dramatically enhance dermal extracellular matrix metabolism, impacting glycosaminoglycan turnover and mitigating wrinkle appearance in human skin *in vivo* (Knott et al., 2008). Additionally, it has been observed that *Arctium lappa* controls gene expression and cell adhesion in canine dermal fibroblasts, influencing the Wnt/β-catenin signaling pathway a crucial regulator of wound healing (Pomari et al., 2013).

Ampelopsis japonica

Ampelopsis japonica is a plant that grows in eastern Asia and eastern North America. Among its traditional uses are for the healing of burns and ulcers (Mi et al., 2014). *Ampelopsis japonica* has been shown to exhibit a variety of pharmacological properties, such as neuroprotective (Park et al., 2013), antibacterial, and anticancer properties (Nho et al., 2015). Rats cutaneous scald injuries healed more quickly when exposed to ethanol extracts made from the desiccated roots of *Ampelopsis japonica*, as shown by Lee (Lee et al., 2015). Topical therapy with ethanolic *Ampelopsis japonica* increased reepithelization, granulation tissue development, vascularization, and collagen deposition when compared to wounds administered Vaseline® (petroleum jelly) or silver sulfadiazine (Lee et al., 2015).

Andrographis paniculata

In China, India, and other south-east Asian nations, *Andrographis paniculata*, often called green chiretta, is employed as a traditional remedy for fever, snake bites, diarrhea, infections, wounds, and itching (Chen et al., 2014). Antioxidant (Adedapo et al., 2015), anti-inflammatory (Shen et al., 2013), antidiabetic (Akhtar et al., 2016), anticancer (Kumar et al., 2004), antimicrobial (Rahman et al., 2014), antiviral (Wiart et al., 2005), antimalarial (Mishra et al., 2011), hypotensive (Zhang and Tan, 1996), immunostimulatory (Kumar et al., 2004), and hepatoprotective (Nagalekshmi et al., 2011) properties are shown by extracts derived from *Andrographis paniculata*. In a particular investigation, it was shown that administering a 10% aqueous leaf extract of *Andrographis paniculata* to rats greatly improved their ability to heal wounds (Al-Bayaty et al., 2012). In healed wounds, animals treated with *Andrographis paniculata* showed decreased inflammation, decreased scarring, enhanced angiogenesis, and an increase in collagen fibers. Clinical investigations have officially studied and demonstrated the critical benefits of andrographolide, a bicyclic diterpenoid derived from the leaves of *Andrographis paniculata*, on a number of autoimmune illnesses (Al-Bayaty et al., 2012).

Caesalpinia sappan

In TCM, the heartwood of *Caesalpinia sappan* is used to minimize discomfort and oedema, enhance blood circulation, and serve as a well-known dye (Zhao et al., 2014). The homosoflavonoids that were extracted from *Caesalpinia sappan* have been shown to exhibit antiallergic (Yodsaoue et al., 2009), anti-inflammatory (Min et al., 2012), and inhibitory effects on viral neuraminidase activity (Jeong et al., 2012). Ethanol preparations of *Caesalpinia sappan* have been shown to have potent antibacterial action against these pathogens *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, and MRSA (Temrangsee et al., 2011). It is surprising to learn that *Caesalpinia sappan's* ethanol root extract also promotes dermal fibroblast migration, proliferation, and collagen production (Tewtrakul et al., 2015), all of which help the skin repair wounds.

Calendula officinalis

Calendula officinalis, sometimes referred to as pot marigold, is a widely distributed herb that is used to heal burns, wounds, and dermatitis, among other skin diseases (Nicolaus et al., 2017). *Calendula officinalis* is credited with a variety of pharmacological properties, such as anti-inflammatory, antioxidant, antibacterial, antiviral, antifungal, and anticancer properties (Chandran and Kuttan, 2008). Nevertheless, the precise processes behind its effects on wound healing are still understood. *Calendula officinalis* extracts have been shown through experiments via cultures of human and murine fibroblasts to promote fibroblast migration and proliferation in a PI3K-dependent manner (Dinda et al., 2015). By modifying the production of connective tissue growth factor (CTGF) and α-smooth muscle actin (α-SMA) in excisional wounds of BALB/c mice *in vivo*, extracts from the flower of *Calendula officinalis* induce the creation of granulation tissue (Dinda et al., 2016). Moreover, it has been shown that it promotes angiogenesis *in vivo* via the use of a cutaneous wound healing model in rats and the chicken chorioallantoic membrane (CAM) experiment (America, 2018). Since prehistoric times, medicinal plants have been the first line of therapy for wounds, illnesses, infections, and trauma. Humans have been able to recognize and use local plant resources for millennia, and as commerce expanded, they were able to use these resources for both food and medicine. Even though they weren't always tested in rigorous scientific studies, a large number of these "ancient" and traditional medicinal plants have been shown to have therapeutic advantages (Dinda et al., 2016).

Shedoeva et al., (2019) documented the several herbal plants with their clinical use, active ingredients, formulations and bioactivities such as Aloe vera, Blumea balsamifera, Andrographis Paniculata, Boswellia sacra Ru Xiang, Camellia sinensis, and Cinnamomum Cassia etc. For example, Aloe vera also known as Lu Hui containing Acemannan, Arctiin, Chlorogenic acid, Caffeic acid active ingredients with their bioactivities such as immunomodulatory, Antiviral. Anticancer, Antidiabetic as wound healing in clinical use (Shedoeva et al., 2019).

Foundations of Botanical Alchemy

The unique combination of herbalism, alchemy, and esoteric knowledge that is botanical alchemy, also known as herbal alchemy, is a source of great interest. By combining the concepts of chemistry, astrology, and mysticism, it is possible to use it curing different wounds that are thought to provide advantages on both the physical and spiritual levels (Bone and Mills, 2012). In the realm of botanical alchemy, the following are some fundamental aspects:

Alchemy Roots

Beginning with the ancient discipline of alchemy, which aimed to turn base metals into gold and uncover the elixir of life, botanical alchemy may trace its roots back to the beginning of the practice. In addition to their belief in the interconnectivity of the universe, alchemists endeavored to discover the mysteries of the natural world. Several cultures all over the world are credited with being the originators of alchemy, which has roots that go back to ancient history (Martelli, 2015; Principe, 2012).

Ancient Egypt

It is common practice to trace the origins of alchemy back to ancient Egypt when its early practitioners endeavored to comprehend the inner workings of the universe and the transformation of matter. Metals and minerals were the primary materials that Egyptian alchemists worked with. Their goal was to learn the mysteries of immortality and turn base metals into gold (Holmyard, 2012; Principe, 2012).

Hellenistic World

In the Hellenistic world, notably in Alexandria, where it was inspired by Greek philosophy and Egyptian mysticism, the practice of alchemy thrived. Alexandria was the epicenter of this transformation. The development of alchemical concepts throughout this historical period is related to figures such as Hermes Trismegistus, who is often regarded as a mythical sage (Place, 2009).

Islamic Golden Age

Significant progress was made in the field of alchemy across the Muslim world throughout the Islamic Golden Age, which lasted from the eighth to the fourteenth century. For the sake of conserving and improving upon alchemical knowledge, Islamic scholars translated books from Greek and Egyptian cultures. As a result of its close relationship with Islamic mysticism, also known as Sufism, alchemy had a significant role in the advancement of chemistry, medicine, and philosophy (Pormann and Savage-Smith, 2007; Renima et al., 2016).

Medieval Europe

The translation of Arabic books into European languages led to the dissemination of alchemical methods among European scientists, philosophers, and alchemists throughout the medieval period. Alchemy was brought to Europe via these translations. During the medieval period in Europe, alchemy was often linked to the search for the philosopher's stone, a mythological item that was thought to provide immortality and turn base metals into gold (Principe, 2012).

Chinese Alchemy

The practice of alchemy thrived in ancient China at the same time as it was gaining popularity in the West. In Chinese alchemy, also known as "Dan Tao," the hunt for elixirs of immortality and spiritual enlightenment was the primary emphasis. The concepts of Taoism, traditional Chinese medicine, and herbalism were all interwoven into those practices (Ho, 2000).

Alchemy in India

The practice of alchemy, often referred to as "Rasayana" or "Rasashastra," has profound origins in the civilization of ancient India. The goal of the alchemists of India was to cleanse and modify the body by the use of various metals, minerals, and plants. In India, the discipline of alchemy was intimately associated with Ayurveda, yoga, and other related spiritual activities (Pole, 2006).

Three Principles

Traditionally, the practice of alchemy is based on the idea of "solve et coagula," which translates to "dissolve and coagulate." To provide a powerful treatment, this method includes first disassembling plant matter (solve) into its constituent parts, then purifying those parts, and then recombining them (coagula). There are three main concepts that are strongly ingrained in alchemical thought and practice, and they are typically used as a guide for the foundations of botanical alchemy. The comprehension of these principles is necessary in order to comprehend the procedures that are involved in the process of botanical alchemy and the production of HMs. These three are often referred as the "Three Primes" or the "Tria Prima (Martelli, 2015)." They are as follows:

Solve (Dissolve)

The first principle, which is called "solve," entails disassembling the plant material, also known as "solving", to extract its necessary components. Several processes, including maceration, distillation, and fermentation, are all potential means by which this breakdown might take place. Through the process of botanical alchemy, plants are disassembled to liberate their active components, which may include volatile oils, alkaloids, flavonoids, and other phytochemicals. The plant material may be solved, which enables the separation of its different parts and the taking out of its essence, which is said to contain the therapeutic powers of the plant (Doughari, 2012; Micozzi, 2014).

Separate (Purify)

The second concept, which is referred to as "separate," includes sterilizing the components that have been removed using filtering, distillation, or other refining procedures. One of the most important steps in the purification process is the removal of contaminants and the isolation of the elements that are wanted in their purest form. The objective of botanical alchemists is to improve the strength and effectiveness of the herbal treatment while also guaranteeing its safety for use. This is accomplished by isolating the purified components (Heinrich et al., 2017).

Coagulate (Combine)

In order to produce a refined and powerful herbal treatment, the third principle, which is referred to as "coagulate," requires recombining the parts that have been purified. All the parts are put together and blended in specified proportions once the purification process has been completed in order to create a blend that is balanced and harmonious. The purpose of this combination procedure is to create a holistic treatment that targets several areas of health and well-being by combining the medicinal capabilities of the separate components in order to create a synergistic effect (Heinrich et al., 2017; Hoffmann, 2003).

Modern Applications

Although the origins of botanical alchemy may be traced back to ancient periods, the technique is still developing and finding new applications in contemporary herbalism and holistic medical methods. An increasing number of practitioners in today's world are using alchemical ideas to make HMs to cure both the body and the soul. Even currently, botanical alchemy continues to uncover applications in a wide variety of sectors, ranging from herbalism and holistic medicine to developing oneself and spiritual growth. The current applications of botanical alchemy include contemporary knowledge and practices, although they are based on old wisdom and alchemical principles (Khan and Ahmad, 2019; Shedoeva et al., 2019). Fig. 2 shows the relationship between traditional and modern medicine.

HM and Holistic Healing

The discipline of botanical alchemy is frequently used in the field of HM and holistic alternative therapies. When it comes to the creation of herbal treatments, such as tinctures, teas, and essences herbalists and holistic practitioners include alchemical ideas in their work. Not only are these remedies thought to treat physical diseases, but they are also thought to treat underlying energy imbalances and spiritual discord when used properly. The practice of botanical alchemy takes into account the interdependence of the body, mind, and spirit, and thus provides a holistic approach to health and wellbeing (Gladstar, 2012).

Alchemy of Personal Transformation

Personal development and self-transformation are two further areas in which botanical alchemy may be used. Alchemical procedures and herbal treatments are used by individuals to enhance inner alchemy, which in turn facilitates emotional healing, spiritual awakening, and personal progress. Self-discovery, empowerment, and integration are all possible outcomes that may be achieved via the use of practices such as alchemical traveling, herbal rituals, and plant spirit medicine. When it comes to investigating consciousness, extending awareness, and connecting with one's actual nature, botanical alchemy provides a set of tools that may be used (deBecker, 2017; Winston, 2019).

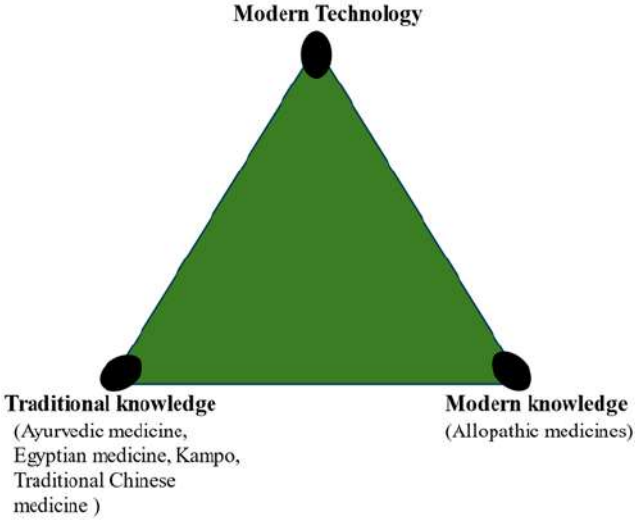

Fig. 2: Relationship between traditional and modern medicine.

Some of the most important characteristics of the contemporary uses of botanical alchemy are as follows:

Alchemy in Ritual and Ceremony

A substantial part in rituals, ceremonies, and other sacred acts is played by the practice of botanical alchemy. In the framework of ceremonial practices, herbal allies are evoked due to the energy characteristics and symbolic importance they possess respectively. Incorporating plant alchemy into rituals might involve ceremonies for healing, shielding, manifestation, and spiritual attunement, among other possible purposes. A sacred environment may be created with the help of herbs, which can also be utilized to generate purpose and strengthen an association with the natural world and the divine (Bird, 2024; Winston, 2019).

Natural Perfumery and Aromatherapy

In the fields of natural perfumery and aromatherapy, whereas plant fundamentals are employed for their fragrant and energetic properties, botanical alchemy has an impact on the activities that surround these fields. Essential oils and plant extracts are combined by aromatherapists and perfumers to produce smells that are designed to elicit certain states of mind, feelings, and emotions. This collection of natural fragrances and fragrant mixtures may be used as instruments for sensory investigation, emotional healing, and spiritual elevation (Rhind, 2014).

Environmental and Plant Conservation

One may develop a more profound appreciation for the natural world via the practice of botanical alchemy, which also encourages environmental care and the preservation of plant life. Practitioners acknowledge the sacred nature of plants and acknowledge the role that plants play as allies in the process of healing and evolving. Specifically, they campaign for the conservation of endangered plant species, as well as sustainable harvesting techniques, ethical wildcrafting, and other similar activities (Hamilton, 2013). Individuals are encouraged to build reciprocal connections with plants and to appreciate the critical contributions that plants make to the well-being of the world via the practice of botanical alchemy, which generates a feeling of reconnecting with nature and reverence for the ground. In general, the current applications of botanical alchemy span a wide variety of activities and fields of study, all of which are brought together by a common respect for the knowledge that plants possess and the transforming potential of alchemy. Botanical alchemy continues to inspire and motivate people on their paths of healing, development, and self-discovery for a variety of reasons, including its use in HM, personal growth, spiritual practice, and environmental activism (Krupnick and Kress, 2005).

Modern Challenges and Solutions

For thousands of years, HM has been a fundamental component of healthcare systems around the globe, providing a sustainable and organic approach to health and well-being. HMs have a long history that is based on indigenous knowledge and antiquated therapeutic techniques. As such, they are still very important in contemporary medicine (Leonti and Casu, 2013). Table 2 represents instances of publications on herbal clinical research.

Respiratory Infections

Infectious diseases of the respiratory system, such as the common cold, influenza, and bronchitis, belong to the most frequent health problems anywhere in the world. It has been established that herbal treatments such as echinacea, elderberry, ginger, and licorice root possess immunomodulatory and antiviral activities, which enables them to effectively alleviate signs and symptoms and shorten the life span of respiratory infections (Hawkins et al., 2019).

Digestive Disorders

Indigestion, gas, bloating, and irritable bowel syndrome (sometimes abbreviated as IBS) are just a few of the digestive diseases that have been treated with herbal medications for a very long time. Carminative, anti-inflammatory, and spasmolytic characteristics are shown by herbs like peppermint, ginger, chamomile, and fennel, which means that they provide relief from pain in the gastrointestinal tract (Bundy et al., 2004; Grigoleit and Grigoleit, 2005).

Table 2: A few examples of publications of clinical research on herbal medicine.

Example	Purpose/Methodology	Conclusion/Reference
The use of herbs to treat irritable bowel syndrome (IBS)	An RCT with a double-blind design was carried out to evaluate the safety and effectiveness of Chinese herbal medication in treating IBS.	An illustration of research showing the herbal TM's safety and effectiveness (Leung et al., 2006)
Treatment with garlic in kids with high cholesterol.	To find out whether garlic extract treatment is safe and effective for kids with hypercholesterolemia, a double-blind RCT was conducted.	An instance of a trial where claims of "effectiveness" in practical applications were made but "efficacy" was not shown (McCrindle et al., 1998).
Trial of niprisan HM in SCD sufferers	A double-blind, controlled, randomized cross-over study to assess Niprisan's effectiveness and safety.	In controlling SCD, niprisan is both safe and "effective" (Ameh et al., 2011).
Clinical Trials of Traditional HMs in India	An overview of the many kinds of herbal clinical studies that the Indian Drug Regulation Authority (DCGI) is likely to authorize. According to the DCGI, TM products must follow the procedures for allopathic drugs; Phase I studies may not be required; animal toxicity testing may be minimized; and toxicity studies may not be required for Phase II trials unless the herb will be used for more than three months or has toxicity.	A clinical trial of a herbal drug in India may be conducted for one of the following purposes: i) to assess the herbal material for similar signs that it is generally used; ii) to assess an extract or compound derived from a plant for a non-traditional indication; iii) to assess a substance which has never been utilized before and has not been mentioned in any TM system; and iv) to assess a herb for potential interactions with other drugs (Gupta, 2011).

Cardiovascular Diseases

One of the primary causes of morbidity and death throughout the globe is cardiovascular disease, which includes hypertension, hyperlipidemia, and atherosclerosis. Garlic, hawthorn berry, olive leaf extract, and ginger are some of the herbs that have been shown to have hypotensive, hypolipidemic, and antioxidant actions, which contribute to the treatment of cardiovascular risk factors for the patient (Ried et al., 2013).

Anxiety and Depression

In the treatment of mental health issues including anxiety and depression, herbal medications are an important component of the treatment process. Ashwagandha, holy basil (tulsi), and rhodiola are examples of adaptogenic herbs that have been shown to have anxiolytic and antidepressant qualities. These herbs assist in controlling the stress response and ultimately enhance mood (Sarris et al., 2013).

Immune Support

Increasing immune function and preventing recurring infections are two major goals that herbal treatments aim to accomplish. Several plants have immunomodulatory effects, including astragalus, reishi mushroom, and echinacea. These plants stimulate both innate and adaptive immunity, hence lowering the risk of illnesses (Liu et al., 2015).

Conclusion:

Botanical alchemy incorporates the knowledge of traditional herbal treatment with the developments in modern medicine. Through the integration of these natural cures with traditional treatments, we may foster a more comprehensive approach to overall health. Botanical alchemy encourages us to embrace the healing potential of the natural world while encouraging a closer connection to the environment, as science continues to uncover the scientific foundation for old plant knowledge. This revival of HM opens opportunities for a time in the future when the bounty of nature will still be essential for fostering harmony and good health. Natural alternatives to traditional pharmaceuticals are provided by HMs, which provide a beneficial therapeutic strategy for the management of a broad variety of disorders at the same time. On the other hand, it is of the utmost importance to emphasize the significance of evidence-based practice and to guarantee the safety and effectiveness of herbal remedies by conducting rigorous scientific research and clinical trials. HM continues to make major contributions to the health and welfare of people all over the world by combining ancient medical practices with a contemporary approach to healthcare.

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Chapter 12

Use of Herbal Plants against Bacterial Pathogens

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ABSTRACT

The widely spread outbreaks of bacterial infections have drawn global concern with the discovery of antibiotics which are unfortunately leading to severe resistance against serious pathogenic agents. Though, herbal plants occupy traditional importance in the perspective of handling medicinal operations. These naturally occurring plants are comprised of versatile biomolecules acting as excellent biological weapons to combat multiple bacterial infections. Thus, the antimicrobial potential hidden in different plant extracts can alternatively serve the purpose of fatal drugs with a more appropriate and safer application. The current chapter is focused on the antibacterial use of many herbal plants with the phytochemical investigation of effective ingredients. In the early years, various plant phenolics with the addition of alkaloids, saponins, and terpenoids have been proven to achieve noteworthy antibacterial significance, largely adopting various mechanisms of anti-biofilm formation, cellular membrane disruption, microbial metabolic activities inhibition, and anti-quorum sensing. To enhance their more suitable applications against a wide range of health-risking bacteria, further inventions in the field of omics with the synergistic investigations of pharmacological attributes would be in demand to recognize developmental pathways of novel antibacterial remedies.

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INTRODUCTION

The bacterial pathogenic attack is a serious threat on a worldwide scale leading to an amplified mortality rate due to multiple bacterial infections mainly including colorectal cancer, whereas others may include inflammatory and irritable bowel infections as the foremost health risks (Jones et al., 2008; Sell and Dolan, 2018). The reason for the frequent bacterial outbreaks may involve the intoxication of foodstuff by multifarious food-borne pathogens including the most commonly occurring: *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, *Mycobacterium tuberculosis, Salmonella typhimurium,* and *Listeria monocytogenes* (Chen et al., 2017). To counter the current situation, worldwide scientists aim and struggle to design and synthesize effective drugs to act against challenging pathogens. With the current perspective, medicinal plants have been gaining the supreme attention of scientists due to their therapeutic importance hidden in their diverse molecules. History also exposed that these biomolecules had been employed as powerful sources of medicine by man even when no other authentic resource was available (Petrovska, 2012; Stéphane et al., 2021). Since medicinal era, the utilization of medicinal/herbal plants reveals a significant pool towards the discovery of novel antibiotics (Atanasov et al., 2015). The exploration of antibiotics against multivariate bacterial infections leads to the reduction of human mortality rate on a worldwide scale. The earliest discovery of penicillin in the year 1928 by Fleming discloses the vast application of other sulphonamide drugs as the advent source of modern antibiotics (Davies and Davies, 2010). Being used during the early 1940s, Penicillin opened great advancements in antibiotic developments, and the 1950s was marked as the "golden era" for the synthesis of novel drugs. These antibiotics have been considered lifesaving drugs for mankind (Conly and Johnston, 2005; Butler and Paterson, 2020).

However, inappropriate and extensive use of antibiotics has resulted in the emergence of resistance to varied antibiotics, making their application ineffective against certain diseases (Baym et al., 2015). Even the WHO has highlighted the serious emerging concern towards antimicrobial resistance (WHO, 2021). Thus, the demand for the development of such antimicrobial compounds or sources has increased which can cut down the indiscriminate use of antibiotics safely without creating any resistance (Tortorella et al., 2018). The current demand has forced researchers to focus on the isolation and identification of effective antimicrobials from plants and declared the consideration of 50% of pharmaceuticals as derivatives of natural compounds (Chavan et al., 2018). In this pursuit, herbal/medicinal plants have been proven as powerful resources with limitless effects of antimicrobial compounds and agents with versatile uses (Nascimento et al., 2000). These herbal plant-based antimicrobial compounds can be not only used alone but their antimicrobial action can be even more enhanced by combining these with other antimicrobial agents (Bazzaz et al., 2018). Still, many medicinal plants are unexplored so worldwide researchers and scientists are trying to sequester the knowledge of the antimicrobial activity of various herbal plants (Savoia, 2012). The special feature of most herbal plants is that their multiple parts can be utilized for essential therapeutic applications, also acting as precursors of various other drugs. Moreover, the majority of medicinal plants include vegetables with economic importance as well (Silalahi et al., 2014). These vegetables impart their role in toxicity reduction besides their other benefits (Lin et al., 2016; Ma et al., 2019). It is very well understood that plants can adopt various inducible and innate mechanisms to combat pathogenic attacks involving the release of barrier compounds, antimicrobial peptides, and amines as well as divergent vital secondary metabolites (Benko-Iseppon et al., 2010; Rodriguez et al., 2019). Some of the naturally extracted compounds have nonantibiotic properties having adequate antimicrobial effect (Yuan et al., 2016; Lee et al., 2017). About 30,000 to 70,000 different plant species have been used in the field of medicine (Javed et al., 2015). Their variable parts including leaves, shoots, roots and even the flowers can act as astonishing medicines for the cure of multiple bacterial pathogens (Abdallah et al., 2023). These herbal extracts have a better mode of action when encountering both types of gram-positive and gram-negative bacteria. Though their application as oil extracts, powder form, distillation, and decoction are frequently used in medicinal products. However, the employment of their phytochemical extracts is the most effective way against bacterial infections (Kumar et al., 2019). Moreover, antibacterial activity may vary with the type of phytochemical extracts made as different ingredients get active with the phytochemical properties (Chen et al., 2021). These plant extracts specifically gain entry into the cell wall of bacteria and prevent their growth ultimately decreasing the number of pathogenic cells.

The drug-resistant bacteria are the major cause of increasing the mortality rate in humans. Amongst bacterial pathogens, worldwide infections of pneumonia and lung organs are caused by *Pseudomonas aeruginosa* which form colonies in many organs like lungs, kidneys, and even in the urinary tract failing the body functions. Sudden attacks of *Escherichia coli* in soft tissues may lead to skin, joint, and bone infections as well as pneumonia, meningitis, gastroenteritis, and urinary tract infections (Todar, 2007). *Bacillus subtilis* has been considered one of the dominant pathogens of humans (Alfiki et al., 2022; Stülke et al., 2023).

Herbal Plants with Antibacterial Action

Among the worldwide plants, the most examined herbal species typically used against bacterial action include the following:

***Alchornea cordifolia* (Schumach. and Thonn.) Müll.Arg. (Christma Bush)**

It is a perennial dioecious shruby plant with the common name of Christmas bush and belongs to the family of Euphorbiaceae. It is a naturally grown vegetation of African countries such as Kenya, Senegal, Tanzania, Ghana, and the Democratic Republic of Congo. The leaf stalks are frequently used in the form of infusions for the management of multiple intestinal and respiratory complications while compressed leaves are used for the cure of typical wounds (Mambe et al., 2016). However, the bark of the roots and leaves is applicable as an antidote to snake poison which may cause leprosy. In addition to these applications, different plant parts are comprised of various phenolics including steroid glycosides, terpenoids, flavonoids, saponins, tannins, alkaloids, and carbohydrates. Different plant extracts especially ethanolic extracts are highly significant for antibacterial and antifungal actions (Mavar-Mangar et al., 2007). According to Owusu et al. (2021), both ethanolic and aqueous extracts of *A. cordifolia* were shown to be effective against *S. aureus,* while they observed the highest antibacterial action of ethanolic extract against *E. coli.* Some other investigations (Ebi, 2001; Igbeneghu et al., 2007) explored the antibacterial properties of its methanolic extracts to be remarkable against *E. coli*, *P. aeruginosa,* and *B. subtilis* (Fig. 1) (Table 1).

***Allium sativum* L. (Garlic)**

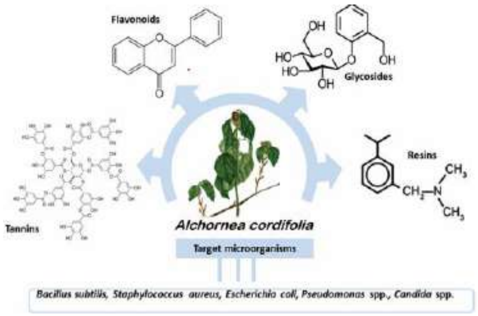
Allicin containing the well-known ayurvedic plant *Allium sativum* L. (commonly called garlic) has been widely used for the treatment of pathogenic bacterial isolates (*Staphylococcus*, *Pseudomonas,* and *Streptococcus*) of lung infections (Reiter et al., 2017). Garlic extracts are reported as strong antibacterial agents for the ailment of *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis,* and *Streptococcus mutans* by Hoglund et al. (2020). The prominent ingredients against bacterial organisms include ajoenes, allicin, diallyl polysulfides, and vinyldithiins which are considered hydrophobic biomolecules showing the antibiofilm formation for the control of the gram-positive and negative types of bacteria (Nakamoto et al., 2020) (Fig. 1) (Table 1).

***Andrographis paniculata* (Burm.f.) (Nees)**

Nees; scientific name: *Andrographis paniculata* (Burm.f.) is popular among ethnic communities for the curative use of infectious diseases of the urinary and upper respiratory systems. 14-Deoxy-11, 12-didehydroandrographolide has been declared as an antibacterial ingredient, to be active in inhibiting around 92% of *P. aeruginosa* growth by the study of Majumdar et al. (2020). The said bioactive plant compound could lessen the synthesis of extracellular polymeric elements which leads to lower levels of pyocyanin and protease production. Rasool et al. (2018) documented that the same plant extract possesses an excellent effect against the *E. coli* organism (Fig. 1) (Table 1).

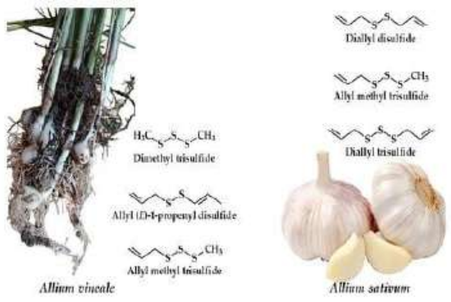
Fig. 1: Active ingredients of herbal plants used against microbial action.

A ***Alchornea cordifolia***



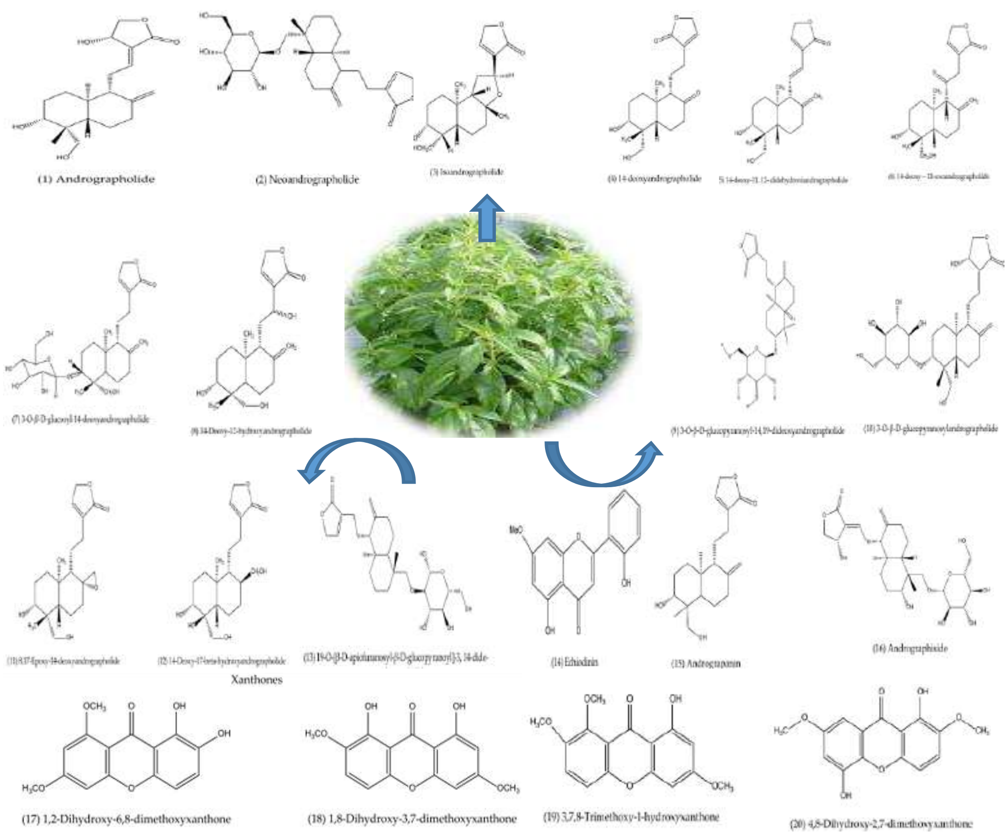
(El-Saadony et al., 2021).

B ***Allium sativum* L.**



(Satyal et al., 2017).

C ***Andrographis paniculata***



(Hossain et al., 2021).

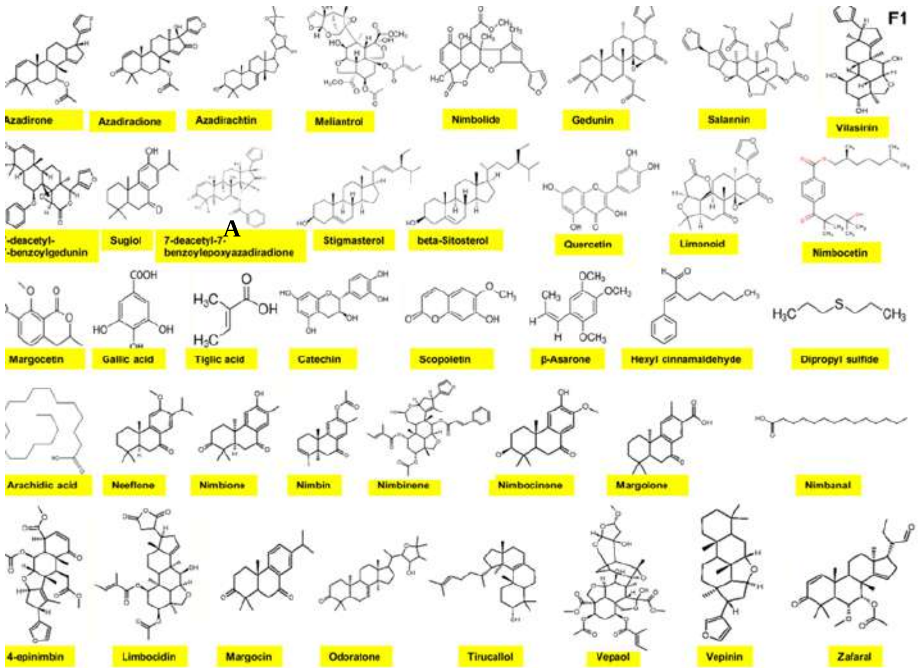
***Azadirachta indica* A. Juss (Neem)**

Neem (*Azadirachta indica* A. Juss) is one of the traditionally used plants that are most appropriately used against *Helicobacter pylori* for the treatment of not only dermatological ailments but also for the control of gastrointestinal and urogenital infections. Its oil has robust antibacterial action, particularly at the MIC range of 25–50 µg/mL and in the MBC range of 40–70 µg/mL (Blum et al., 2019). According to Mustafa (2016), its leaf extract could strongly inhibit the cultivation of *Enterococcus faecalis* (Fig. 2) (Table 1).

***Calotropis gigantea* (L.) Dryand. (Crown flower, Giant milkweed)**

Dryand [*Calotropis gigantea* (L.)] plant possesses noteworthy significance in the medicinal control of dermal, arthritic, oral, and gastrointestinal infections in India. The antimicrobial potential is hidden in its aqueous leafy extract which has been proven as a strong antimicrobial agent against varying pathogenic isolates of *S. aureus*, *K. pneumoniae*, *B. cereus*, *P. aeruginosa*, *Micrococcus luteus*, and *E. coli*. (Kumar et al., 2010). In an important article based on the investigation of its antimicrobial biomolecules, quercetin-3-O-rutinoside has been disclosed as a predominating naturally occurring phytochemical in the plant extract, exhibiting remarkable bioactive potential against gram-positive bacteria (*B. subtilis* and *S. aureus*) in contrast to gram-negative (*Salmonella enteritidis* and *P. aeruginosa*) species (Nenaah, 2013). However, research by Bhat and Sharma (2013) publicized cardiac glycosides, asclepin, calactin, cymarin, and calotropin as active biomolecules of the plant (Fig. 2) (Table 1).

A ***Azadirachta indica*** **A. Juss**



(Gupta et al., 2017).

B ***Calotropis gigantea*** **(L.) Dryand.**

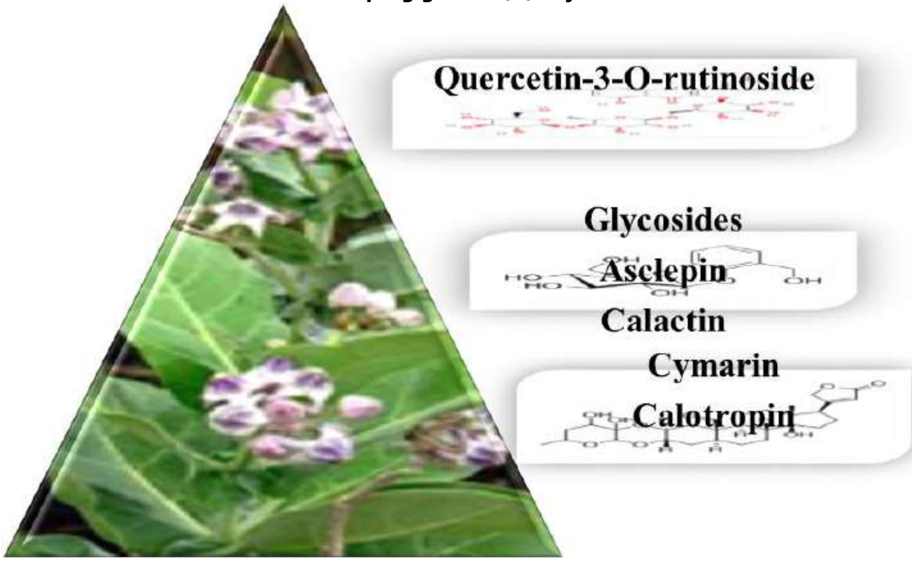


Fig. 2: Active ingredients of herbal plants used against microbial action.

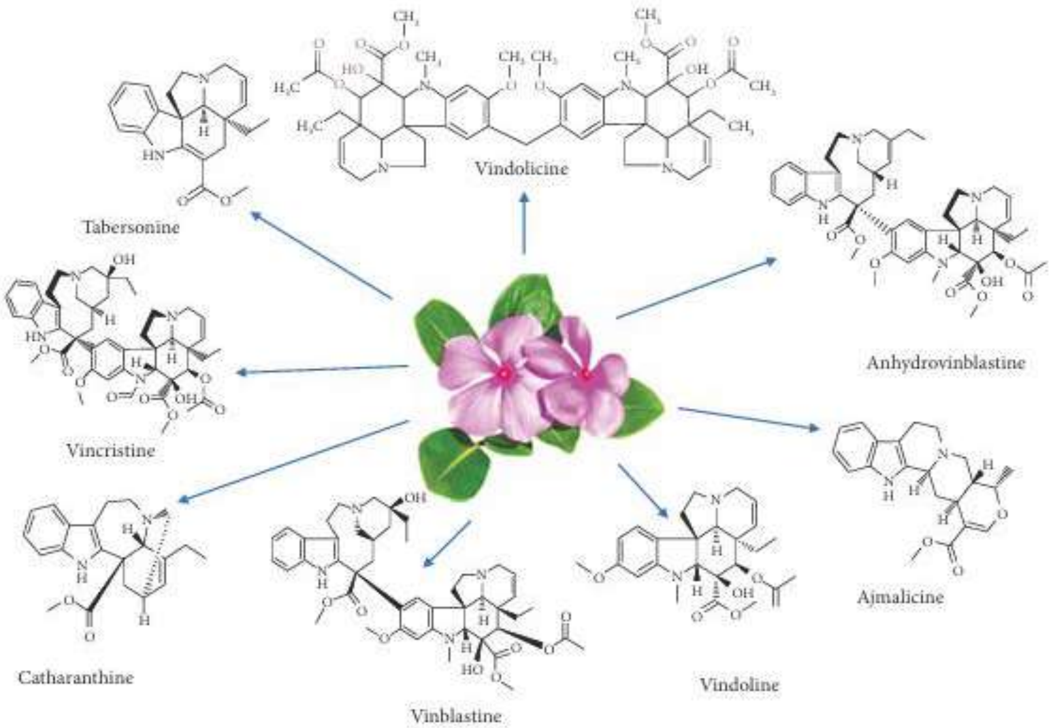
Catharanthus roseus **(L.) G. Don (Jasmine)**

This plant is native to Madagascar and is commonly called bright eyes. The screening of its antibacterial activity by the well diffusion method revealed powerful action against *Bacillus licheniformis* (Naz et al., 2015). Whereas, 100 mg/mL of its alcoholic extract had a magnificent effect against the famous strains of *S. aureus* and *E. coli* (Khalil, 2012). In addition to these findings, Rani et al. (2017) further reported that an alcoholic extract of canthaxanthin is more suitable for the antibacterial action than other extracts such as ether, petroleum, aqueous, and chloroform. This makes sense that the large number of phytomolecules get solubilized in alcoholic extract and show antibacterial efficacy as compared to other extracts (Fig. 3) (Table 1).

Coccinia grandis **(L.) Voigt (Ivy Gourd)**

The antibacterial action has been shown by various protease inhibitors of *Coccinia grandis* extract. These protease inhibitors were reported to potentially inhibit the growth of bacterial pathogens including *B. subtilis*, *K. pneumoniae*, *S. aureus*, *E. coli,* and *Proteus vulgaris* (Satheesh and Murugan, 2011). Different research presented that alcoholic and aqueous fruit extracts had an outstanding role in combating the negative effects of *E. faecalis*, *S. aureus*, *P. aeruginosa* and *E. coli* when checked with disc diffusion methodology, associated with erythromycin comparison (Sakharkar and Chauhan, 2017) (Table 1).

A ***Catharanthus roseus* (L.) G. Don**



(Kandiah and Chandrasekaran, 2021).

Fig. 3: Active ingredients of herbal plants used against microbial action.

B ***Curcuma caesia* Roxb**

***Croton bonplandianum* Baill (Ban tulsi)**

This plant is famous for curing many wound infections. The freshly collected latex of the plant presented the maximum inhibitory activity against the growth of the Enterobacteriaceae family. Among these, *Enterobacter aerogenes* with 26 mm, *E. faecalis* with 30 mm, and *E. coli* with 32 mm inhibitory zones have been found. Similarly, benzene and ethanol extracts from its leaves could fight the battle against *S. aureus* as well as showing an inhibitory zone of 20 mm. However, maximum inhibitory action has been revealed by chloroform extracts specifically against *E. coli* strains having 21 mm of inhibition zones when compared with the effects of other extracts (Vennila and Udayakumar, 2015) (Table 1).

***Curcuma sp*.**

Camphor, epicurzerenone, and eucalyptol are verified as predominant bioactive chemicals found in the crucial oily extract of *Curcuma caesia* Roxb. Its oil had robust effectiveness against *B. cereus* and *B. subtilis* (Paw et al., 2020). A polyphenolic complex called curcumin of the *Curcuma longa* L. plant which is commonly called turmeric has enriched antibacterial properties. Curcumin has been reported to produce lipid peroxidation in the bacterial strains of *E. coli* and *S. aureus*. Whereas in *S. aureus* strains curcumin triggered the redox homeostasis which led to generating the kynurenine trail causing microbial DNA damage as a result of oxidative stress there (Adeyemi et al., 2020) (Fig. 3) (Table 1).

***Cuscuta reflexa* Roxb. (Giant dodder)**

The most commonly found parasitic weed, *Cuscuta reflexa*, is famous for having therapeutic and Ayurvedic properties due to which this weed is greatly used in medicine (Saini et al., 2015). However, the ethanolic extract of *C. reflexa* when screened against *P aeruginosa*, *B subtilis*, and *E coli*, was found to be most effective against *E. coli* and *B. subtilis* (Mishra and Dixit, 2019; Ali et al., 2023). Others have reported the antibacterial action of *C. reflexa* against *Salmonella typhimurium* (Manore et al., 2012), *Proteus vulgaris*, *E. coli*, *Xanthomonas campestris*, *Paracoccus denitrificans* and *Klebsiella pneumonia* (Islam et al., 2015) (Table 1).

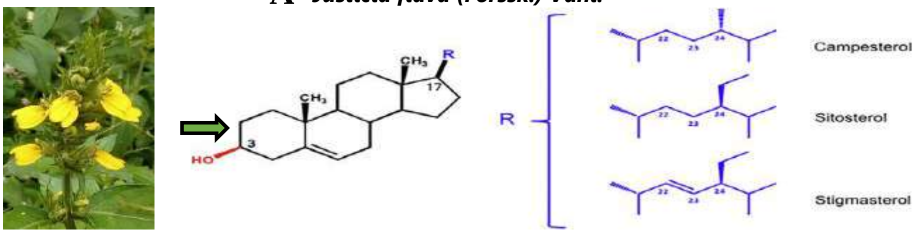
***Fagonia cretica* L. (Virgin's Mantle)**

Likewise, *Fagonia cretica* belonging to Zygophyllaceae is popular for promptly treating many adverse and prevalent diseases (Qureshi et al., 2016). Ali et al. (2023) documented the outstanding role of *F. arabica* specifically in the form of its ethanolic and aqueous extracts against *P. aeruginosa* and *B. subtilus*. According to Ali et al. (2023), the ethanolic extract of *S. chirata* acts as a suitable antibacterial agent against *P. aeruginosa*, *E. coli,* and *B. subtilus*. The extract of *F. arabica* made with dichloromethane is highly efficient in controlling the *E coli* pathogens (Syed et al., 2013) (Table 1).

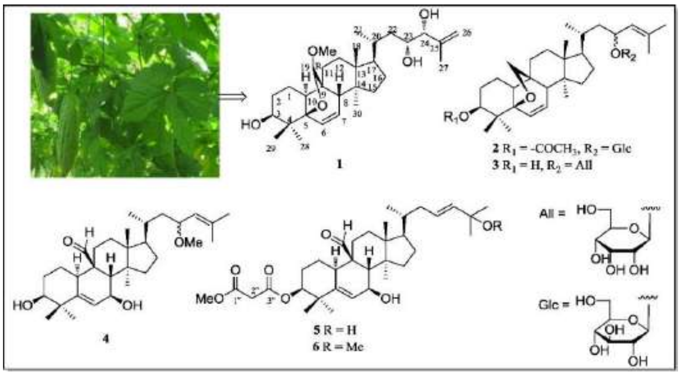
Justicia flava **(Forssk.) Vahl. (Water-willow and shrimp plant)**

This plant belongs to the family Acanthaceae and is commonly disturbed in varying habitats of semi-shaded and sunny regions with an array of soil categories. It has been reported as a common flora of Africa and its leafy extracts have excellent activity against typical strains of *Pseudomonas aeruginosa* ATCC 4853, *Escherichia coli* ATCC 25922, and *Staphylococcus aureus* ATCC25923 (Agyare et al., 2013). It's being employed as a traditional medicine to cure disorders of dysentery, diarrhea, epilepsy, fever, cough, and skin problems (Agyare et al., 2009; Asante-Kwatia et al., 2023). On the other hand, Corrêa and Alcantara (2012), reported the pharmacological importance of *J. flava*. Adding to these, some other scientists disclosed various steroids comprising the active ingredients of sitosterol, campesterol, and stigmasterol for controlling bacterial infections (Amborabé et al., 2002; Rajakumar and Shivanna, 2009) (Fig. 4) (Table 1).

A ***Justicia flava (Forssk.) Vahl.***

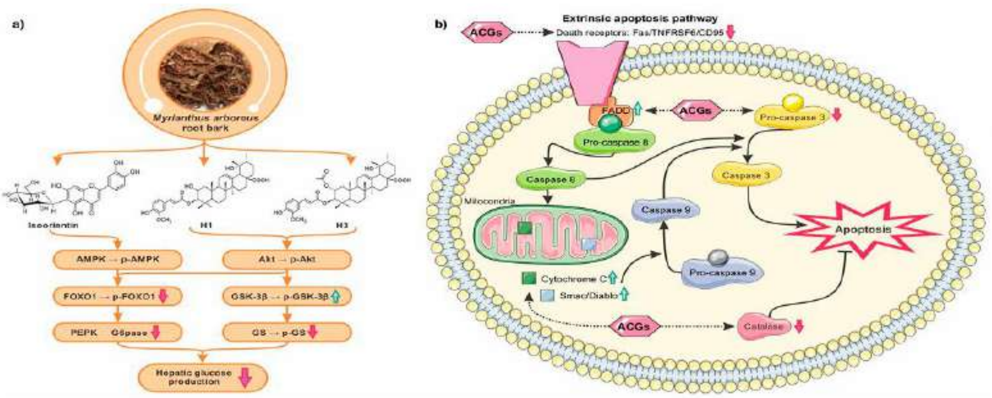


B ***Momordica charantia*** **L.**



(Zhao et al., 2014)

C ***Myrianthus arboreus*** **P. Beauv.**



(García-Pérez et al., 2023).

D ***Viola odorata*** **L**

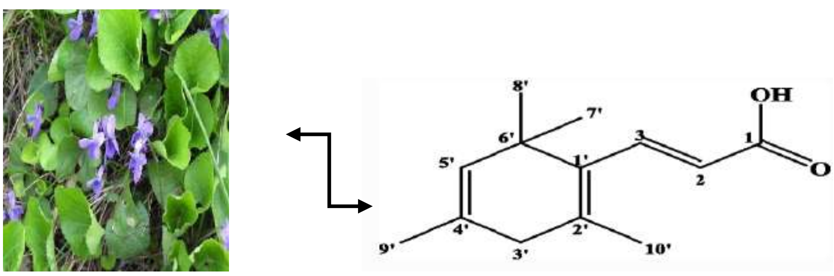


Fig. 4: Active ingredients of herbal plants used against microbial action; A new derivative of ionone (3-(2′,4′,6′,6′-tetramethylcyclohexa-1′,4′-dienyl)acrylic acid) from aerial parts of *Viola odorata* Linn. and its antibacterial role against respiratory pathogens (Gautam et al., 2017).

Table 1: Mechanism of actions against target pathogens using active ingredients from various sources of herbal plants.

Sr. No.	Herbal plant	Source	Active ingredients	Mechanism of action with target pathogens			References
1.	*Alchornea cordifolia*	Leaf stalks/ leaves, Root barks	Steroid glycosides, terpenoids, flavonoids, saponins, tannins, alkaloids, carbohydrates	Aqueous extract *S. aureus*	Ethanolic extract *S. aureus*	Methanolic extract *E coli,* *P. aeruginosa* *B. subtilis*	(Mambe et al., 2016) (Mavar-Mangar et al., 2007) (Owusu et al., 2021) (Ebi, 2001) (Igbeneghu et al., 2007)
2.	*Allium sativum* L.	Bulb	Ajoenes, allicin, diallyl polysulfides, vinyldithiins	*Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis* and *Streptococcus mutans*			(Reiter et al., 2017) (Hoglund et al., 2020); (Nakamoto et al., 2020);
3.	*Andrographis paniculata* (Burm.f.)	Leaves	14-Deoxy-11, 12-didehydroandro grapholide	Methanolic extract *P. aeruginosa,* *E coli,* *Mycobacterium tuberculosis*, *Enterococcus faecalis*, *Staphylococcus aureus*			(Mishra et al., 2013) (Majumdar et al., 2020) (Rasool et al., 2018)
4.	*Azadirachta indica* A. Juss	Leavesseed s, bark, stems	Isoprenoids (e.g., terpenoids containing limonoid structures) and non-isoprenoids (e.g., tannins)	Aqueous extract *Bacillus anthracis,* *Enterococcus faecalis,* *E coli,* *Klebsiella pneumoniae,* *Helicobacter pylori,* *Pseudomonas aeruginosa,* *Salmonella spp.* *S. aureus,* *Streptococcus mutans,* *Vibrio parahaemolyticus*	Ethanolic extract *Klebsiella pneumoniae,* *Helicobacter pylori,* *Bacillus subtilis,* *Enterococcus faecalis,* *E coli,* *Lactobacillus acidophilus,* *Listeria monocytogenes,* *Pseudomonas aeruginosa,* *Porphyromonas gingivalus,* *Staphylococcus aureus,* *Salmonella spp.* *Staphylococcus epidermidis,* *Streptococcus mutans*	Methanolic extract *Helicobacter pylori,* *Klebsiella pneumoniae,* *Alcaligenes faecalis,* *E coli,* *Pseudomonas aeruginosa,* *Pseudomonas gingivalis,* *Salmonella spp.* *Salmonella typhi,* *Shigella spp.* *Staphylococcus aureus,* *Streptococcus viridans*	(Blum et al., 2019) (Mustafa, 2016) (Saleem et al., 2018) (Wylie and Merrell, 2022)
5.	*Calotropis gigantea* (L.)	Leaves	Quercetin-3-O-rutinoside, Glycosides, Asclepin, Calactin, Cymarin, Calotropin	Aqueous extract *S. aureus*, *K. pneumoniae*, *Bacillus cereus*, *P. aeruginosa*, *Micrococcus luteus,* *E. coli,* *Salmonella enteritidis,* *B. subtilis*			(Kumar et al., 2010). (Nenaah, 2013) (Bhat and Sharma, 2013)
6.	*Catharanthus roseus* (L.) G. Don	N/A	Canthaxanthin	Alcoholic extracts *Bacillus licheniformis,* *S. aureus,* *E. coli*			(Naz et al., 2015) (Khalil, 2012) (Rani et al., 2017)
7.	*Coccinia grandis* (L.)	N/A	Protease inhibitors	Aqueous + Alcoholic extracts *B. subtilis*, *K. pneumoniae*, *S. aureus*, *E. coli,* *Proteus vulgaris*, *E. faecalis*, *S. aureus*, *P. aeruginosa*			(Satheesh and Murugan, 2011) (Sakharkar and Chauhan, 2017)
8.	*Croton bonplandianum* Baill	N/A	N/A	N/A *Enterobacter aerogenes* *E. faecalis E. coli*	Benzene + Ethanolic extracts *S. aureus*		(Vennila and Udayakumar, 2015)
9.	*Curcuma sp.* *Curcuma caesia* Roxb	Crucial oil	Epicurzerenone, Eucalyptol, Curcumin, Kynurenine	*B. cereus*, *B. subtilis*, *E. coli* and *S. aureus*			(Paw et al., 2020) (Adeyemi et al., 2020)

10.	*Cuscuta reflexa* Roxb.	Whole plant	Alkaloids, Oil, Fat glycosides, Carbohydrates, Phenolics, Tannins, Lignin, Saponins, Flavonoids, Terpinoids	Ethanolic extract *E coli, B subtilis, Salmonella typhimurium, Proteus vulgaris, Xanthomonas campestris, Paracoccus denitrificans, Klebsiella pneumonia*		(Saini et al., 2015) (Manore et al., 2012) (Islam et al., 2015) (Noshad et al., 2023) (Dhale, 2022)
11.	*Fagonia cretica* L.	Leaves stem	Gallic acid, Quinic acid, Cyclo-l-leu-l-pro, Vidalenolone, Liquirtigenin, Rosmarinic acid, Cerebronic acid, Succinic acid, cyclo (l-Leu l-Pro), Liquirtigenin	Aqueous + Ethanolic extracts *B. subtilis, E. coli, P. aeruginosa*	Methanolic extract *E. coli, Klebsiella pneumoniae, S. carnosus, E. coli S. typhi*	(Qureshi et al., 2016) (Ali et al., 2023) (Syed et al., 2013) (Arsalan et al., 2022) (Tabassum et al., 2022)
12.	*Justicia flava (Forssk.) Vahl.*	Leaves	Sitosterol, Campesterol Stigmasterol	*Pseudomonas aeruginosa ATCC 4853, Escherichia coli ATCC 25922, Staphylococcus aureus ATCC25923*		(Agyare et al., 2013) (Amborabé et al., 2002; (Rajakumar and Shivanna, 2009).
13.	*Momordica charantia* L.	Leaves Fruit	Phenolic, Saponins, Terpenoids	*Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli*		(Mwambete et al., 2009) (Agyare et al., 2014)
14.	*Myrianthus arboreus* P. Beauv.	Leaves Bark	Linoleic acids	*Enterobacter aerogenes, Esrichia coli, Klebsiella pneumoniae, Providencia stuartii, Pseudomonas aeruginosa*		(Agyare et al., 2009) (Seukep et al., 2015)
15.	*Onosma bracteatum* Wall.	Leaves	Alkannin, Ferulic acid, Vanillic acid, Flavonoids	*E coli, S. aureus, P. aeruginosa*		(Rahman et al., 2015) (Kumar et al., 2013) (Yasmin et al., 2018)
16.	*Phyllanthus emblica L.*	Fruit Seeds	1, 2, 3-benzene-triol	*Salmonella enteritidis Salmonella typhi P. aeruginosa, Chromobacterium violaceum, S. aureus, Serratia marcescens*		(Nair et al., 2020) (Patel et al., 2020)
17.	*Swertia chirata Roxb.*	LeavesStem , Roots	Alkaloids, Coumarin, Glycosides, Steroids, Quinones, Flavonoid, Terpenoids	*E. faecalis, P. aeruginosa, S. aureus, K. pneumonia*		(Manjulika et al., 2016) (Khan et al., 2018) (Subedi and Karki, 2018)
18.	*Viola odorata L.*	N/A	Saponins, Terpenes, Tannins, Alkaloids, Flavonoids, Glycosides, Steroids	Ethanolic extracts *B. cereus, E. coli, B. subtilis, K pneumonia, M. luteus.*		(Aslam et al., 2018) (Das et al., 2021)

***Momordica charantia* L. (Bitter melon)**

This plant belonging to the family Cucurbitaceae is available with the common names of bitter melon, bitter cucumber, or bitter gourd in Africa, Asia, and the Amazon. It's highly famous for curing sort of skin diseases. The main components of its leaves and fruits, effective for multiple ailments have been observed to contain phenolic and saponins (Lopes et al., 2020). However, different plant parts have the crucial potential for controlling diabetes, the growth of tumors, anti-viral particles causing severe infections of measles and hepatitis, and other menstrual health issues (Nagasawa et al., 2002). The most prominent bacterial pathogens including *Staphylococcus aureus*, *Pseudomonas aeruginosa,* and *Escherichia coli* could be better controlled by extracts *of M. charantia* (Mwambete et al., 2009). Further investigation by Agyare et al. (2014) revealed that terpenoids present in the plant extract are responsible for inhibiting the non-mevalonate pathway that could indirectly block the synthesis of bacterial cell membranes (Fig. 4) (Table 1).

***Myrianthus arboreus* P. Beauv. (Giant yellow mulberry or Monkey fruit)**

This is one of the essential medicinal plant of the family Cecropiaceae which is included in the emergently growing vegetation of Ghana and the surrounding forests of African zones. Leafy extracts are very effective in various health problems such as diarrhea, dysmenorrhea, dysentery, incipient hernia, boils, and wounds which are caused by bacteria. In case of skin problems, linoleic acids as the chief composition of its oil can better manage the impermeability of skin to water and safely control such bacterial infections (Agyare et al., 2009).As well as, bark and leaf extracts of Myrianthus have been reported to be significantly effective (78.6%) against multiple bacterial strains of *Enterobacter aerogenes*, *Esrichia coli*, *Klebsiella pneumoniae*, *Providencia stuartii* and *Pseudomonas aeruginosa* (Seukep et al., 2015) (Fig. 4 (Table: 1).

***Onosma bracteatum* Wall. (Gaozaban)**

The cell wall of *Onosma bracteatum* (universally known as Gaozaban) comprises effective chemicals including alkannin, ferulic acid, vanillic acid, and essential flavonoids with pharmacologic importance. It is used as the basic ingredient of many Ayurvedic formulations in different parts of world (Rahman et al., 2015)to cure human problems including constipation, chronic diarrhea, dyspepsia, dysentery as well as heart and brain issues (Rao et al., 2003).. The leafy extracts of *O. bracteatum* were reported to be most effective against *E coli*, *S. aureus,* and *P. aeruginosa* by Kumar et al. (2013) and Yasmin et al. (2018). The leaves and stems of this herb can act as a potential drinking constituent (called the Joshanda) for the cure of bronchitis and asthma (Patel et al., 2008) (Table: 1).

Phyllanthus emblica **L. (Amla)**

Another widely used herbal plant: *Phyllanthus emblica* with the common name of Amla was reported to exhibit the 1, 2, 3-benzene-triol as an active biomolecule which in the form of its fruit extract indicated exceptional antimicrobial effect against *Salmonella* strains of species: *enteritidis* and *typhi* (Nair et al., 2020). The seed extracts of the plant exhibited antibacterial action against *P. aeruginosa, Chromobacterium violaceum*, *S. aureus,* and *Serratia marcescens* (Patel et al., 2020) (Table: 1).

Swertia chirata **Roxb. (Bitter stick)**

One of the popular members of the family Gentianaceae is *Swertia chirata* which plays a critical role as a traditional medicine to cure digestive issues, fever, loss of appetite, diabetes, and many skin problems due to its bitter toxicity (Aleem and Kabir, 2018). Moreover, ingredients of *S. chirata* exhibited an active role against *E. faecalis*, *P. aeruginosa*, *S. aureus,* and *K. pneumonia* (Manjulika et al., 2016; Khan et al., 2018; Subedi and Karki, 2018) (Table: 1).

Viola odorata **L. (Sweet voilet)**

Among the herbal medicines, the significance of *Viola odorata* can't be ignored as it is highly effective in various health issues the most common including the common cold, cough, headache, fever, dysuria, constipation, dyspnea, palpitation, epilepsy, insomnia, and multiple skin infections (Feyzabadi et al., 2018). The antibacterial action of *V. odorata* in the form of ethanolic extract has been revealed by Aslam et al. (2018) against the five most dominating pathogenic strains including *B. cereus*, *E. coli*, *B. subtilis*, *K pneumonia*, and *M. luteus.* However, saponins, terpenes, tannins, alkaloids, flavonoids, glycosides, and steroids are declared as potential phytochemicals (Das et al., 2021) (Fig. 4) (Table 1).

Conclusion

Although pathogenic bacteria prevail worldwide, their antibiotic properties persist, imposing a serious threat to the medicinal industry. To control the current scenario, understanding of key mechanisms of bioactive compounds is becoming a major challenge for the scientific community. However, the role of herbal plants in this perspective cannot be ignored which can be the key solution for the development of therapeutic drugs to be effective against multifarious communities of bacteria. As only a considerable amount of phytochemical ingredients have been investigated yet, further efforts for the screening and exploring of the bioactive chemicals along with the recognition of suitable molecular mechanisms are in urgent demand, for the benefit of the global population.

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Chapter 13

Herbal Treatment of *Salmonella* Pullorum Infected Broilers with Cinnamon: A Comprehensive Review

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ABSTRACT

The poultry industry plays a significant role in the country's GDP, being a major agricultural stakeholder. The presence of certain viruses and bacteria can lead to fatal diseases in poultry. One of the major bacterial diseases is salmonellosis, which has a high morbidity and mortality rate causing significant economic losses all over the world. The losses are exacerbated by an emerging antibiotic/ antimicrobial resistance. Being a global threat, it is crucial to carefully choose antibiotics or shift to antibiotic alternatives. Cinnamon and its derivatives may be a viable alternative to antibiotics for treating salmonellosis due to their antimicrobial properties. Cinnamon possesses antioxidant, antidiabetic, antifungal, and antibacterial properties, and can replace the irrational use of different antibiotics to treat various *Salmonella* infections including Pullorum disease. This chapter provides a comprehensive overview of cinnamon's pharmacological properties in preclinical and clinical investigations against bacterial infection and highlights the crucial need for additional research to provide a thorough and definitive conclusion for its ideal application in the treatment of *Salmonella* Pullorum infection in poultry.

KEYWORDS
Salmonella Pullorum, Cinnamon, Phytochemical, Antimicrobial Resistant, Poultry.

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INTRODUCTION

The poultry industry is responsible for providing a significant portion of the protein requirement and a source of livelihood in numerous countries, including Pakistan. In the past decade, this industry has been affected by various diseases. The major concern in this sector is Pullorum disease, mainly caused by *Salmonella* Pullorum (*S.* Pullorum) (Javed et al., 2018). This disease occurs at a very young stage about 2-3 weeks of age. The chicks that survive the disease outbreak and even do not show any clinical signs and symptoms become carriers for the spread of the disease to other flocks or even to consumers (Collett et al., 2020). The morbidity or mortality in the chicken flock due to Pullorum disease is very high and it is mainly dependent on the flock's age, management, nutrition, exposure rate, and disease stress in the flock (Berhanu and Fulasa, 2020). *S.* Pullorum is a motile, asporogenous, rod-shaped bacterium in the family Enterobacteriaceae and the tribe Salmonellae. This is characterized by causing Pullorum disease in poultry and can persist in the environment for months to several years when conditions are favorable. The extracellular lipopolysaccharide in *Salmonella* is an important tool of pathogenesis that interacts with the immune system of the respective host to induce an inflammatory response and septic shock including fever that eventually causes death (Coburn et al., 2007).

The multidrug-resistant bacterial infections are increasing day by day due to the irrational use of antibiotics. The rising global problem of antibiotic resistance requires suitable alternatives or substitutes in comparison to the currently available antibiotics. An emerging strategy to cope with this issue is the use of antibacterial substances acquired or developed from natural resources. Specifically, for the treatment of *S.* Pullorum, florfenicol is usually used in field practice. The minimum withdrawal period for florfenicol is around 25 days, and if it is used excessively in salmonella cases, there will be a higher chance of antibiotic residue being transferred to the human body after consumption of contaminated meat. Cinnamon could be an alternative to treat salmonellosis due to its antimicrobial activities and it is also safe for human consumption. *Trans*-cinnamaldehyde which is obtained from the bark of cinnamon trees can be successfully used as an alternative antimicrobial compound against *S.* Pullorum. Besides its significant antimicrobial properties, *trans*-Cinnamaldehyde has many other therapeutic properties including its anti-diabetic, anti-inflammatory, and antioxidant effects (Singh et al., 2021). Cinnamaldehyde commonly known as "dar cheeni", an aromatic aldehyde, reported having antibacterial activity against a variety of foodborne pathogens. It is the main component of cinnamon bark, and possess good inhibitory effect on various bacteria and fungi (Doyle and Stephens, 2019). The cinnamaldehyde (a major portion of cinnamon extract) was previously evaluated as an antibacterial agent against various gram-negative bacteria. Therefore, understanding of the antibacterial mechanism of these derived compounds will aid in the development of new antibacterial substances (Utchariyakiat et al., 2016).

This chapter discusses various *Salmonella* virulence factors that are important in the pathogenesis of salmonellosis. These factors include the stages, mechanism of pathogenesis in conjunction with systemic infection, commonly used treatments, and a brief discussion of the characteristics of cinnamon and its application in the treatment of salmonellosis in poultry.

Salmonella Pullorum

S. Pullorum causes an acute disease in young chickens with high mortality known as Pullorum disease. Almost all birds of different breeds are susceptible to this disease. The Pullorum disease is more susceptible to young chicks aged less than 14 days, however, in adult birds, the disease can be present in chronic form. The clinical signs of pullorum disease may include less feed intake, dehydration, depression, and white watery diarrhea. Whereas early infected chicks show mortality without exhibiting any clinical sign of the disease. Furthermore, the reduced growth rate and poor feathers development are common in the surviving birds. In adult birds, the signs and symptoms are not shown but they act as a carrier. Pullorum disease also has zoonotic importance, like poultry products and by-products contribute a great deal to human salmonellosis (Snoeyenbos, 2019). Salmonellosis causes about 94 million food-borne cases annually (World Health Organization, 2015). *Salmonella* mainly causes gastroenteritis at a young age and shows a systemic infection, septicemia, and eventually death in immunocompromised or elder patients. Mainly salmonellosis occurs by consuming different food items contaminated with various *Salmonella* serovars. These food items include eggs, chicken, or pork but nowadays, disease occurrence is increasing because of consumption of contaminated nuts, fruits, and vegetables (Ferrari et al., 2019). *Salmonella* in different healthy individuals can cause watery diarrhea, abdominal pain, nausea, vomiting, and fever which is termed as self-limiting gastroenteritis. Some affected individuals may suffer from profuse "cholera-like" diarrhea. However, in some individuals, diarrhea with blood and mucus is also reported. The infection is invasive and usually limited to the underlying tissue of the intestine (Manatsathit et al., 2002).

Transmission of *S.* Pullorum

S. Pullorum is mainly transmitted by two main sources of transmission in chicks, such as vertical transmission, and horizontal transmission as shown in Fig. 1. In horizontal transmission *S.* Pullorum shed through the feces of the chicken, contributes as a major source of transmission among chicks in a flock. The other sources may also include water, feed, and litter. The transmission through direct or indirect contact such as the respiratory route usually causes death at a very early age in chickens (Wales and Davies, 2020). The vertical transmission occurs when the contamination occurs in the eggshell membrane, albumen, and yolk. The pathogen localization in the ovule before the ovulation is also the main mode of vertical transmission. This transmission may result in embryonic death and chick mortality (Klyachko et al., 2007).

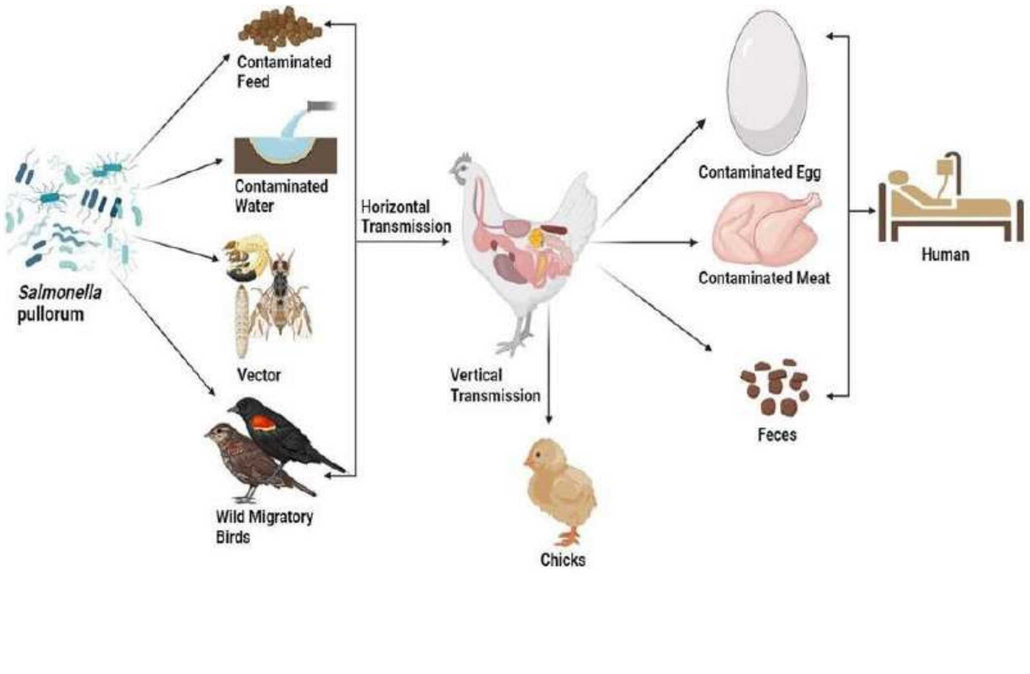

Fig. 1: Horizontal and Vertical Transmission of *S.* Pullorum

Salmonella Virulence Factors

The initial attachment of the bacterial cell to the host has a key role in the pathogenesis of that pathogens. In *Salmonella*, the different specialized structures are present on the bacterial cell wall. It has many virulence factors such as various types of secretion systems, many types of fimbrial and afimbrial adhesins, flagella, capsules and plasmid (Sora et al., 2021). The extracellular filamentous structure having the complex apparatus and the binding site at its tip is known as fimbriae. The fimbriae are mainly of three types, which are based on different assembly mechanisms. The fimbriae functions include biofilm formation, cell-cell attachment, intestinal persistence, and bacterial aggregation. Its numbers vary with the serovars, and its role depends on the type of serovars. *Salmonella* fimbriae plays an important role in understanding the new insight into *Salmonella* pathogenicity (Rehman et al., 2019). The *Salmonella* genetic structure reveals the cluster of genes localized in the chromosome region that mainly controls the virulence of pathogens known as pathogenicity islands. These genes are mainly acquired through horizontal transmission. The pathogenicity islands mainly consist of multifunctional virulence genes that are specific for their phenotype. The *Salmonella* Pathogenicity Island (SPI) has various types such as SPI-1, SPI-2, and so on. These SPIs have specific functions and roles in the pathogenicity of *Salmonella* for example SPI-1 encodes various genes for the invasion of the epithelial cells and plays a vital role in intestinal secretion and inflammatory response (Que et al., 2013).

Pathogenesis

The virulence factors including flagella, fimbrial adhesins, plasmids, and toxins facilitate the *Salmonella* to establish infection in the host. In the small intestine, the pathogen forms a biofilm, aggregates at the site of infection, and invades the intestinal cells. *Salmonella* infects and multiplies within the different types of cells including mononuclear phagocytic cells in the chicks (Setta et al., 2012). The digestive system is the principal site for the infection and the multiplication of *Salmonella. S.* Pullorum infection mainly targets the bursa of Fabricius in the chicks. The organism is ultimately taken up by the macrophages after the invasion from the intestinal mucosa and enters the main bloodstream causing bacteremia. In blood, *Salmonella* travels to the different body organs including the liver, lungs, kidney, and spleen. Through blood, the pathogen also travels and infects the reproductive organs in the chicks. Different organs show pathological changes. *Salmonella* forms the intracellular vacuole rather than the multiplication in the cytoplasm like other various pathogens (Jantsch et al., 2011). The macrophage engulfs the *Salmonella* in the lamina propria in sub-epithelial space. After the macrophages engulf the *Salmonella,* it causes the apoptosis of the macrophage (Yang et al., 2019). The clinical signs include white diarrhea which is a typical sign of the pullorum disease with high mortality. Affected chicks show generalized infection and swollen tissues including the spleen, liver, and kidney with different-sized hemorrhages in respective tissues (Islam, 2023).

Treatment

Commercial layers and broilers infected with pullorum disease can be treated by the application of antibiotics via oral or intramuscular route. However, antibiotic treatment of pullorum disease is contraindicated in the case of breeder flocks. The culling of pullorum-infected flocks is always recommended. For the treatment of systemic infections, it is suggested to use antimicrobial drugs like beta-lactams, aminoglycosides, and fluoroquinolones in recommended doses (Muller et al., 2018). The treatment of the infected birds is the only available option for preventing the transmission of the disease and decreasing the mortality rates. To control the infection in birds, antimicrobial drugs can be used orally or intramuscularly. Before the application of antimicrobials, the antibiotic sensitivity test is recommended to avoid the issue of antimicrobial resistance (AMR) (Gray et al., 2021). The presence of R-plasmid in *Salmonella* causes this bacterium to show resistance against multiple drugs including antimicrobials such as penicillin, oxytetracycline, aminoglycosides, and sulfa drugs, therefore, we have to make careful choices of antibiotic or have to shift to antibiotic alternatives to overcome the antimicrobial resistant (Singh et al., 2010). Cinnamon and its derivatives exhibit antimicrobial properties, suggesting their potential as alternative antibiotics for treating salmonellosis. Furthermore, these compounds are considered safe for human use.

Cinnamon and Its derivatives used as Natural Antimicrobial Agents

Cinnamon has been utilized as a spice as well as a perfume in rubbing oils during biblical times. Cinnamon was also used by Egyptians as a fragrance to preserve the bodies in the past years, however, due to its antibacterial, antiviral, and antifungal properties, it is being used in the fields of medical, veterinary, and agriculture as a bactericidal, and fungicide during recent years (Yang et al., 2019). The cinnamon plant contains different bioactive compounds and essential oils in its leaves, bark, and root. Cinnamyl acetate and coumarin are found in the fruit of cinnamon. Eugenol, cinnamaldehyde, and eucalyptol are predominantly found in the leaf oil, while trans-cinnamaldehyde, camphor, linalool, and benzoic acid, is the primary or fundamental compound present in the cinnamon bark or root bark oil (Basavegowda and Baek, 2022). In recent studies, edible antimicrobial films containing cinnamaldehyde has caused the inactivation of the foodborne pathogens by various mechanisms (Benbettaïeb et al., 2019; Zhu et al., 2014, 2020). The presence of non-pathogenic organisms causing food spoilage is also reduced in cinnamaldehyde incorporated antimicrobial films. So, various derivatives of cinnamaldehyde can be used as natural antimicrobial agents against a variety of microorganisms in a cost-efficient manner. In recent studies, *Trans*-cinnamaldehyde is used for further development of its various derivatives Apart from mechanism of actions, many studies have been carried out to test the antibacterial properties of *trans*-cinnamaldehyde and its derivative compounds (Doyle and Stephens, 2019; Usai and Di Sotto, 2023). The antibacterial mechanism of cinnamon is shown in Fig. 2.

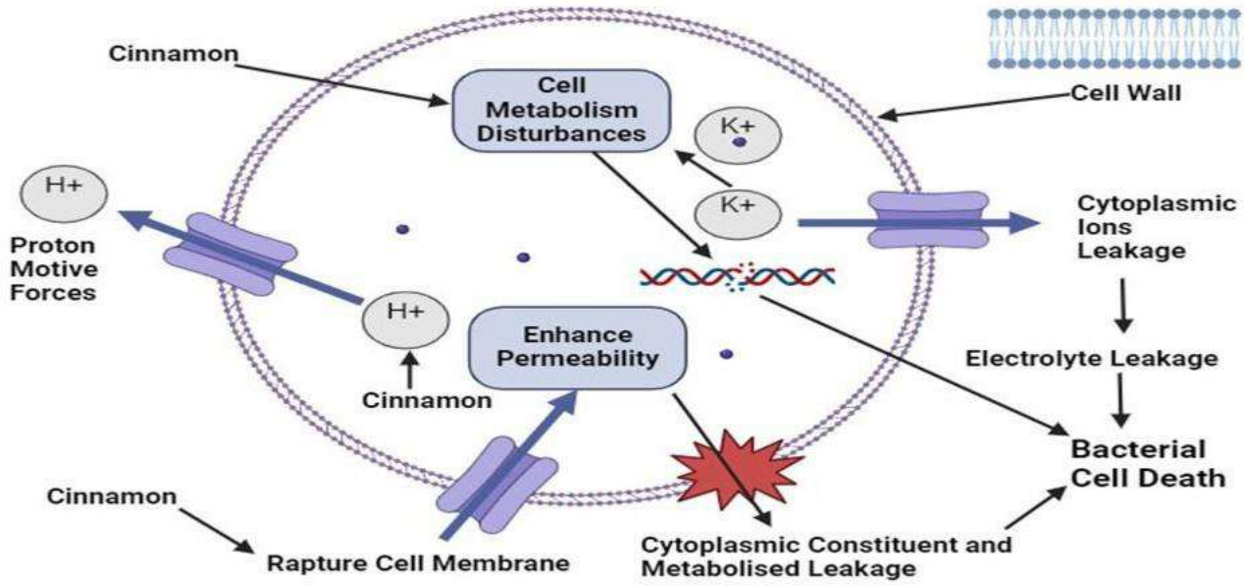

Fig. 2: Cinnamon's Antibacterial Mechanism of Action

Cinnamaldehyde

The main source of cinnamaldehyde is the species from the genus *Cinnamomum,* which is found in many states of India. Cinnamaldehyde is widely found in majority of the Indian food, cosmetic, and medicinal products. So, it can be stated that cinnamaldehyde is highly consumed by the human population in India (Jayaprakasha and Rao, 2011). Cinnamaldehyde is "Generally Recognized as Safe" (GRAS) by the United States Food and Drug Administration (FDA) and the Council of Europe has given "A" status to Cinnamaldehyde which means it may be utilized in foodstuffs (Doyle and Stephens, 2019). Besides its uses in foodstuffs, cinnamaldehyde also possesses various medicinal, and Ayurveda properties such as antibacterial, antifungal, antidiabetic, and antioxidant properties of cinnamon. Cinnamon has been employed as an anti-ulcer, anti-inflammatory, and anticancer agent. The risk of colon cancer can be decreased by cinnamon by enhancing colon health. Cinnamon acts as a coagulant to stop bleeding. Additionally, cinnamon promotes tissue regeneration and improves uterine blood circulation (Murtaza et al., 2024).

Yang et al. (2015) studied, *the antiplatelet and anti-thrombotic properties of* cinnamaldehyde. The cardiovascular effects including lowering of blood pressure and left ventricular systolic pressure have also been observed in some studies using anesthetized rats. After contractions stimulated by the application of norepinephrine, PGE2α, and potassium, cinnamaldehyde caused rat aorta to relax. These studies suggest that cinnamaldehyde shows cardiovascular effects as it carries out signals beyond the receptors (Yang et al., 2015).

Cinnamon (*Cinnamomum zeylanicum*) is said to be, one of the oldest medicinal plants. It is a valuable spice that is currently being used across the world. It is native to Sri Lanka and South India. Important chemical constituents of cinnamon are cinnamaldehyde, eugenol, and Tran's cinnamaldehyde. The specific fragrance and different biological activities of cinnamon are because of these chemicals. E-cinnamaldehyde is a part of essential oil extracted from cinnamon and possesses an anti-tyrosinase activity (Suriyagoda et al., 2021). A study conducted by Chao et al. (2008) evaluated the effects of cinnamon and reported the antibacterial activities of this herbal plant. Another study was conducted by Mathew and Abraham. (2006) evaluated the antioxidant properties of cinnamon and found them significant in their studies. Similarly, Tanwar (2019), revealed the anti-diabetic, anti-ulcer, and anti-inflammatory activities of cinnamon. Feed intake is also reported to be improved by the inclusion of cinnamon alone or in combination with essential oils in the poultry diet. Didehdar et al. (2022) evaluated the efficiency of cinnamon in terms of protecting against various kinds of bacteria including *S. aureus, E. coli, S. epidermis, P. aeruginosa, H. pylori, E. faecalis, Salmonella* spp., and *parahaemolyticus*. Due to its various medicinal and preventive properties, the importance of cinnamaldehyde is increasing day by day (Shariati et al., 2022). Cinnamaldehyde has been shown to treat complex metabolic conditions including type-2 diabetes.

In a study conducted on mice, cinnamaldehyde was used to observe the changes in parameters like excessive eating due to a high-fat diet, levels of digestive hormones, inflammation, and breakdown of adipose tissue. The microorganisms including *Lactobacillus, Bifidobacteria*, and *Roseburia* were collected and counted from cecal contents after giving cinnamaldehyde to the mice. It was found that cinnamaldehyde inhibited the accumulation of lipids and also changed the expression of genes toward lipolytic phenotype on preadipocyte cell lines when it was used at the concentration of 40 μM

(Li et al., 2013). When administered *in vivo*, cinnamaldehyde not only caused a decrease in high-fat diet-induced weight gain, but also decreased the leptin and leptin/ghrelin ratio in circulating blood. Moreover, changes in the serum levels of free fatty acids and glycerol were also observed due to lipolytic roles of cinnamaldehyde. At the genetic level, there was an increased expression of the lipolytic gene in the white adipose tissue and also an increased expression of an anorectic gene in the hypothalamus due to the use of cinnamaldehyde (Khare et al., 2016). A decrease in the inflammatory genes' expression was observed due to cinnamaldehyde in the visceral fat tissue and also the serum levels of interleukin-1β were fall. However, no change was observed in the population of selected gut microbes obtained from the cecal contents. It was concluded from the study that cinnamaldehyde can promote the lipolysis of adipose tissues, can decrease the inflammation and fasting-induced weight gain, and can also play a role in stabilizing the levels of leptin and other energy-related hormones when given to high-fat diet-fed mice (Tuzcu et al., 2017). Cinnamaldehyde and its associated compound possess various bioactive characteristics as discussed in Table 1.

Table 1: The Bioactive Characteristics of Cinnamaldehyde and Associated Compounds

Property/Effect	Compound	Mechanism of Action	Description	Reference
Antibacterial Activity	Cinnamaldehyde	Disrupts the integrity of bacterial cell membranes, Inhibiting bacterial growth.	Effective against both *B. subtilis and E. coli* bacteria.	(Doyle and Stephens, 2019)
Cardiovascular Effects	Cinnamaldehyde	Inhibits the aggregation of platelets and promotes Vasodilation through the release of nitric oxide.	Lowers blood pressure and exhibits antiplatelet and vasodilatory effects.	(Lu et al., 2022)
Antidiabetic Effects	Polyphenols	Enhances the body's sensitivity to insulin and reduces cholesterol synthesis.	Improves insulin sensitivity and lowers cholesterol levels.	(Zhang et al., 2008)
Hematological Effects	Thymol and carvacrol	Stimulates the production of red blood cells but may reduce the count of immune cells.	Stimulates the generation of red blood cells while potentially decreasing immune cell counts.	(Saadat Shad et al., 2016)
Hepatoprotective Effects	Carvacrol and thymol	Protects the liver by lowering serum levels of ALT and AST enzymes.	Safeguards the liver by reducing serum ALT and AST enzyme levels.	(El-Sheikh et al., 2022)
Antioxidant Effects	Cinnamaldehyde	Acts as an antioxidant, shielding cells from oxidative stress.	Protects cells from damage caused by oxidative stress.	(Azab et al., 2011)
Anti-inflammatory Effects	Cinnamaldehyde	Suppresses pro-inflammatory pathways.	Exhibits anti-inflammatory properties by inhibiting signaling pathways.	(Murtaza et al., 2024)
Neuroprotective Effects	Cinnamaldehyde	Enhances antioxidant defenses and mitigates oxidative stress.	Protects nerve cells by enhancing antioxidant defenses.	(Lv et al., 2017)
Lipid-lowering Effects	Polyphenols	Inhibits enzymes involved in the synthesis of cholesterol.	Blocks enzymes responsible for cholesterol synthesis, reducing lipid levels.	(Chao et al., 2008)
Anticancer Effects	Cinnamaldehyde	Inhibits the proliferation of cancer cells and induces Programmed cell death.	Suppresses cancer cell growth and triggers Apoptosis.	(Murtaza et al., 2024)

Effect of Cinnamaldehyde on Meat Quality and FCR

Several parameters like weight loss on cooking, intensity of red and sheer force of breast meat of birds fed with phytogenic based diets have been evaluated in many previous studies, discussed below. Effects of cinnamaldehyde on meat quality and FCR of poultry have been illustrated in Fig. 3. A study was conducted in which birds were given diets having carvacrol and thymol and the results showed an increase in intensity of red and sheer force of breast meat of birds (Prioriello, 2020). According to a study conducted by Mastromatteo et al. (2009) the increase in red intensity will negatively affect the sensory evaluation scores and may eventually decrease the utilization rates of such breast meat. However, these findings were opposite to that of previous study as they found that the use of thyme essential oil and thymol caused a decline in the sheer force in breast meat (Rimini et al., 2014). Moreover, studies showed that no effect was observed on the oxidant status of breast meat of birds fed with phytogenic or zinc bacitracin in diet. In a study, a prominent increase in the activity of Glutathione S-transferases and reactive oxygen species was observed after cooling of meat for 4 days. This increase in activity of enzymes was believed as a defending mechanism against the reactive oxygen species (ROS) (Reis et al., 2018). The phytogenic feed additives prevented the formation of ROS because the ROS levels were found to be same in both control groups and PFA treated groups. The peroxidation of lipid was found to be elevated in the birds given phytogenic-based diets. The performance of Glutathione S-transferase also remained unchanged in the birds fed with a phytogenic-based diet as Glutathione S-transferase has role in inhibiting the lipid peroxidation. So, it was concluded from the study that the lipid peroxidation caused by freezing temperatures was not controlled by the thymol and carvacrol-based phytogenic diets (Karásková et al., 2015).

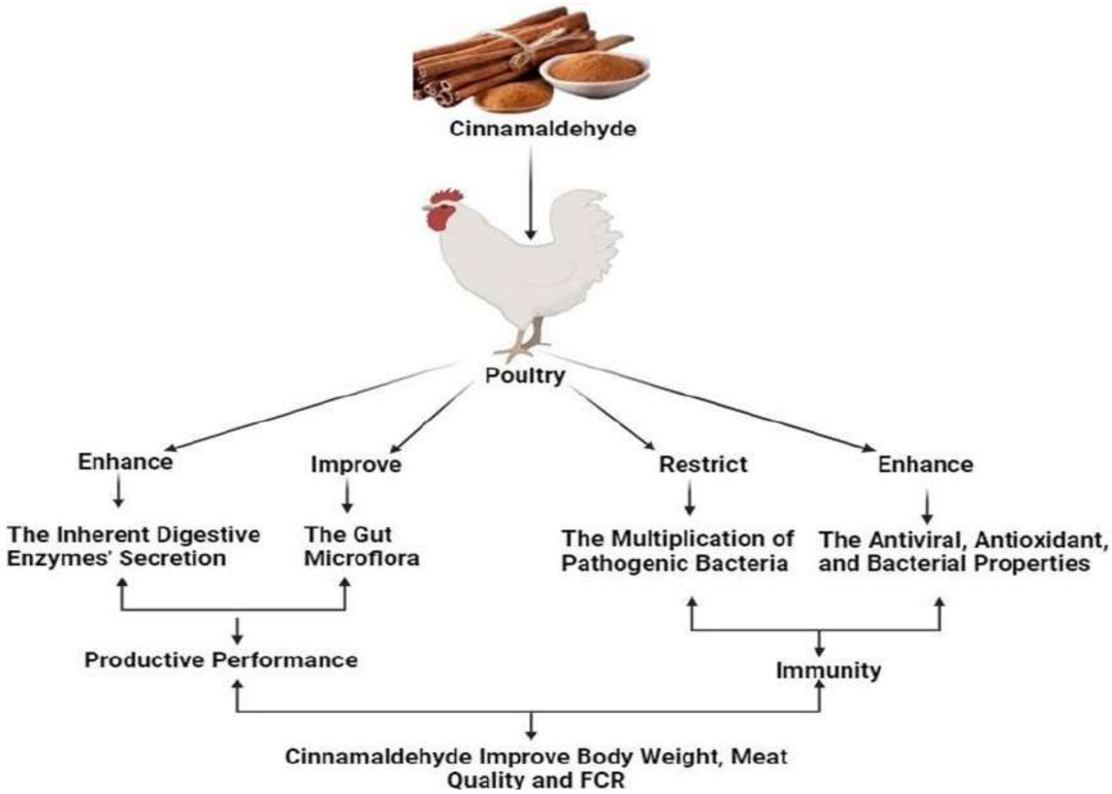

Fig. 3: Cinnamaldehyde Effect on Body Weight, meat quality and FCR.

Conclusion

Cinnamon, a well-known phytochemical plant, is widely used in medicine worldwide. It contains a number of components that exhibit significant antibacterial effects on various bacterial infections, including *S.* Pullorum. Cinnamon bark, oils, and its active compounds have been proven to be safe for consumption without any adverse effects. Cinnamon and its derivatives pose antimicrobial properties and can be used as an antibiotic replacement for patients infected with *S.* Pullorum. Various cinnamon derivatives have been evaluated for health benefits, but still more research is needed, for its generalized use against the bacterial infections.

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Chapter 14

Effect of *Capparis spinosa*, *Syzygium aromaticum* Plant Extracts on Some Bacteria and Parasites in Basrah Province/Southern Iraq

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ABSTRACT

Cysticercosis is a parasitic tissue infection caused by larval cysts of the tapeworm. These larval cysts are a major financial loss in most low-income countries. Two Plant extracts: *Capparis spinosa* and *Syzygium aromaticum* were applied as antiparasitic to *Cysticercus tenuicollis*.
Which showed that *Syzygium aromaticum* extract was more effective against *E. coli* and less effective against *S. aureus*. While *C. spinosa* extract revealed more effectiveness against *S. aureus* and less effective against *E. coli*.
SDS-page for untreated and treated cysts with plant extracts were applied to separate proteins of larval stage *Cysticercus tenuicollis*. In *vitro* and in *vivo*, plant extracts bands ranged from 17- 67 KD and 17 - 67 KD, respectively. Plant extracts of *Capparis spinosa* did not show any bands. There was a clear effect on protein cotenants of *C. tenuicollis* which was treated with two plant extracts *C. spinosa* and *S. aromaticum* in *vitro* and in *vivo* by SDS- PAGE compared with untreated.
GC-mass analysis was applied to detect a chemical compound in liquid and scolex of Cysticercus *tenuicollis* exposed to two plant extracts. And scanning electron microscopy was applied to characterize the morphological changes of scolex and membrane cyst. The result revealed differences in morphological characters between the scolex and membrane cyst during exposure to plant extract compared with control.

KEYWORDS			
Capparis spinosa, Syzygium aromaticum, Plant Extracts	Received: 07-Jun-2024 Revised: 15-Jul-2024 Accepted: 25-Aug-2024	USP	A Publication of Unique Scientific Publishers

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INTRODUCTION

Many excellent studies about the supposed effects of plants were found without proof that they were true (Klimpe et al. 2011). As a result, it is vital to test plants again to see if they are efficient against various bacteria and parasites since many have evolved resistance to various chemotherapeutics. Recently, research has been resurgent into plant antiparasitic benefits (Schmahl et al. 2010).

Most of the animals used in the research were mice and rats; however, a few researchers used in vitro investigations or non-typical lab animals (Bryda, 2013).This highlights the need for more investigation into the effectiveness of certain plants in combatting parasites in farm animals, whereas comparatively little research has been conducted on their effectiveness against parasites in humans (Mehlhorn et al. 2011).

According to Benseghir and Seridi (2007), the *Capparis spinosa* herb is a long-lived plant that belongs to the Capparidaceae family. Vegetative components of *Capparis spinosa* have antioxidant, antifungal, antihepatotoxic, anti-inflammatory, antiallergic, antihistamine, chondroprotective, hypolipidemic, and photoprotective properties (Bonina et al. 2002). In addition, *C. spinosa* contains biogenic salts including potassium, magnesium, calcium, sodium, zinc, copper, and phosphorus, essential oils, fatty acids, steroids, glucosinolates, carotenoids, and tocopherols (Tlili et al. 2009). The protein-rich plant contains bioactive salts including potassium, magnesium, calcium, sodium, zinc, copper, and phosphorus (Rodrigo et al. 1992).

Syzygium aromaticum, also known as *Eugenia cariophylatis*, is a medium-sized tree that is added cloves. For hundreds of years, the Asian region's economy and agriculture flourished due to the clove trade and the hunt for this prized spice. Because they are employed in so many aspects of everyday life, cloves are significant to people's lives around the world (Kamatou et al. 2012).

Over generations people have utilized this plant as a medicinal and food preservation herb, mostly as an antioxidant with antibacterial qualities. The antibacterial, antifungal, antiviral, and anticarcinogenic properties of this herb have been shown by several recent investigations. Clove is particularly popular due to its antioxidant and antibacterial properties (Shan et al. 2005).

Plant Extracts

Capparis spinosa

Capparis spinosa is a xerophytic plant that grows at cooler alpine heights and dry deserts. It is a member of the Capparidaceae family (Pugnair, 1989). It has huge, white to pinkish blooms and round, meaty leaves (Ramezani et al. 2008).

There are just two species that can be found in Iraq: *C. spinosa* L. and *C. cartilaginea* (Blakelock and Townsend, 1980). Moreover, *Capparis* L. belongs to the Capparoideae subfamily (Capparidaceae) (Linnaeus, 1753; 1754). It is composed of more than 250 species from various kinds that can be found in tropical and subtropical areas like southern region of America, Europe, and Africa (Willis, 1988; Inocencio et al. 2006).

The many beneficial parts of *C. spinosa*, from its young shoots and flower buds to its leaves and seeds, are used in medicine, cooking, and cosmetics (Aliyazicioglu et al. 2013). Different parts of *C. spinosa* are employed in traditional medicine for treating various diseases (Eddouks et al. 2004; Mishra et al. 2007). Arab traditional medicine treats spleen, stomach, skin, ear, kidney, and hepatic disorders using *C. spinosa* leaves, roots, and buds (Sher and Alyemeni, 2010 Tlili et al. 2011). It has traditionally been used to treat paralysis, convulsions, and gum disease. The fruits have long been used to treat diabetes, migraines, fever, and rheumatism (Rivera et al. 2003; Jiang et al. 2007). Iranian traditional medicine has used C. spinosa for antimalarials, diuretics, and tonics for years (Miraldi et al. 2001; Ahvazi et al. 2011; Mosaddegh et al. 2012). *C. spinosa* leaves treat analgesia, hemorrhages, rheumatics, and inflammation (Tliliet al. 2011). Asthmatics and coughers may benefit from *C. spinosa* (Jiang et al. 2007).

C. spinosa has different pharmacological performances like anti-hepatotoxic, antioxidant, anti-diabetic, anti-parasite, anti-bacterial, anti-fungal, anti-sclerosis, immunostimulant, anti-cancer. *C. spinosa* has been used in phytomedicine for anti-inflammatory and anti-arthritic properties (Tlili et al. 2011; Al-Said et al. 1998; Feng et al. 2011). Canapés in traditional economies include pickled flower buds, immature fruits, and shoots with olives, cheese, and other vegetables (Sher et al. 2010). The GC MASS analysis also found chemical components in *C. spinosa's* roots, fruits, and seeds that support caper's use in traditional medicine (Sher and Alyemeni, 2010).

Fig. 1: *Capparis spinosa* plant

Syzygium aromaticum

Syzygium aromaticum or clove is the dried flower bud of a plant in the Myrtaceae family that is native to the Maluku islands of Indonesia but is now widely cultivated elsewhere across the world (Batiha et al., 2019). The clove tree's commercial element is its leaves and buds, and flower buds grow four years after planting. After that, they are picked before they bloom either by hand or with a natural phytohormone (Diego and Wanderley,2014). Clove trees are evergreens that grow 10–20 m. It has large oval leaves and numerous terminal clusters of crimson blooms. Clove buds start pale and become green. When they are ready for collection, their color changes to brilliant crimson. The length of a clove, when plucked, ranges from 1.5 to 2 cm. Its calyx consists of four sepals that spread out and four petals that remain closed, creating a small ball in the center. Cloves, which have a powerful perfume and a spicy, pungent flavor, are used to flavor various foods, particular meats, and baked goods (Yousif, 2015).

The flower species is well-known, and the warm area is home to the carnation tree, which is tiny and evergreen and produces a wide variety of crimson blossoms. Before the drought, the flower buds are green or red, and they change into a screw-shaped, easily fractured structure (Azeredo and Soares, 2013). Clove is a moderate variety of cinnamon with an astringent, anti-bulging aroma. Its oil is therefore widely recognized for its medicinal and spasticity properties, as well as its efficacy in treating tooth pain (Lane et al., 1991). South-east Asians have utilized clove oil for thousands of years as a cure for most tropical ailments. It also lowers Nematoda survival by 50% compared to the control group due to more dead eggs (Meyer et al. 2008).

S. aromaticum is regarded as one of the most valuable spices; it is mostly processed into clove oil, which is widely used in medicine due to its antioxidant, antibacterial, antinociceptive, antiviral, and anesthetic characteristics linked to the presence of eugenol as its predominant ingredient (Cortés-Rojaset al., 2014). According to Teles et al. (2021), *S. aromaticum's* essential oil exhibits antimicrobial, antioxidant, and antitrypanosomal activity, with eugenol (53.23%) serving as the primary material that was confirmed. This results from the chemical elements included in its plant-based products, such as flavonoids and total phenolic compounds.

Fig. 2: *Syzygium aromaticum*

Preparation of Plant Extraction

Plants of *C. spinosa* and *S. aromaticum* were purchased from a natural plant nursery located in the Basrah area. As previously said, they were cleaned, dried, and ground with mortal (Hamza, 2005).

For *C. spinosa* extraction, 100 gm plant leaves were combined with 200 ml ethanol in a beaker for 30 min with a magnetic stirrer and centrifuged at 3000rpm for 15 min. After that, the plant material was placed on glass plates and oven-dried at 60°C (Hamza, 2005).

Condensed solvent (dichloromethane) was added to a distillation flask and 200g of the plant material for *Syzygium aromaticum* was put in a Soxhlet thimble holder (Wenqiang et al. 2007).

GC-Mass Analysis

GC-Mass analysis was done briefly, the cyst isolated from the affected organ was transferred to the Basrah Oil Company lab for GC-Mass analysis.It was 30 m long, 0.32 mm wide, and 0.25 m thick fused silica capillary column (DB5MS). It was composed of phenyl and 95% methyl polysiloxane. The sample was injected into the capillary column in split mode, maintaining a 40°C temperature differential between the injector and detector. For the first 5 min, the column was heated at 40 °C and then it was heated at 28 ℃ each min until it reached its final temperature at 280 °C (Al-Ataby, 2022).

Gas chromatography mass spectrometry (GC-Mass) combines the properties of substances inside a test sample, as described by (Kell et al., 2005). The current study used GC-Mass analysis to identify the parasite sample's constituent chemicals. The sample was transferred to Basrah Oil Company lab to analyses the sample (Nahran-Omer).

The study used two distinct plant extracts, *C. spinosa* and S. aromaticum, and found that both extracts exhibited a similar amount of Phenol. The alcohol content, in contrast, was highest in *S. aromaticum* in contrast with *C. spinosa* is present. Nevertheless, *C. spinosa* contains a substantial number of ketones. Compared to *C. spinosa*, S. aromaticum possesses more organic acid, cyclic compounds, ester, and unsaturated fatty acids. Conversely, *C. spinosa* did not contain eugenol, aldehyde, steroids, or saturated organic compounds, which were exclusively detected in *S. aromaticum*.

Disc Diffusion Method

There are two different types of plant extract were used: *S. aromaticum*and *C. spinosa* against two types of bacteria: *S. aureus* and *E. coli* in six concentrations:1,5, 10,25, 50 and 100 mg/ml for each plant extract. The findings indicated that S. aromaticum exhibited a greater antibacterial effect against *E. coli* than *S. aureus*. Conversely, *C. spinosa* demonstrated a higher antibacterial effect against *S. aureus* than against *E. coli*, as shown in Tables (1 and 2).

Table 1: *Syzygium aromaticum* extract's antibacterial efficacy against *Staphylococcus aureus* and *Escherichia coli* bacterial isolates

Syzygium aromaticum	Types of bacteria	viability cm Inhibition zone (cm)					
		1 mg/ml	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml	100 mg/ml
	Staphylococcus aureus	2.4	2.4	2.6	3	2.4	0
	Escherichia coli	2.3	2.5	2.7	2.7	2.9	3.1

Table 2: *Capparis spinosa* extract's antibacterial efficacy against *Staphylococcus aureus* and *Escherichia coli* bacterial isolates

Capparis spinosa	Types of bacteria	viability cm Inhibition zone (cm)					
		1 mg/ml	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml	100 mg/ml
	Staphylococcus aureus	0	1.4	1.4	1.3	1.3	1.2
	Escherichia coli	0	1.2	1.2	1.3	1.3	1.3

Bacterial Viability by Primary Tissue Culture

After being stained with acridine orange stain, *S. aureus* (A) is treated with *S. aromaticum* (a), *C. spinosa* (b), in the Figure (3). The dark red cells in these Figure represent the pancreatic cancer cells that were treated to plant extracts *S. aromaticum* and *C. spinosa*.

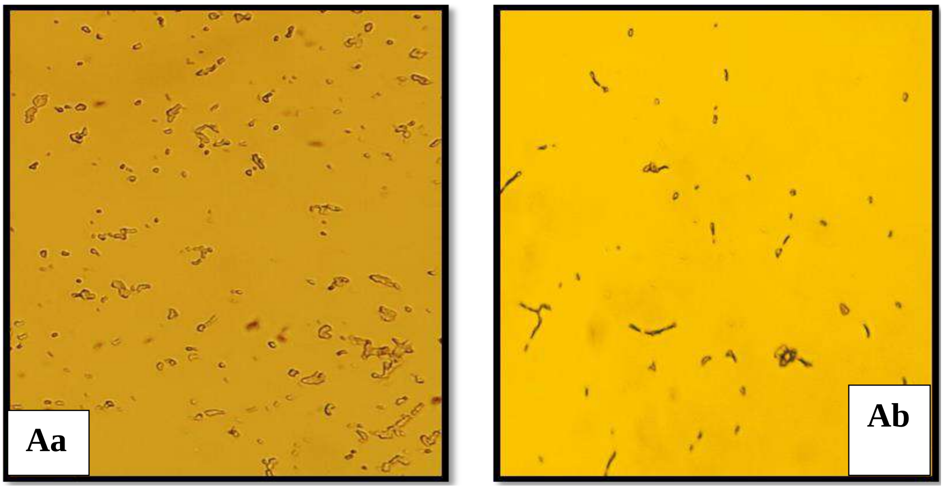

Fig. 3: Bacterium A (*S. aureus*) treat with (Aa, Ab)

A: Bacterium (*S. aureus*), a: *Syzygium aromaticum*(Cloves), b:*Capparis spinosa*

While the Figures (Ba, Bb) depict bacteria *B. cereus*(B)being treated with *S. aromaticum*(a), *C. spinosa*(b), after being staining acridine orange stain. These Figure depict the amount of pancreatic cancer cells that were exposed to plant extracts *S. aromaticum* and *C. spinosa*, with the cells being dark red.

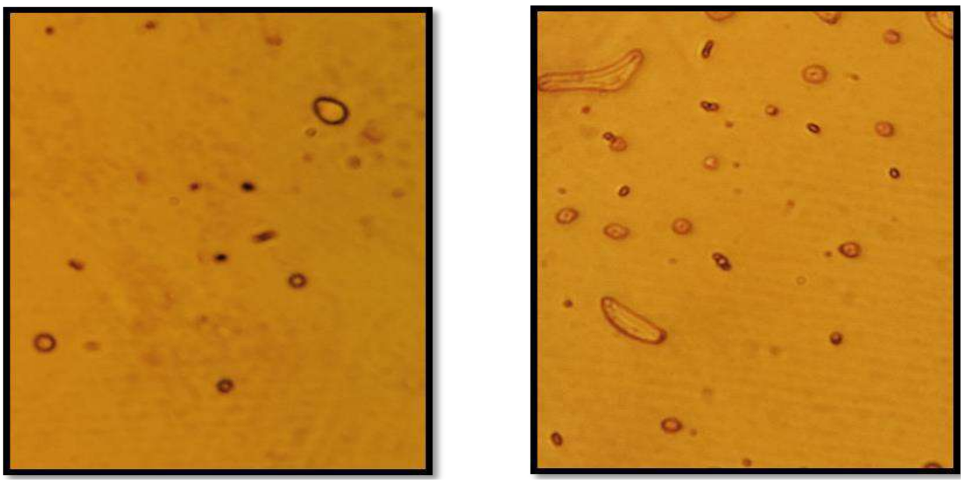

Fig. 4: Bacterium B (*B. cereus*) treat with (Ba, Bb)

B: Bacterium (*B. cereus*), a: *Syzygiumaromaticum*(Cloves), b:*Capparis spinosa*.

Additions shown are the *E. coli* (C) treated with *S. aromaticum*(a), *C. spinosa* (b), after being stained with acridine orange stain in Fig. 5. The cells' dark red color denotes the pancreatic cancer cells that were treated to plant extracts *S. aromaticum* and *C. spinosa*.

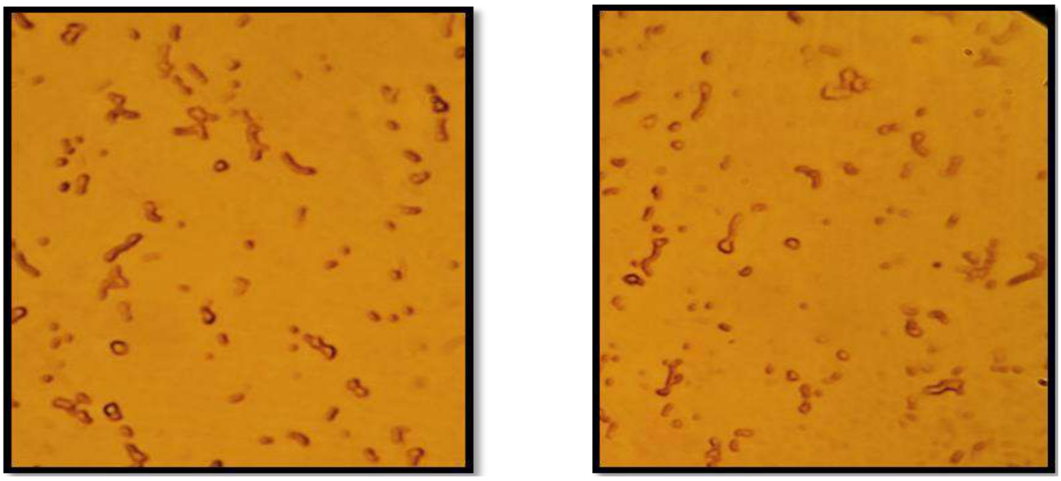

Fig. 5: Bacterium C (*E. coli*) (Ca, Cb)

C: Bacterium (*E. coli*), a: *Syzygium aromaticum*(Cloves), b:*Capparis spinosa*

Additionally, the treatment of *S. typhimurium* (D) with *S. aromaticum* (a), *C. spinosa* (b) after staining them with acridine orange stain is explained in Figures (6). These figures illustrate how many dark red pancreatic cancer cells were exposed to the plant extracts *S. aromaticum* and *C. spinosa*.

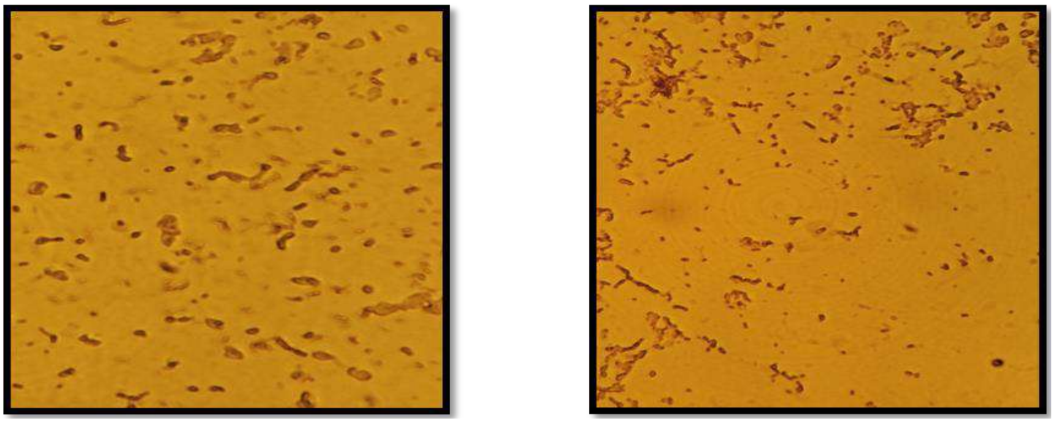

Fig. 6: Bacterium D (*Salmonella typhimurium*) (Da, Db). D: Bacterium (*Salmonella typhimurium*), a: *Syzygium aromaticum*(Cloves), b:*Capparis spinosa*.

Table 3: Bacterial viability % using acridine orange

Bacterial strain	Extracts		Controls			
	A	B	Control cell suspension	Cell suspension/no bacteria	Cell suspension/no extract	bacterial broth
A (*S.aureus*)	40	28.5	83.3	66.6	81.8	0
B (*B. cereus*)	16.6	52.3	71.4	69.2	70	0
C (*E. coli*)	27.2	54.5	33.3	60	66.6	0
D (*S. typhimurium*)	38.8	37.5	64.2	81.8	63.6	0

According to a Table (3) which displays the cell count after staining acridine orangereveals that extract *C. spinosa* and compound 4 are the most effective against the four different species of bacteria. The effectiveness of *S. aromaticum* against S. aureus was higher than that of *B. cereus*, whereas the effectiveness of *C. spinosa* against *E. coli* was lower than that of *S. aureus*.

SDS-PAGE (Polyacrylamide gel electrophoresis)

In the present study, SDS-PAGE analysis was carried out *C. tenuicollis* in vitro (Fig. 7,8) and in *vivo* (Fig.9,10).

SDS-PAGE In Vitro

In vitro, the size of the protein bands seen in control cysts ranged from 17 to 250 KD. These were 62, 55, 26, and 17KD in cysts treated with *S. aromaticum* (A) and *C. spinosa* (B) the protein bands varied from 26 to 67 KD. (Fig.7) and the same as in (Fig. 8).

In *vivo*, the protein bands of control cysts varied between 17 and 250 17KD. While in cysts treated with *S. aromaticum*(A) the protein bands ranged from 37 to 67 KD, and in cysts treated with *C. spinosa*(B), no protein bands were found (Fig. 9, 10).

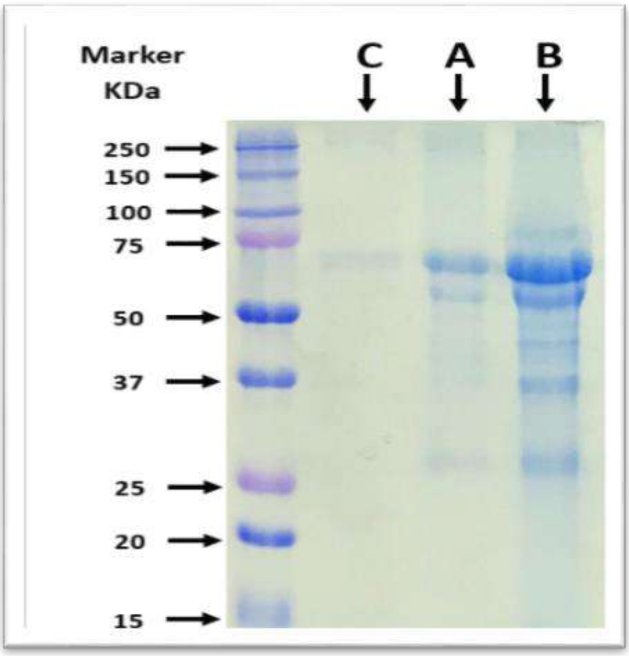

Fig. 7: SDS-PAGE separation gel of (*Cysticercus tenuicollis*). Lanes (C) control, *Syzygium aromaticum*(A), *Capparis spinosa*(B).

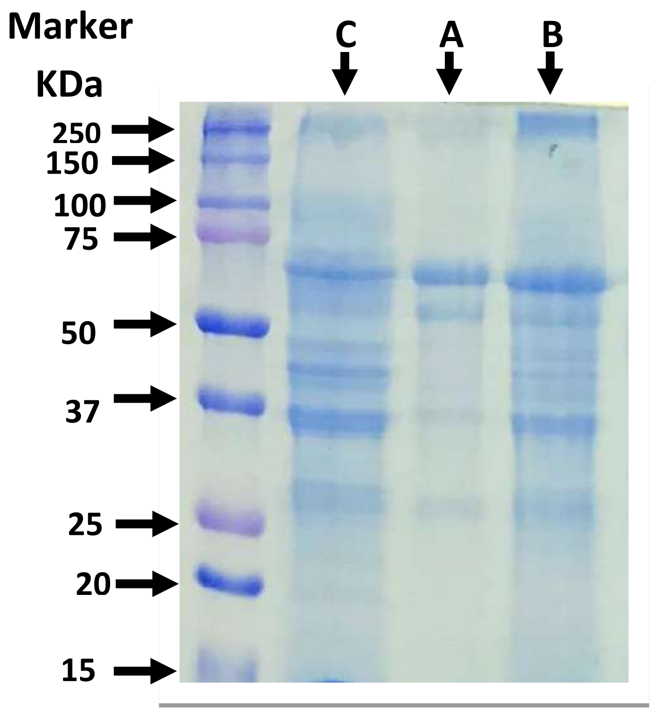

Fig. 8: SDS-PAGE separation gel of (*Cysticercus tenuicollis*). Lanes (C) control, *Syzygium aromaticum*(A), *Capparis spinosa*(B).

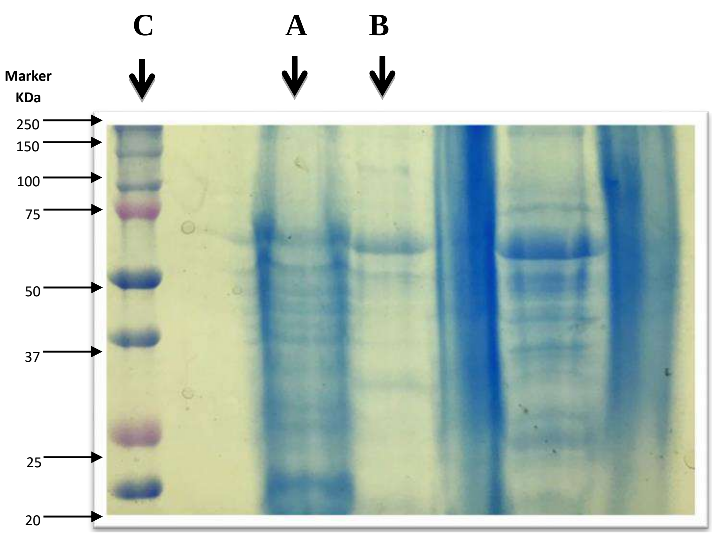

Fig. 9: SDS-PAGE separation gel of (*Cysticercus tenuicollis*). *Syzygium aromaticum*(A), *Capparis spinosa*(B).

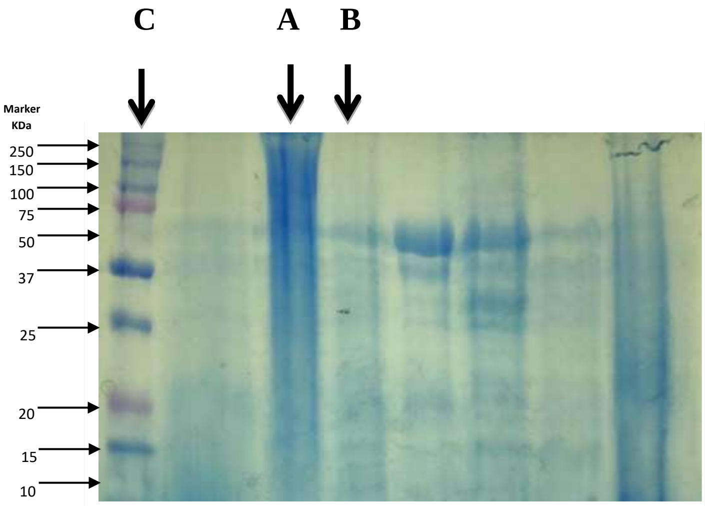

Fig. 10: SDS-PAGE separation gel of (*Cysticercus tenuicollis*). *Syzygium aromaticum*(A), *Capparis spinosa*(B).

Scanning Electron Microscope (SEM)

The technique is especially useful for detecting cystic membranes, which were formerly employed to characterise the surface and hooks. Samples from the membranes of scolex and cysticercus that were extracted from butchered sheep are used in the present study. Figures 11a, b, c, d, and 12a, b show that some samples were normal, while others received treatment with the plant extracts *S. aromaticum* and *C. spinosa*. It displays several morphological traits in addition to clear degradation of the scolex membrane and hooks. Moreover, *S. aromaticum* affects the cyst more than *C. spinosa* (Fig. 13 a, b, 14–15 a, b, 16).

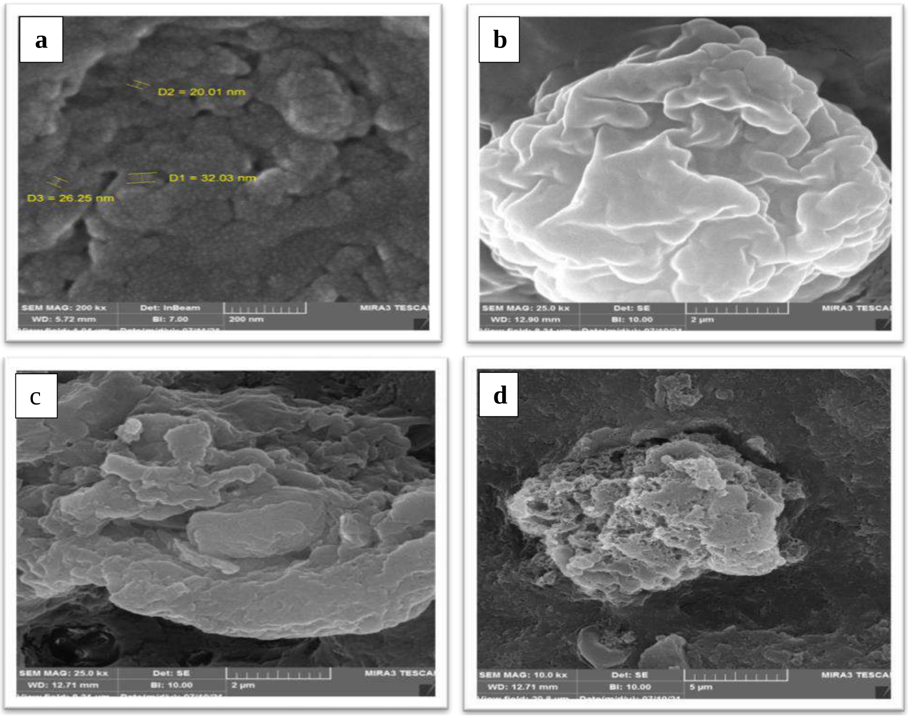

Fig. 11 a, b, c, d: Scolex scanning electron microscopy of untreated *C. tenuicollis*

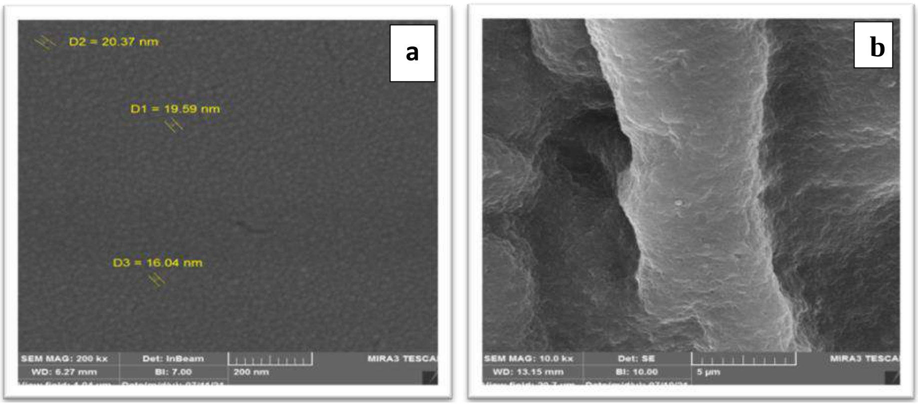

Fig. 12 a, b: Scolex scanning electron microscopy of *C. tenuicollis* untreated

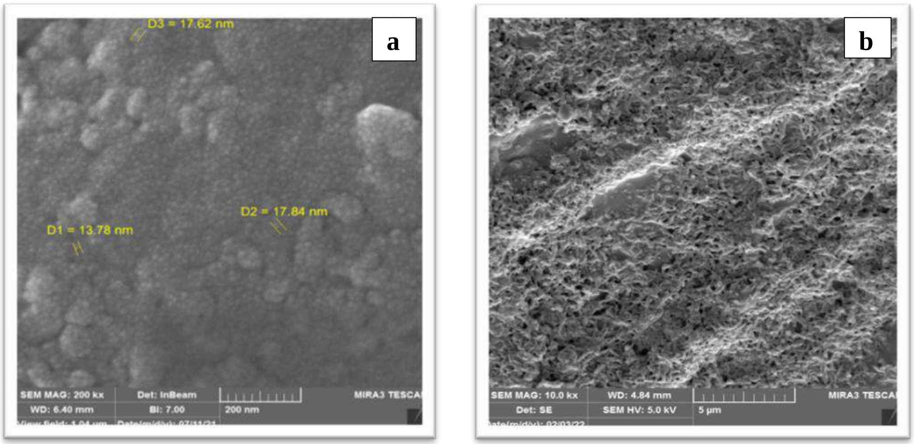

Fig. 13 a, b: Scanning electron microscopy of a *C. tenuicollis* cyst treated with *Syzygium aromaticum*

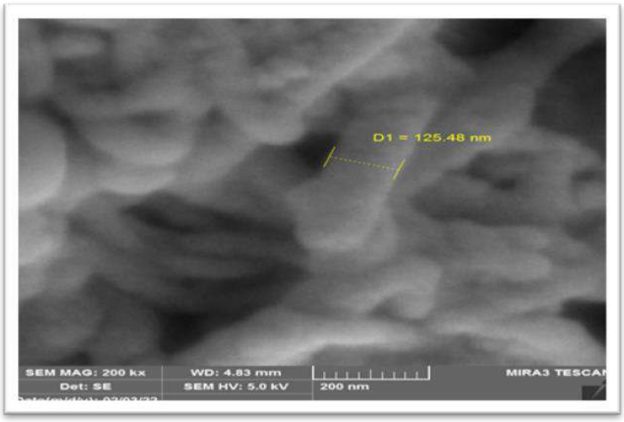

Fig. 14: Scolex scanning electron microscopy of *C. tenuicollis* treated with *Syzygium aromaticum*

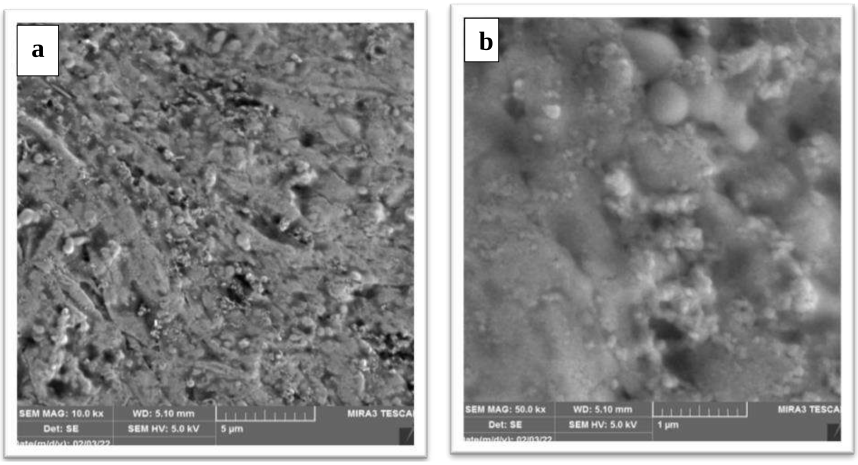

Fig. 15 a, b: Scanning electron microscopy of *C. tenuicollis* cysts that had been treated with *C. spinosa*

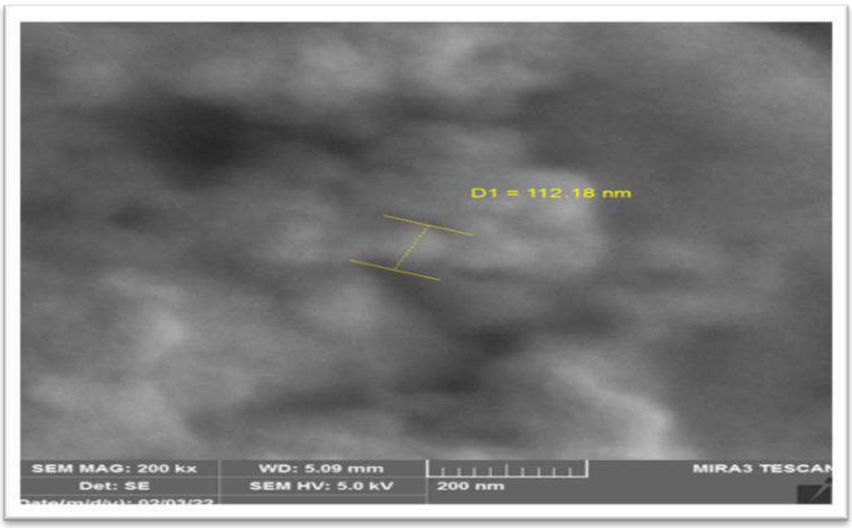

Fig. 16: Scolex scanning electron microscopy of *C. tenuicollis* treated with *C. spinosa*

Conclusions

Plant extracts showed significant antibacterial and antioxidant action against *S. aureus* and *E. coli*, making them suitable for therapy.

A apparent effect on protein cotenants of *C. tenuicollis*, which was treated with two plant extracts (*C. spinosa* and *S. aromaticum*) in *vitro* and in *vivo* by SDS- PAGE compared with untreated.

A clear destruction of the scolex, membrane, and liquid of C. tenuicollis was identified using plant extract to compare with untreated cysts.

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Chapter 15

Medicinal Plants for the Treatment of Diabetes

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ABSTRACT

Diabetes is a complex and multifactorial disease that affects the metabolic pathways of carbohydrates, proteins, and lipids. Chronic high blood glucose levels, a result of altered insulin secretion and/or insulin resistance, is the main characteristic of this disease that affects the function of multiple organs, deteriorates the patient´s quality of life, and finally causes death. In its development and progression, the interaction of genetic and environmental factors plays a very important role. In 2021, 537 million adults between 20-79 years old had diabetes. Despite the arsenal of medications and treatments, according to estimates, this number will increase to 643 million in 2030 and 783 million by 2045. This increase is associated with late diagnosis, lack of treatment adherence, the high costs of medications, and unhealthy lifestyles. In recent years, much scientific research has been done to demonstrate the hypoglycemic properties of many plants and the reduced side effects, so that the use of medicinal plants is gaining strength, as a safe alternative that can contribute to the control of this disease.

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Diabetes, Hypoglycemic effect, Secondary metabolites,	Revised: 12-July-2024	Unique Scientific
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INTRODUCTION

Disease has accompanied human beings since their origins and obviously increased when humans settled down and started living in groups. To survive, humanity had to find healing alternatives and so, the use of medicinal plants was one of their options. Initially, the use of the different plants was in a “trial and error” manner, but with time the “healers” were able to identify the benefits of the different plants, or parts of the plants, that had healing properties and their adequate usage to combat the different diseases (Eknoyan and Nagy, 2005). We must point out that in ancient times, disease was associated with the punishment of gods, and the participation of demons, and so the treatment required breaking the enchantments and curses and prayers to the gods, and in some cultures this relationship still exists.

Although archeologists are finding evidence of the presence of some diseases in the skeletons of humans of various cultures, we don´t have reliable information related to the presence of different diseases that affected humans before the appearance of the first writing system, due to the knowledge was only orally transmitted and, the information may not be accurate. Writing systems appeared more or less at the same time in Mesopotamia and Egypt in 3000 BC. The first reports of the presence and treatments of different diseases and especially of diabetes can be found in the Ebers papyrus (1500 BC) where a description of symptoms related to diabetes, like excessive thirst, and copious urination that was treated with plant extracts, can be found. In India (500 BC), the Samhita document describes diabetes based on its symptoms such as the sweet taste of urine, its sticky sensation, and its ability to attract ants, associating this disease with excessive consumption of foods, especially sweets. In ancient China (475 BC), they also considered classic symptoms such as polyuria, polydipsia, polyphagia, and weight loss and was defined as wasting-thirst (xiao-ke) (King and Rubin, 2003; Loriaux, 2006).

In the 2nd century AD, Aretaeus of Cappadocia introduced the term diabetes, its origin is the Greek verb *διαβαινω* (diabaino) which means siphon because the liquid does not remain in the body and runs out. In his work, he mentioned that the kidneys and bladder never stopped producing water and made a broad and detailed description of this condition. Curiously, he pointed out that “this disease is not very common in men”. For treatment, he recommended the consumption of cereals, milk and wine, the topical application of poultices and the administration of the miraculous remedy “*Theriac*” composed of 70 ingredients including minerals, herbs, poisons and animal meat, combined with honey, which with modifications has been used for more than two millennia (Laios et al., 2012).

Diabetes as a Multifactorial Disease

Diabetes is one of the diseases that humanity has historically faced. It is a multifactorial and complex disease that affects the metabolic pathways of carbohydrates, proteins, and lipids and is mainly characterized by chronic high glucose levels, a consequence of altered insulin secretion and/or insulin resistance (Deepthi et al., 2018). This chronic hyperglycemia alters the function of multiple organs, progressively deteriorates the quality of life, and finally causes death with a high economic and social cost for the family and health systems. The interaction of genetic and environmental factors plays a very important role in the development and progression of this disease. Ethnicity, family history of diabetes, previous gestational diabetes, older age, overweight and obesity, unhealthy diet habits, sedentary lifestyle, and smoking are risk factors that increase the probability of developing diabetes and in consequence, the chronic complications that are characteristic of this disease and responsible for the high morbidity and mortality related to this condition (ADA, 2023).

The complications that affect patients to different degrees are of two type macro and microvascular. The latter are more prevalent and include neuropathy, nephropathy, and retinopathy. Cardiovascular disease, stroke, and peripheral artery disease are the macrovascular complications that affect these patients. A special complication is the diabetic foot syndrome, which is associated with neuropathy, peripheral artery disease, and infection and is responsible for the high frequency of amputations. Gum disease and alterations in the ability to resist infections are complications that affect the quality of life of diabetic patients (Ali and Ahmed, 2021; Tomic et al., 2022).

The American Diabetes Association (ADA) has classified this disease into the following categories:

1. Type 1 diabetes (T1D) caused by autoimmune destruction of β cells, usually leading to absolute insulin deficiency, including latent autoimmune diabetes in adulthood.
2. Type 2 diabetes (T2D) has a multifactorial origin, characterized by a progressive loss of adequate insulin secretion, or by increased resistance to it.
3. Other specific types of diabetes are due to other causes, such as illness or the use of medications. Among the first is the monogenic diabetes syndrome, which includes neonatal diabetes and juvenile diabetes with onset in maturity. Exocrine diseases of the pancreas, such as cystic neoplasms, neuroendocrine tumors, pancreatitis, pancreatic insufficiency, or cystic fibrosis. On the other hand, induced diabetes caused by the prolonged consumption of drugs or chemical substances. This consumption may be associated with diseases or specialized surgical procedures, such as glucocorticoids, used in the treatment of HIV/AIDS, or medications administered after an organ transplant.
4. Gestational diabetes mellitus (GDM, diagnosed in the second or third trimester of pregnancy, and that was not clearly overt diabetes before pregnancy.

Each of the different types of diabetes has specific characteristics and treatment requirements; therefore, its identification using established diagnostic criteria is of utmost importance and can contribute to personalized and more effective management. (ADA, 2023).

Global Dimensions of Diabetes

Diabetes is a highly prevalent disease, affecting all age groups. According to the IDF (International Diabetes Federation) report published in 2021, 537 million adults (20-79 years) live with diabetes (1 in 10), estimating that this number will increase to 643 million in 2030 and 783 million in 2045 (IDF, 2021). Table 1 compiles the data recorded for this disease in 2021, by modality.

Table 1: Global prevalence of diabetes by regions (2021)

REGION	T2D (> 19 years)	Undiagnosed proportion (%)	T1D (0-14 years)	T1D (0-19 years)	Gestational Diabetes (GDM) (%)
Africa	23,633,900	53.6	26,300	59,500	13
Europe	61,425,100	35.7	162,600	294,900	15
Middle East and North Africa	72,671,900	37.6	108,900	192,500	14.1
North America and Caribbean	50,547,000	24.2	98,200	192,500	20.7
South and Central America	32,497,100	32.8	64,600	121,300	15.8
South-East Asia	90,204,500	51.3	132,200	244,500	25.9
Western Pacific	205,640,200	52.8	58,900	107,900	14
Average	76,659,957	41.1	93,100	173,300	16.9

Source: Preparation with data reported by IDF (2021)

Although the most prevalent type of diabetes is T2D, the rest of the data is alarming. Based on average values, this means that 41.1% of the world's population suffering from diabetes is still undiagnosed, which would significantly increase the numbers in each region. Additionally, 16.9% of newborns developed in a hyperglycemic environment, a condition that is a risk factor for developing T2D, obesity, insulin resistance and other metabolic disorders in adulthood. Due to its distribution and prevalence, the largest number of adults with diabetes live in low- and middle-income countries. In 2021, diabetes was responsible for 6.7 million deaths. Health expenditures amounted to 966 billion dollars, increasing 315% in the last 15 years (IDF, 2021). Table 2 integrates the data by region comparing the most prevalent countries.

At the regional level, the highest number of cases corresponds to the Western Pacific and South East Asia, associated with the population of India and China, respectively. In terms of real impact, when comparing the prevalence with the total population by country, the highest percentage value corresponds to Pakistan with 14.25% of the population (1.4 out of 10) that has T2D, followed by Mexico (11.15%) and Turkey (10.72%) (World Bank, 2021; IDF, 2021).

Table 2: Prevalence of cases and deaths associated with diabetes by region. Most prevalent countries (2021)

Region	Cases	Deaths	Country	Prevalence (Thousands)	Population (Millions)	With diabetes (%)
Africa	23,633,900	416,163	South Africa	4,234.0	59.4	7.13
			Nigeria	3,623.5	213.4	1.70
			Tanzania	2,884.0	63.6	4.54
Europe	61,425,100	1,111,201	Turkey	9,020.9	84.1	10.72
			Russia	7,392.1	144.1	5.13
			Germany	6,199.9	83.2	7.45
Middle East and North Africa	72,671,900	796,362	Pakistan	32,964.5	231.4	14.25
			Egypt	10,930.7	109.3	10.00
			Iran	5,450.3	87.9	6.20
North America and Caribbean	50,547,000	930,692	United States	32,215.3	332.0	9.70
			Mexico	14,123.2	126.7	11.15
			Canada	2,974.0	38.2	7.78
South and Central America	32,497,100	410,206	Brazil	15,733.6	214.3	7.34
			Colombia	3,443.6	51.5	6.68
			Venezuela	2,280.0	28.2	8.09
South-East Asia	90,204,500	747,367	India	74,194.7	1,407.6	5.27
			Bangladesh	13,136.3	169.4	7.76
			Sri Lanka	1,417.6	22.2	6.40
Western Pacific	205,640,200	2,281,732	China	140,869.6	1,412.4	9.97
			Indonesia	19,465.1	273.8	7.11
			Japan	1,005.0	125.7	0.80
Total	536,619,700	6,693,723				

Source: Preparation with data reported by IDF (2021) and World Bank (2021)

These data allow us to understand the magnitude of the problem that diabetes represents. According to the Pan American Health Organization, prevalence is increasing most rapidly in low- and middle-income countries. This disease increases the risk of suffering from cardiovascular diseases, one of the main causes of strokes, heart attacks, and loss of limbs due to amputation (mainly due to the development of diabetic foot). These conditions place diabetes among the main causes of death and disability-adjusted life years (PAHO, 2021).

Despite knowledge about the risk factors associated with diabetes and the arsenal of hypoglycemic medications, different treatments, combinations of drug, and algorithms that have been proposed, reality shows that the progress made to control this disease is not very encouraging. Faced with this problem, some international agencies are proposing different strategies, like the ADA/EASD Precision Medicine in Diabetes Initiative (PMDI) (2018), and the Global Diabetes Pact, proposed by WHO (2021). (PAHO, 2021; Nolan et al., 2022).

Achieving the objectives of these initiatives will undoubtedly provide great benefits for the control and treatment of diabetes. While this happens, treatments based on hypoglycemic drugs, remain the conventional option. These include Sulfonylureas, Glinides or Metaglinides, Biguanides, Thiazolidinediones, α-glucosidase inhibitors, GLP-1 agonists and DPP-4 antagonists, mainly (Rodríguez-Rivera et al., 2017).

These drugs have different mechanisms of action, either by increasing insulin sensitivity, as a complement to insulin, by increasing insulin secretion levels, or by promoting glucose absorption. Although they manage to control blood glucose levels, they also induce adverse effects. Some of these effects include the development of hypothyroidism, tachycardia, liver failure and, lactic acidosis, among many others. In addition to this, the resistance that patients can develop to drugs, supports the search for other alternatives like the development of new drugs, where plants are the best option, due to the bioactive compounds they generate as part of their metabolism (Alam et al., 2022).

Plant Metabolism and Bioactive Compounds

From a physiological point of view, unlike the rest of living beings, plants are the only ones with a double metabolism. Secondary metabolism in plants is essential in the production of defensive agents that increase both their adaptation to changing environmental conditions, as well as their defense mechanisms against their predators. During this process, the plant carries out the biogenesis of different compounds, which have particular properties and specific mechanisms of action. They constitute the "natural compounds" that give plants their medicinal properties. The synthesis of these compounds occurs from the products generated in the primary metabolism processes of plants (Photosynthesis, Citric Acid Cycle, Glycolysis, Transamination and Amino acid synthesis, among others). For example, a product of glycolysis is Acetyl-

CoA, which is the precursor of acetogenins, terpenes, and steroids. While propanoids, flavonoids and alkaloids come from products of photosynthesis (Rungsung et al., 2015; Chomel et al., 2016; Deepa et al., 2018).

Due to their chemical composition, the functions that these bioactive compounds fulfill in plants are diverse. This composition is what also gives medicinal properties to the plants. Table 3 presents a comparison in this regard, considering exclusively the medicinal properties associated with diabetes.

Table 3: Function of some active compounds in plants and medicinal properties in diabetes

Compound	Functions in the plant	Medicinal properties against DM	Source
Alkaloids	Nitrogen storage. Defense against predators (bitter taste and toxic properties for animals).	Increased glucose uptake.	Chomel et al. (2016); Ríos et al. (2016)
Phenolic acids	Allelopathy (influence on growth and development). Decreases decomposition time. Protection of DNA and lipids of the cell membrane.	Prevent oxidative damage Reduce metabolic alterations associated with TD2 (increased circulating glucose, lower insulin secretion)	Chomel et al. (2016), Cereceres-Aragón et al. (2019)
Flavonoids	They define the aroma and pigments of plants. Function as antioxidants, antifungal and antibacterial	Hypoglycemic agents Antihyperglycemics Antidiabetic	González-Sánchez et al. (2011), Chomel et al. (2016)
Tannins	Polyphenols most abundant in woody plants. They protect the plant against herbivores and pathogens.	Glycation inhibition Hypoglycemic effect Inhibition of tyrosine phosphatase (negative regulator of the insulin signaling pathway)	Chomel et al. (2016), Kumar et al. (2021)
Terpens	Confer resistance to the plant against biotic and abiotic stress	Inhibition of carbohydrate metabolism enzymes	Castro et al. (2014), Chomel et al. (2016)

Source: Self-made

Due to the medicinal properties associated with the bioactive compounds of plants, these compounds are incorporated in the preparation of more than 25% of current drugs. Many studies report that plants under abiotic stress – caused by adverse environmental conditions – activate the production of new compounds or increase the concentrations of those they already produce; to strengthen their adaptation mechanisms. These plants offer greater possibilities for therapeutic use. This characteristic is very important since the conditions in which the plants grow are fundamental. The differences in the effectiveness of treatments, as well as the diversity of plants used, largely depend on the places and conditions in which the plants grow (Yeshi et al., 2022).

Approaches to the Study of the Therapeutic Properties of Active Plant Compounds

Secondary metabolites represent an incalculable natural resource, due to their great abundance and diversity.
The development of cutting-edge techniques (such as mass spectrometry), through which greater and better characterization of these compounds is achieved, supports this consideration. However, it is also pertinent to consider that, despite the progress made, in many cases, a limitation for the study of the effects and properties of these compounds is the yields obtained. Despite this, the number of investigations carried out to verify the therapeutic effects increases progressively.

The selection of plant species is not arbitrary, as it depends on the background and objectives of the research, as well as the availability and access to the plants in question. With all this, the differentiation of the properties of each plant allows us to go from generalization to deepening, by characterizing the attributes of plants, and glimpse their possibilities as a complementary alternative in the control or treatment of different diseases (Li et al., 2020).

As part of the knowledge currently available, there is certainty that the identification of different biosynthetic routes gives secondary metabolites different chemical characteristics, and therefore, different properties as therapeutic agents. Identifying three groups of a) Nitrogen compounds, which include alkaloids, glucosides, and cyanogenic glucosinolates; b) Phenolic compounds, such as flavonoids and phenylpropanoids; and c) Terpenes, which include carotenoids, glycosides, saponins and steroids (Fang et al., 2011; Yeshi et al., 2022).

Other factors that affect the medicinal potential of plants is the environmental conditions in which they develop. The concentration of nutrients in the soil, temperature, and relative humidity, among other environmental factors, are determining factors. Likewise, the accumulation and distribution of secondary metabolites is variable from one plant to another, as well as between the components of the same plant. Assessments made in this regard show that the concentrations of metabolites are similar between roots (or rhizomes) and stem, but different from the leaves, and these with respect to the flowers, fruits, and seeds, in which they are very similar. In general, the leaves have the highest content of metabolites, which is why they are widely used in the studies carried out (Belheir et al., 2016; Borges et al., 2017).

Medicinal Plants for Diabetes

Diabetes is a rapidly and actively spreading disease, in which the number of cases increases constantly and significantly. Although it does not meet the requirement of being restricted to a certain geographic area, it is an epidemic. Its global distribution, although it brings it closer to a pandemic, being present on all continents, definitively distances it from this denotation, as it is a non-contagious or transmissible disease. This places diabetes between these two epidemiological notions (Kharroubi and Darwish 2015; Barba, 2018).

The above reflects the magnitude and complexity of this disease, as well as the impact it generates on the world. The problem tends to become more acute due to changes in social habits that have been setting a trend to increase calorie consumption and reduce energy expenditure due to the lack of physical activity. This, in addition to increasing the number of overweight and obese people, increases the chances of developing the disease, especially those who have a genetic predisposition. Part of the complexity is that a large percentage of people who suffer from diabetes remain undiagnosed. Of those diagnosed, a significant number do not follow their treatment adequately. The lack of access to medications, abandonment of treatment, inadequate diet, and lack of physical activity aggravates this problem and, promote the increase in the T2D complications. (Ginter and Simko, 2013; Heredia-Morales and Gallegos, 2022).

In addition, and no less important, is the fact that although there are different pharmacological options to treat diabetes, their effectiveness is being compromised, both due to resistance and the side effects caused by the treatments. An alternative that is gaining more strength is the use of medicinal plants that contribute to the care of this disease. Beyond recovering the popular herbal tradition, various studies carried out for just over half a century have demonstrated the effectiveness of the use of plants in diabetes care. Among other aspects, they show the effectiveness of increasing and improving insulin secretion, promoting the absorption of glucose by muscle and adipose tissues, as well as inhibiting both the absorption of glucose in the intestine and the production of glucose from liver cells and inflammatory activities (Li et al., 2013; Alam et al., 2022).

With the results of the research, it has been possible to know the secondary metabolites of different plants. Table 4 shows the bioactive compounds identified for different botanical species. Variations in the content of metabolites confer different properties to plants.

Table 4: Bioactive Compounds identified in some of the different medicinal plants with antidiabetic properties.

Botanical Species	Bioactive Compounds	Source
Ficus spp.	Flavonoids	Deepa et al. (2018)
F. benghalensis,	Phenolic acids	
F. carica	Tannins	
F. glomerata	Alkaloids	
F. glumosa	Glycosides	
F. racemosa	Coumarins	
F. religiosa	Triterpenoids	
	Sterols	
	Vitamin E	
Tecoma stans	Alkaloids	Alonso et al. (2010)
	Triterpenes	
	Phenolic compounds	
Costus pictus	Phenolic acids	Sidhu et al., (2012)
	Flavonoids	
	Proanthocyanidins	
Cistus laurifolius	Favonoids	Orhan et al. (2013)
Hunteria umbellate	Alkaloids	Igbe et al. (2009)
	Flavonoids	
	Glycosides	
Rehmania glutinosa	Iridoids Monoterpenes Glycosides Phenols Flavonoid	Jeonga et al. (2013)
Vaccimium arctostaphylos	Anthocynins	Feshani et al. (2011)
Amaranthus viridis	Alkaloids Steroids Glycosides Saponins Tannins	Pandhare et al. (2012)

Source: Self-made

Knowledge about secondary metabolites in plants makes it possible to carry out research to identify their mechanisms of action, in this case, for diabetes. Table 5 integrates some examples of research generated around diabetes. In general, each study´s results vary, depending on the used methodology. They can vary from the type of research (in vitro, in vivo, ex vivo, in silico, preclinical and clinical studies), extraction methods, and plant parts, among others. The common point is the evaluation of the medicinal properties of plants, as an alternative for the treatment of diabetes.

Table 5: Studies that exemplify the assessment of the effectiveness of medicinal plants in the treatment of diabetes

Location	Characteristics and Results of the study	Source
Bosnia y Herzegovina	*in vitro* study Objective: Determination of the polyphenolic composition and anti-diabetic activity Measurement of anti-diabetic activity: % inhibition of α-amylase and α-glucosidase Leaves of 5 plants for traditional use against DM: *Agrimonia eupatoria*: 94% flavonoids. Activity: Excellent (the best) *Salvia officinalis*: 60% flavonoids, 40% phenolic acids. Activity: Weak *Trifolium pratense*: 45% flavonoids, 55% phenolic acids. Activity: Excellent *Cichoriuma intybus*: 52% flavonoids, 48% phenolic acids. Activity: Moderate *Vica minor*: 20% flavonoids, 80% phenolic acids. Activity: The weakest	Kukavica et al. (2024)
Mexico	*In vitro* study Objective: Test the inhibitory activity of α-glucosidase in butanolic extracts of four Mexican plants and effect on plasma glucose (PG) levels. *Cecropia obtusifolia*: Greater reduction in PG. IC (50) 14μ/ml. *Equisetum myiochaetum*: No effect on PG. IC (50) No effect. *Acosmium panamense*: Significant decrease in PG. IC(50) 109 μ/ml. *Malmea depressa*: Significant decrease in PG. IC (50) 21 μ/ml	Andrade-Cetto and Heinrich (2005)
Paraguay	Clinical study Objective: Description of medicinal plants and phytotherapeutics used against T2D. 63.4% of patients consume medicinal plants and phytotherapeutics for T2D. Use of 23 different medicinal plants Most consumed plants: *Jungia floribunda* (52%), *Artemisia absinthium* (40%), *Moringa oleifera* (36%) and *Cissus verticillata* (28%). Average plant consumption/patient: 3 Most consumed portion: Leaves (90.8%) Frequency of use: Daily Average use time: 64 months	Acosta-Recalde et al. (2018)
South Africa	*In vitro* study Objective: Evaluation of antidiabetic activity of plants used locally against T2D Evaluation of antidiabetic activity: α-amylase and α-glucosidase activity and excretory activity of the islets of Langerhans In extracts with hexane: *Cymbopogon citratus*: α-amylase inhibition 34.99% *Cucurbita pepo*: α-amylase inhibition 72.29% *Hypoxis hemerocallidae*: Inhibition of α-amylase 54.0% *Cinnamomum cassia*: α-amylase inhibition 99.93% *Senna alexandrina*: Inhibition of α-amylase 97.10%	Boaduo et al. (2014)
Turkey	Experimental study Objective: To evaluate the hypoglycemic effects of aqueous (AE) and ethanolic (EE) extracts of Cistus laurifolius Effect evaluation: Inhibition of α-amylase and α-glucosidase enzymes Normal rats (Control) Glucose-loaded hyperglycemic rats: Weak hypoglycemic effect (11-20%) Diabetic rats induced with stretozocin (STZ): Decrease in blood glucose levels (EE) EEs were better inhibitors than AEs	Orhan et al. (2013)

Source: Self-made

The results of these investigations make it possible to know the effects of each plant with medicinal properties. Table 6 shows some of these effects.

Table 6: Effects of different plant species associated with DM.

Botanical Species	Effect	Source
Acacia catechu	Significant anti-hyperglycemic effect Reduction in serum glucose levels Inhibition of glucose absorption in the intestine	Rahmatullah et al. (2013)
Ageratum conyzoides	Reduction of blood glucose levels Inhibition of hyperglycemia Inhibition of α-glucosidase and α-amylase enzymes	Rafe (2017)

Aloe vera	Reduction of blood glucose levels Improves insulin secretion Improves glucose metabolism	Unuofin and Lebelo (2020)
Anacardium occidentale	Antidiabetic activity Hypoglycemic activity	Vargas-Arana et al. (2023)
Andrographis paniculata	Inhibition of hyperglycemia Inhibition of α-glucosidase and α-amylase enzymes Antidiabetic activity	Rafe (2017)
Anoectochilus roxburgii	Reduction of blood glucose levels Improvements in the body's antioxidant capacity Modulation of enzymes that metabolize glucose	Ye et al. (2017)
Berberis aristata	Regulation of glucose homeostasis Reduced gluconeogenesis Reduction of oxidative stress Strong antihyperglycemic activity	Potdar et al. (2012)
Cajanus cajan	Hypoglycemic effect Anti-hyperglycemic effect Antidiabetic activity	Vargas-Arana et al. (2023)
Cinnamomum verum	Suppression of α-glucosidase and α-amylase activity Improvements in postprandial blood glucose	Beejmohun et al. (2014)
Dendrobium chrysotoxum	Decreases the activation of retinal microglia (in diabetic retinopathy)	Ojha et al. (2017)
Momordica charantia	Inhibition of insulin degradation Hyperglycemic activity	de Menezes et al. (2023)
Panax ginseng	Reduction of blood glucose levels Decreased β-cell function Decreased insulin resistance	Unuofin and Lebelo (2020)
Portulaca oleracea	Inhibition of α-glucosidase and α-amylase enzymes Anti-hyperglycemic activity Antidiabetic activity	Vargas-Arana et al. (2023)
Salvia officinalis	Significant reduction in blood glucose levels (humans)	Behradmanesh et al. (2013)
Tecoma stans	Stimulate the uptake of 2-NBDG by insulin-sensitive adipocytes Antidiabetic effect	Alonso et al. (2010)
Terminalia arjuna	Hypoglycemic effect Antidiabetic activity	Rafe (2017)
Trifolium pratense	Reduction of glycated hemoglobin Reduction of hyperglycemia Improvement in insulin sensitivity Improvement in liver glycogen levels	Alam et al. (2022)

Source: Self-made

Conclusion

The challenges to control the progressive increase in people suffering from diabetes are multivariate and it is necessary to demonstrate the benefits provided by the active compounds produced by plants. The use of medicinal plants, in addition to contributing to the development of new drugs, gives us the possibility of providing accessible treatments, ideally free of unwanted side or adverse effects to treat not only diabetes but also the associated complications at a much lower cost, affordable to patients. Much research is needed to demonstrate the effects of the plant extracts not only in animal models but also in humans by increasing the number of clinical double-blind placebo-controlled trails and very important the absence of adverse effects.

We have to keep in mind that natural products are not synonymous with non-toxic and safe. For this reason, scientific research is required to support ethnobotanical and ethnopharmacological knowledge.

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Chapter 16

Plant as Anthelmintic Allies in the Fight against Fasciolosis: A Review

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ABSTRACT

Plants are the primary food source for ruminating mammals; therefore, using different medicinal plants (extracts, oils, and bioactive compounds) could be effective fasciolicides to prevent economic losses due to fasciolosis. The problem of anthelmintic resistance in flukes due to the excessive and inappropriate use of fasciolicides poses an alarming threat and urges the development of new and alternative fasciolicides. Now, the focus is diverging towards plant-based fasciolicides because of their safe and environment-friendly nature. Different plants' essential oils and active compounds are effective in controlling egg hatching and causing the mortality of adult flukes. The *Artemisia* and *Etlingera* extracts exhibited significant efficacy against eggs and adults of *Fasciola spp.* The plants (*Zingebar officinalle* and *Potentilla fulgens*) also showed considerable efficacy against miracidia, sporocyst, rediae, and cercarial stages. The use of plant oils in controlling parasitism has been practiced all over the world. Oils from (*Pelargonium graveolens*, *Citrus aurantium*, *Helianthus annuus*, and *Cuminum cyminum*) plants actively inhibit egg development. Moreover, plants' active compounds, diterpenoids, thymoquinone, curcumin, flavonoids, acids, artemisinin, and saponins also show promising effects on egg development and adult fluke productivity.

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INTRODUCTION

Fasciolosis (Fascioliasis) is a zoonotic disease that affects animals and humans worldwide. A trematode parasite, *Fasciola* (*F. hepatica* and *F. gigantica*) also called liver fluke, causes the disease and can be transmitted to animals and humans through its infective stage (metacercariae). The life cycle of this parasite consists of two hosts. The eggs are shed in the faeces of ruminants as sheep, cattle, and goat, and are hatched into the miracidia that infect the first host snail (Lymnid). There, it progresses asexually into its two stages, sporocysts and rediae, after which snail starts shedding cercariae in the water. These cercariae swim randomly, and after a few hours, they lose their tail, get enclosed in a wall and become metacercariae (infective stage) and attached to the watercress or leaves. When the final host mammals (sheep, cattle, and goat), ingest watercress, undercooked vegetables or leaves, the infective metacercariae become converted into immature flukes which excyst in the duodenum, penetrate the intestinal wall and migrate through liver parenchyma to biliary ducts (FAO, 2020; Mia et al., 2021).

Prevalence of Fasciolosis

Fasciola hepatica is prevalent worldwide, while *Fasciola gigantica* is distributed in the tropics (Urquhart et al., 1996). The overall infection rate is increasing due to climate change, drug resistance, and its ability to intrude new areas. It infects more than 2.4 million people worldwide, with 180 million at risk of infection in 66 countries. In livestock, it is hard to quantify, but according to an estimate, it infects over 600 million domestic ruminants annually, which causes heavy economic losses (Collado et al., 2019). The global prevalence of fasciolosis in livestock ranges from 0.72 to 94% (Khan et al., 2013). Humans are accidental hosts which may be due to the ingestion of raw or undercooked vegetables. The infection rate in humans is low with an estimated 4.5% of people worldwide are thought to have fasciolosis (Infantes et al., 2023).

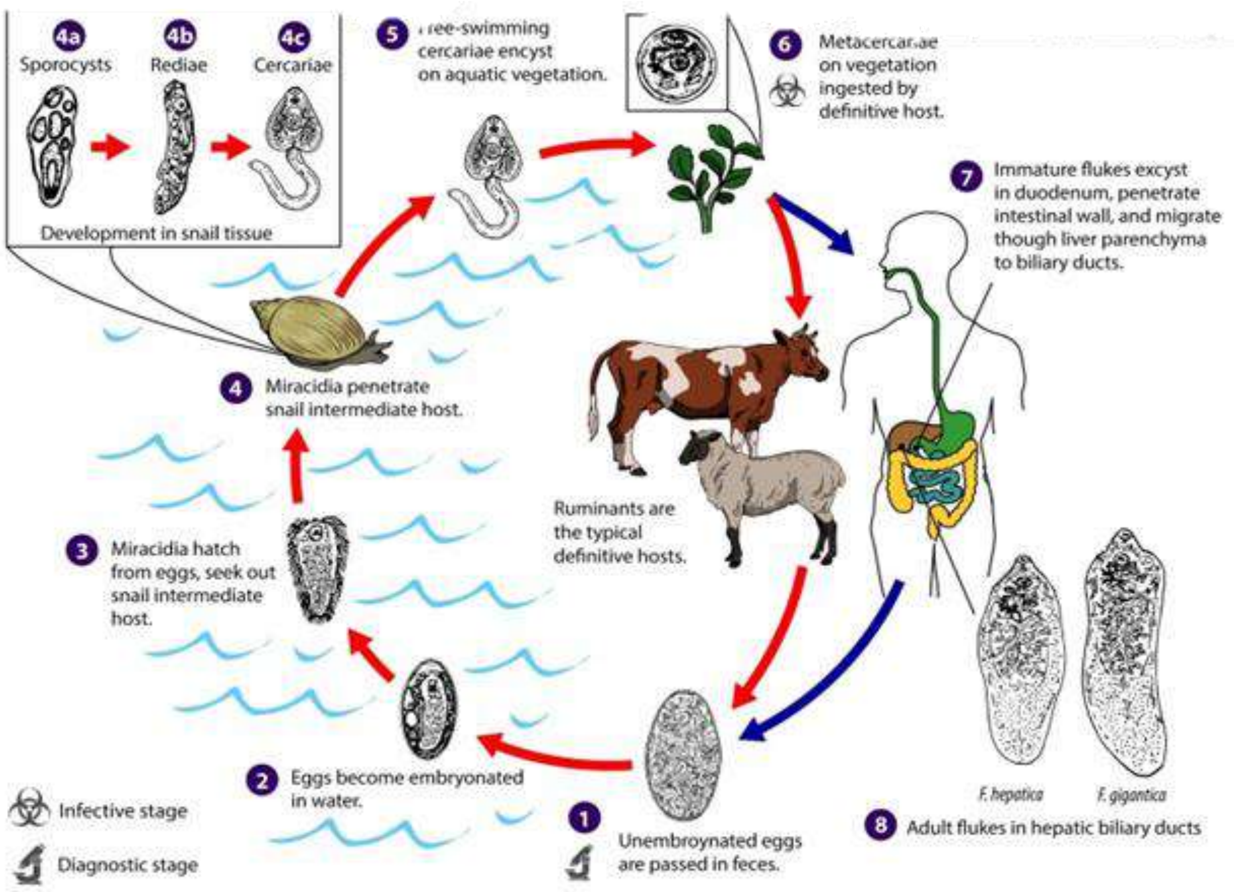

Fig: Life cycle of *Fasciola* spp.

The prevalence of fasciolosis in Pakistan from 2000-2020 was reported in a study. It was 42.70% in Sindh, 25.20% in Baluchistan, 17.70% in Punjab, 10.70% in KPK, and 1.50% in Islamabad. The prevalence was highest among sheep in Punjab at 65.7%, in Baluchistan cows at 28.5%, and in KPK buffalo at 15.9% (Rizwan et al., 2022).

Economic Impact

Helminthes infection costs the agriculture sector an annual loss of US$20 billion towards animal productivity, out of which, the liver fluke infection was predicted to cause annual losses of about US$3.20 billion worldwide (Mehmood et al., 2017; FAO, 2020). The following Table 1 summarizes the economic losses throughout the world due to *Fasciola* infection.

Table 1: Economic Losses in Different Regions of the World

Regions	Countries	Economic Loss through	Economic Loss	Reference
Asia	Iraq	Liver condemnation	US$ 8801.69	Kadir et al. (2012)
	Saudi Arabia		US$ 0.2 M	Degheidy and Al-Malki (2012)
	Sudan		US$ 1.94 M	Abebe et al. (2010)
Africa	Uganda	Liver condemnation	US$ 92 M	Joan et al. (2015)
America	Brazil	Weight loss	35 US$ PH	Dutra et al. (2010)
	Mexico	Productivity loss through reduced milk and meat yield	US$ 4.2 M	Rodriguez et al. (2017)
Australia	Australia	Productivity loss through meat and milk, liver condemination	60–90 M A$	Toet et al. (2014)
Europe	Switzerland	Reduced milk yield, fertility and meat	52$ M	Schweizer et al. (2005)

Control of Fasciolosis

Chemotherapy

Chemotherapy has a primary role in controlling parasitic diseases as it is affordable and effective (Khan et al., 2017). The control of fascioliasis is mainly achieved using synthetic anthelmintics such as albendazole, triclabendazole, and nitroxynil (Nixon et al., 2020; Kouadio et al., 2021). Among the benzimidazole derivatives, triclabendazole (TCBZ) is the most important and widely used drug of choice that can effectively control fasciolosis (Castro Hermida et al., 2021). It is the only drug that has an efficacy of >98% against adults and especially immature flukes as compared to other flukicides that target only adult flukes (Kahl et al., 2023).

Resistance against Anthelmintics

The liver fluke infection is increasing due to climate change, changes in the land use, increased movement of livestock, and its ability to intrude into new areas, which is compounded by the rising issue of anthelmintic resistance in *Fasciola* spp. (Beesley et al., 2023). The problem with the triclabendazole (TCBZ) resistance may be due to the farmers using less effective substitutes or even administering the dose inadvertently (Fairweather et al., 2012). In the recent years, many studies have shown that TCBZ is ineffective against *F. hepatica* in ruminants all over the world. The threat of drug resistance requires serious attention, as many reports have demonstrated drug resistance worldwide, including Scotland **(**Sargison and Scott, 2011), Spain (Martinez Valladares et al., 2014), and New Zealand (Hassell and Chapman, 2012), Wales (Gordon et al., 2012), Peru (Ortiz et al., 2013), Australia (Brockwell et al., 2014), Ireland (Hanna et al., 2015), and Argentina (Larroza et al., 2023).

Besides the issue of anthelmintic resistance, chemical residues found in derived products like milk and meat and their environmental effects are additional crucial factors to be aware of (Da Silva et al., 2020). Thus, for sustainable livestock production, the management of fasciolosis towards TCBZ resistance and the development of new alternatives as flukicides are necessary.

Plants as Anthelmintic Allies

Currently, the livestock sector is under threat due to the problem of increasing resistance to anthelmintics, which is because of factors including inappropriate dosage and repeated exposure of anthelmintics for deworming. Hence, search for alternative anthelmintics is necessary. For this, plant-based anthelmintics could be a preference for coping with this problem. Plant-based anthelmintic are becoming a growing trend because they are safer than the synthetic ones. Moreover, plants provide cost-effective substitutes that are more effective than synthetic anthelmintics (Zirintunda et al., 2022).

Around 80% of people use traditional medicine all over the world, and out of them, about 85% depends on medicinal plants (Nascimento et al., 2000; Oyebode et al., 2016; Romero-Benavides et al., 2017; Sanchez et al., 2020). Plants have been used as medicinal agents from millennia and become the integral part of animal's life. Moreover, plants are also immune boosters that protects against many diseases and also provide many vital nutrients to animal's body. Plants have some of the nature's most effective medicinal compounds. Their extracts and bioactive substances have the potential to become new medicinal agents because of their diversity and environment friendly nature (Abbas et al., 2020; Nurlaelasari et al., 2023). Many medicinal plants can be used as antibacterial agents (Chassagne et al., 2021), antiparasitic (Benlarbi et al., 2023), and antifungal agents (Nigussie et al., 2021). Hence identifying and validating different compounds and their extracts as effective fasciolicide is also necessary. For this, during the recent decades, many plants and their extracts have been evaluated for their anthelmintic activity worldwide (Pessoa et al., 2002; Kozan et al., 2006; Eguale et al., 2011; Ahmed et al., 2013; Payne et al., 2013; Acharya et al., 2014; Esteban Ballesteros et al., 2019).

Plant Extracts

Use of plants as a whole requires a lot of plant mass moreover these are not as much effective. Instead, plant extracts and purified fractions must be used which can provide effective alternative to fasciolicides. The efficacy of plant extract depends on the solvent (water, methanol, ethanol, etc.) used for the extraction and also the mechanism of extraction (hot or cold maceration, proclation, soxhlet extraction, etc.). The solvents provide a medium for the extraction of active phytochemicals like phenols, alkalines, tannins, saponins, etc., and these should be extracted in a preferred medium. Plant extracts provide a combination of different phytochemicals that collectively act as fasciolicide. There are many studies that use different plant extracts to validate their efficacy against *Fasciola spp*. Nurlaelasari et al. (2023) conducted an experiment to evaluate the antifasciolic activity of Mugwort (*Artemisia vulgaris)* extract on the both adult and eggs stages of *Fasciola gigantica.* They assessed the ovicidal efficacy by incubating the eggs with the *A. vulgaris* extract at 5%, 2.5%, and 1.25% for 5, 9, 11, 14, and 16 days. The adult mortality assays were performed after incubating with the extract for 5, 10, 20, 40, 80, 160, 320, and 640 min. All the extract concentrations show significant anti-fasciolic activities. Among these, a 5% concentration of extract showed high level of ovicidal activity, whereas a concentration of 20% extract inhibits 66.67% of eggs hatching after 40 min of exposure. The extract also had high flukicidal efficacy, causing disintegration of different physiological structures (vitelline follicles, intestine, acetabulum, tegument, and spine) of adult fluke. This study has indicated that *A. vulgaris* extract exhibits potential antifasciolic properties. In another study conducted by Wulandari et al. (2023), Torch ginger (*Etlingera elatior)* ethanolic extract was evaluated on eggs and adults of *Fasciola gigantica*. The egg-hatching assay was performed at different concentrations. The ova development was reduced by 56.67%, 56.67%, and 36.67%, at 5%, 2.5%, and 1.25% concentrations, respectively, on day 11 post-incubation, and after 14 days, these developed eggs were decreased by 70%, 50%, and 13.33%, respectively. The flukicidal efficacy was recorded at 10% and 20% of the extract concentration, and the death of flukes was noted after 640 min and 80 min, respectively. The skin was damaged, the inner membrane of spina has erosions and syncytium was detached from the tegument. The study showed that *E. elatior* extract has antifasciolic activity against different stages of flukes. The ginger (*Zingebar officinalle*) hydroalcoholic extract was evaluated on the miracicidal stage of *Fasciola hepatica* by Ghafari et al. (2021). The hatched miracidia was incubated at 2, 5, and 10 ug/mL concentrations. The extract concentrations of 10, 5, and 2 ug/ml cause the fatality of miracidia within 105, 275, and 520 sec. and reduce the speed of miracidia movement to 0.08, 0.77, and 0.82 mm/s, respectively. The comparative efficacy with triclabendazole shows that the extract has antimiracidial efficacy. Kumar et al. (2020) performed the *in-vitro* larvicidal assay on sporocyst, redia, and cercaria stages of *Fasciola*. The Lined Cinquefoil (*Potentilla fulgens*) organic extracts and column-purified fractions larval motility was time and concentration-dependent. The highest toxicity against sporocyst, redia, and cercaria after 2h (LC50) of exposure was column purified fraction 62.4, 59.5, and 45.1 mg/L, respectively. In contrast, the lowest toxicity at this time was of ethanol extract 66.2, 64.7, and 51.3 mg/L, respectively. The same trend was found after 8h (LC50) of exposure, where column purified fraction has the highest toxicity while ethanol extract has the lowest toxicity.

Plant Oils

A number of plant derived natural products including the natural oils have been shown to possess anti parasitic activity, as they have been used against different parasites *in-vitro* and *in-vivo*. De Mello et al. (2023) evaluated the antifasciolic activity of essential oils (EOs) from two plants, Geranium *(Pelargonium graveolens)* and Sour orange (*Citrus aurantium)*, on *Fasciola hepatica*. The essential oils from both plants show 100% efficacy to inactive egg hatching. The Geranium extract showed a mean mortality time of 15 h at both concentrations tested 0.0675 and 0.03375 mg/mL, while Sour orange extract promoted death within 18 h of incubation at concentration of 0.06375 mg/mL. The accumulation of liquid in the tegument was observed. It indicates that essential oils have potential ovicidal and adulticidal activities. Another research conducted by Da Silva et al. (2020) evaluated the Sunflower (*Helianthus annuus)* fixed oil and Cumin (*Cuminum cyminum)* essential oil against *Fasciola hepatica*. The *in-vitro* assay was assessed at different concentrations both fixed and essential oils and also the combination of both oils. The essential oil at concentration of 0.03 mg/mL showed 99% efficacy and the combination of both oils at 0.035+0.03 mg/mL showed 94% effectiveness, while the fixed oil was active insufficiently as an ovicidal. Overall, the results of the experiment showed that the essential oil of Cumin could be used as a new alternative for fascioliasis control.

Plant Active Compounds

Plant compounds and their active ingredients have great potential in the control of various parasites, thus interest is increasing for the search and use of new alternatives. The botanical-derived compounds harboring potential parasiticidal properties are tested as therapeutic agents worldwide. The most common phytochemical constituents of plants are diterpenoids, thymoquinone, curcumin, carbohydrates, terpenoids, fats, enzymes, amino acids, flavonoids, chicoric acid, phenols, polyphenols, alkaloids, artimisinin, saponins, anthocyanins, tannins, isoflavones and carotenoids etc. Interest in the studies with bioactive compounds has been growing as they show direct or indirect negative effects against endoparasites. Several natural diterpenoid molecules have been studied against parasitic trematodes, and their anthelmintic properties have been evaluated. In a study, Chakroborty et al. (2022) evaluated the use of nineteen chemically modified natural active compounds, abietic acid diterpenoid analogues (MC001 to MC088) were first evaluated for their anthelmintic activities against newly excysted juveniles (NEJs) of *Fasciola hepatica*. The six analogues that were proven effective against NEJs (MC008, MC009, MC010, MC052, MC058, and MC061) were secondly evaluated for their anthelmintic activities against adult wild strain flukes. From these analogues MC010 was highly effective against 8-week immature- and 12-week mature Italian strain flukes. The damage to the dorsal side of the fluke was observed. They deducted that the use of abietic acids can be a potential candidate for the development of new anthelmintics. Thymoquinone and curcumin are the active ingredients of *Nigella sativa* and *Curcuma longa,* respectively. Ullah et al. (2017) used these active ingredients as flukicidal agents against *Fasciola gigantica.* The worm motility and egg shedding were both time and concentration-dependent. The adult flukes were exposed to different concentrations (20, 40, 60 µM) of thymoquinone and curcumin. The reduction in motility was observed at 60 µM, but the worms remained alive for 3h post-exposure. The tegumental disruptions and spine erosion were observed in the posterior region and around the acetabulum. Thus, thymoquinone and curcumin have the potential to have a flukicidal effect.

Conclusion

Fasciolosis control using plant-based medicines is proving to be more effective than synthetic anthelmintic, i.e. albendazole. Moreover, plant-based medicines are a growing trend towards a sustainable and nature-friendly environment. In phytotherapy, the time and concentration-dependent factors are the most important; hence, determining toxicity is necessary. Further research using different plant extracts, oils, and their active compounds in this field should be evaluated. However, to confirm which concentrations effectively control eggs, miracidia, larvae, and adult stages is required. Moreover, the mechanism of action should also be understood through different methods like the molecular docking method to eradicate fasciolosis from the livestock industry completely.

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Chapter 17

Phytotherapy against Eimeriosis; as an Alternative Approach to Synthetic Drug

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ABSTRACT

Eimeriosis is prevalent worldwide caused by protozoan parasite i.e. *Eimeria* specie, mostly in developing, tropical and subtropical regions. It is considered to be a disease of major economic importance affecting many species of farm and domestic animals. Due to its high infection rate, synthetic drugs i.e. sulfaquinoxaline and diclazuril was used to treat this infection in the past. The problem of synthetic drug resistance increased with the repeated usage. Due to the development of resistance, the need of the hour is to develop new effective anticoccidials such as medicinal plants are the preference for coping with this problem. Plants can potentially treat eimeriosis as they contain many significant phytocompounds that mitigate the effect of *Eimeria* oocysts. Many studies have been conducted in vitro and in vivo on different animals to control eimeriosis. It is concluded that *Moringa oleifera* and *Vernonia amygdalina* are the plants that are more convenient to use against the *Eimeria* species and exhibit maximum efficacy.

KEYWORDS
Eimeria, Eimeriosis, Plants, Phytotherapy, Photochemical

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INTRODUCTION

Eimeriosis is an intestinal disease in livestock with severe illness and death throughout the world (Das et al., 2015; Ranasinghe et al., 2023). The causative agent of eimeriosis is an Apicomplexan parasite, i.e. *Eimeria* species (Wang et al., 2021). These parasites are host-specific (Dubey, 2018) and are found all over the world, but they are most prevalent in developing tropical and subtropical regions (Ekawasti et al., 2019; Tamrat et al., 2020). There are around 1,700 species of *Eimeria* that parasitize animals. Most of these parasites affect many mammals worldwide, including domestic and wild animals. Livestock species hosting *Eimeria* parasites include ruminants, e.g., alpaca, bison, cattle, goats, guanacos, llama, sheep,vicunas, water buffalo, yaks, and old world camelids and also some non-ruminants species like donkeys, horses, pigs, rabbits, and guinea pigs (Bangoura et al., 2022).

Eimeria species are the protozoan parasites responsible for the most significant cases of calf eimeriosis (also known as 'Coccidiosis'). 20 distinct species of *Eimeria* have been reported throughout the world in cattle (Daugschies and Najdrowski, 2005; Ashfaq et al., 2023). However, *Eimeria zuernii* and *Eimeria bovis*, are the two *Eimeria* species that pose a great risk of causing eimeriosis in calves of between six and twelve months, thereby, affecting young animals more than adults since they could lead to severe diarrhea and weakness in livestock animals (Jahanzaib et al., 2017; Ekawasti et al., 2019). *Eimeria* spp. infections result in diarrhea, illness, lowered growth, and occasionally death (ruvinel et al., 2021). The intestine is a preferred location for *Eimeria* species in ruminants, particularly around weaning (Odden et al., 2019). The main mode of infection in calves is the consumption of sporulated oocysts of *Eimeria*. Infection can transfer from cow to calves and from calves to cow when animals are kept in overcrowded farms (Tamrat et al., 2020). *Eimeria* infections are among the most significant parasitic illnesses influencing the profitability of ruminant livestock farms.

Prevalence of *Eimeria* spp.

Ruminant eimeriosis is a widespread disease that affects livestock globally, with high prevalence rates observed in goats, young calves, and sheep in England, the United States of America, and Louisiana, reaching 98.00, 86.00, and 86.00%, respectively (Keeton and Navarre, 2018). Currently, the prevalence of ruminant Eimeriosis is currently 28.57% in India (Bangoura and Bardsley, 2020), up to 100% in Malaysian goats, 78.68% in Ethiopian goats (Paul et al., 2020) and 48.13% in Ethiopian sheep (Barre et al., 2023), 39.80% in the Amazon, and 39.27% in Egyptian goats (Paul et al., 2020). In Iran, the prevalence of *Eimeria* specie in cattle and sheep was 81.80 and 78.20%, respectively (Dau et al., 2021; Hatam-Nahavandi et al., 2023). In cattle and bufffaloes, the prevalence of *Eimeria* spp. has been widely reported throughout the world (Chandra Deb et al., 2022). Prevalence of the same reported in Indonesia was 65.40% in cattle (Ekawasti et al., 2021). The overall prevalence of *Eimeria* spp. in buffaloes, was 49.60% reported in District Toba Tek Singh, Punjab, Pakistan (Khan et al., 2013).

Life Cycle

All *Eimeria* species follow a similar life cycle. Infected animals excrete unsporulated oocysts, which remain in the environment for a considerable amount of time. Under specific conditions, these oocysts undergo sporulation and release sporocysts, which are then ingested by the calf and release sporozoites. The sporozoites then move to the location of their choice to begin cellular invasion. Fig. 1 shows the life cycle of *Eimeria*.

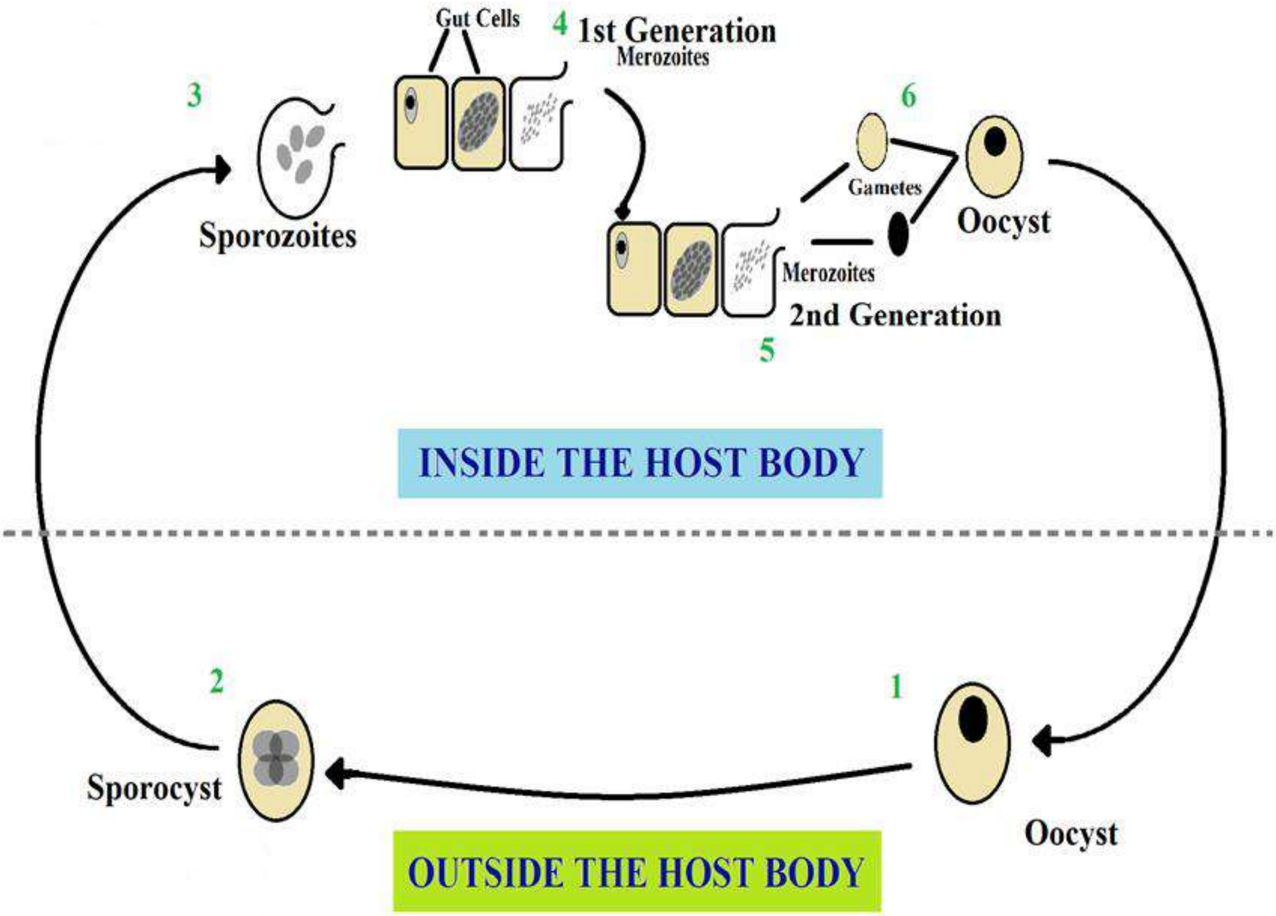

Fig. 1: Life Cycle of *Eimeria* spp.

The schizont, a huge multinuclear cell in which merozoites are generated, is formed by a series of nuclear divisions in this process, followed by sexual replication through gametogony. The dimorphic phases of microgametes (male gamete) and macrogametes (female gamete) are formed by a single cycle of sexual replication referred to as gametogony, which occurs after numerous generations of merozoite formation. Finally, microgametes and macrogametes fuse to form a zygote, which will then grow into an oocyst and be able to cause infection when released through the feces (Burrell et al., 2020; Ashfaq et al., 2023).

Control of Eimeriosis

Synthetic Drug against Eimeriosis

Controlling parasites in ruminants depends on group-based diagnostics and cure because it can be hard to handle separate tests and treatments for each animal (Charlier et al., 2014; Calvete et al., 2020). The synthetic drugs have a primary role in controlling gastrointestinal parasites. A drug's efficacy is affected by different factors including drug misuse and a lack of knowledge about how to properly handle, administrate and control the drug. Utilizing drugs in wrong concentrations will waste time and money. To come up with an eimeriosis treatment plan, discussion with veterinarian is required (Desta, 2015).

Anticoccidial medications are used to treat eimeriosis; however, their effectiveness has decreased due to drug resistance issues, due to this reason, the mostly used method for controlling eimeriosis now a days with sulfaquinoxaline and diclazuril drugs is unreliable (Abbas et al., 2011; Grandi et al., 2016). The employment of various coccidiostats (synthetic drugs) and other chemicals is also not cost-effective. Furthermore, traces of these drugs have been detected in livestock products i.e. in meat, which is potentially threatening regarding consumer's health (Khan et al., 2012; Alzahrani et al., 2016; Song et al., 2020; Abd-ELrahman et al., 2022).

Phytotherapy as Alternative to Synthetic Drug Treatmment

Traditional medicine is considered the sum of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not. It is used in the maintenance of health as well as in the prevention, diagnosis, improvement, or treatment of physical and mental illnesses (Salmeron-Manzano et al., 2020). The WHO reports that 80% of underdeveloped nations still utilize traditional plant-based medicines (Vaou et al., 2021).

Phytotherapy is defined as the practice of using medicinal compounds obtained from plants for the purpose of treatment (Saeed and Alkheraije, 2023). Animals can be treated with plants, which may include using the plants as a whole or in part (herbal weeds used as fodder), extracts, or essential oils (Salman et al., 2020; Hussain et al., 2021; Akhtar et al., 2023; Saeed et al., 2023). Plants play an essential role in the daily lives of many people around the world, including those in Africa (Mukazayire et al., 2011). Because of their lower cost, lower risk of side effects, and potential efficacy compared to synthetic drug, the pharmaceutical industry is focusing on medicinal herbs (Mukazayire et al., 2011; Pushpanathan et al., 2021). Herbal medicines have played a vital role in treating and diagnosing disease throughout human history (Sharma et al., 2021; Agidew, 2022). These have long been recognized as a reliable and secure source of medicinal compounds (Agidew, 2022).

The utilization of herbal plants plays a significant role in promoting health and preventing diseases in communities (Talebi et al., 2022). The key finding is that less than 10% of the 600,000 plant species have been recognized and utilized worldwide that serve more than the biological purpose (Wagner and Wolff, 2012). For the reduction of coccidiostat's residues in livestock products, it is necessary to substitute them with plant-based preparations such as supplements or oils of medicinal plants, which having effective and unique biological activities that can be used for the treatment or control of coccidial infection (Liaqat et al., 2016; Kostadinovic et al., 2019). The medicinal plant components (like leaves, fruits, and roots) are used to control the coccidial infection as an anticoccidial and therapeutic agent in livestock (Mahmood et al., 2018; Ahmad et al., 2019). These have great potential as sources of new anti-parasitic agents. In addition to killing parasites, these drugs may shield the affected organs from further damage (Alzahrani et al., 2016). Plant based medication not only impact growth rate and production improvements but also have other beneficial effects like improving intestinal microbial population, disease antibody concentration, blood parameters and overall health status of livestock (Castillo-Lopez et al., 2017).

Plants used against Eimeriosis

Eimeria species has become immune to the synthetic drugs currently being utilized. Now a day's researchers are aiming to access the efficacy of plants as alternatives to synthetic drugs. Table shows the work done by some researchers to evaluate the anticoccidial efficacy of different plants on various animals. Table 1 shows evaluation of different plant efficacy on *Eimeria* species.

Phytochemical used against Eimeriosis

The term "phytochemical" refers to these naturally occurring bioactive substances obtained from plants that are added to animal feed to increase their productivity (Lillehoj et al., 2018). In order to mitigate the adverse effects of enteric infections, the combination of various phytochemicals shows synergistic effects. Phytochemicals like saponins, tannins, terpenoids, amino acids, N-3 fatty acids, flavonoids, carotenoids, chicoric acid, vernoside, allicin, alkaloids, phenols, and betaine are effective against eimeriosis (Muthamilselvan et al., 2016). Some of the potential phytochemicals used against eimeriosis are described as below:

Saponins

The plants like *Ucca schidigera* and *Trigonella foenum-graecum have* the ability to disrupt cellular membranes as it contains saponins in their active compound that help in the disruption of *Eimieria* membrane (Benarbia et al., 2022).

Tannins and Chicoric acid

Emblica officinalis and *Echinacea purpurea* contain tannins and chicoric acid that have been shown to improve chickens' humoral immune reaction to coccidial infections (Muthamilselvan et al., 2016). Tannins are present in many feeds such as fodder legumes, browse leaves and fruits (Lillehoj et al., 2018).

Table 1: Evaluation of different plant efficacy on Eimeria spp. of various animals

Plant	Test organism	Eimeria Specie	Findings
Mulburry (*Morus nigra*)	Mice	*Eimeria papillata*	The treatment with mulberry significantly reduced oocyst output and parasitic stages in the jejunum, while increasing goblet cell reduction, suggesting that mulberry has potent antiparasitic properties (Thagfan et al., 2020)
Mastic tree (*Pistacia lentiscus*)	Chicken	Mixed *Eimeria* Spp.	Mastic tree reduced oocyst counts and improved growth performance, suggesting the potential protective and growth-promoting effects of lentiscus oil against Coccidiosis (Rahmani et al., 2021)
Garlic (*Allium sativum*)	Chicken	*E. tenella*	Garlic shown strong oocysticidal action and reduced infectivity, making them superior disinfectants compared to chemical alternatives (Abd-ELrahman et al., 2022)
Olive pulp (*Olea europaea*)	Chicken	Mixed *Eimeria* Spp.	Olive pulp is effective in reducing the maximum oocysts number after only 8 hours of incubation. Also, increasing extract concentration decreased the number of *Eimeria* oocysts. A direct relationship was observed between the concentration of the extract and the reduction in oocysts. The results suggest that the extract has anti-Eimeria spp. activity (Debbou-Iouknane et al. 2019).
Bitter leaf and Drumstick tree (*Vernonia amygdalina* and *Moringa oleifera*)	Rabbit	*E. media* and *E. magna*	The Bitter leaf and Drumstick tree showed enhanced production of interleukin (IL) and immunoglobulins (Ig), suggesting their potential as a substitute for synthetic anticoccidials in rabbit farms (Konmy et al., 2023)
Grape (*Vitis vinifera*)	Mouse	*E. papillata*	Grapes significantly reduced the oocyst output and inhibited the sporulation and harm caused by *E. papillata*. These findings suggest that grape vines have potent anticoccidial properties (Murshed et al., 2023)
Marigold and Summer savory (*Calendula officinalis* and *Satureja hortensis*)	Pig	*Eimeria* spp.	*S. hortensis* and *C. officinalis* show potential as effective natural antiparasitic options for treating gastrointestinal parasites in swine. The *S. hortensis* and *C. officinalis* show potential as effective natural antiparasitic options for treating gastrointestinal parasites in swine (Baies et al., 2023).
Neem (*Azadirachta indica*)	Japanese quail	*E. tenella*	Neem extracts supplemented quails showed mild sloughed epithelium of cecal villi. In conclusion, neem extract is recommended as a naturally effective alternative to an anticoccidial drug to mitigate *Eimeria* infection in Japanese quails (Ishaq et al., 2022).
Onion (*Allium cepa*)	Chicken	*E. acervulina*	*Allium cepa* is a promising alternative to coccidiosis treatment (Aguinaga-Casañas et al., 2022).
curcumin (*Curcuma longa*)	Chicken	*E. tenella*	Curcumin has shown a significant inhibitory impact on *E. tenella* sporozoites, causing morphological alterations and lowering the vitality and infectiousness of the sporozoites (Khalafalla et al., 2011).

Note: E. stands for Eimeria

Allicin

The compound Allicin found in Allium Sativum acts as an antioxidant which protects against lipid peroxidation and providing hepatoprotective effects, while also contributing to the herb's aroma, flavor, and various health benefits such as antibacterial, antiviral, anticancer, and antiparasitic properties. Allicin possesses both antioxidant and antiparasitic properties, and it also triggers immunity by prolonging the profiling antibody response, instantly eliminating the sporozoites. Since allicin is readily absorbed through the cell membrane, it is recommended to employ its anti-proliferative or oxidative damage-inflicting properties to harm cells.

Flavonoids

A wide and varied class of phenolic chemicals found in plants are called flavonoids. Numerous plants possessing active flavonoids, like Syzygium aromaticum and Moringa oliefera, have anticoccidial properties. Additionally, flavonoids can pass through cell membranes and kill oocysts and sporozoites. Because flavonoids are known to reduce oxidative stress, they can minimize eimeriosis (Saeed and Alkheraije, 2023).

Conclusion

The development of synthetic drug resistance against eimeriosis in the livestock industries is alarming as it causes severe diarrhea. Sometime it may lead to the death of the animals. There is a need to develop alternatives such as plant-based medication. Plant based treatment is useful as it is less expensive, easily available to the farmers, reduces resistance issues, and also decreases the disease prevalence in the animals without losses. Extensive research is required to understand the mode of action of the plants-based medicine and their dose concentration to reduce the consequences and leading to obtain the maximum results.

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Chapter 18

Phytochemicals as Potential Alternatives to Chemical Insecticides for Controlling Animal Lice

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ABSTRACT

Lice is an ectoparasites that are more prevalent globally. Lice belonging to the order Phthiraptera. Two types of lice are found around the world i.e. chewing and suckling lice. Lice are host specific. The common host for the lice is human, dog, cats, horses, cattles, sheep and goats etc. it is highly infected all over the world due to which synthetic drugs were used to treat this infestation due to the development of resistance by using the same king of drug. It is difficult to control the lice infestation. It is necessary to develop plants-based alternative to cope with this global problem. Plants can control the lice infestation as it contains different type of phytochemicals like saponins, tannins, flavones and fatty acid etc. that can show effective acaricidal effect against the lice. Plants are easily accessible to the poor farmer, cheap and non-toxic source to control the lice infestation. It is concluded that citronella, cloves, ginger, lemongrass, makwan and litsea oil show maximum efficacy against the lice infestation in chicken.

KEYWORDS
Phthiraptera, Insecticides, Acaricidal, Plants, Phytochemical

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INTRODUCTION

Animal lice, also known as ectoparasites, are tiny insects that live on the skin or in the fur of animals, feeding on their blood, skin, or other tissues. These afflict both people and animals' hair and scalps. There are several types of lice that infest animals, including: Trichodectes (chewing lice), Anoplura (sucking lice), Phthiraptera (biting lice) (Burgess, 2009). Common hosts for animal lice include: humans, Dogs, Cats, Horses, Cattle, Pigs, Sheep and Goats. Signs of lice infestation may include: Excessive scratching or biting, Hair loss or thinning, Skin irritation or redness, tiny eggs (nits) or lice visible on the skin or in the fur and Anemia or weight loss (in severe cases). Lice can transmit diseases and cause discomfort for animals. Treatment options include: Insecticides (shampoos, sprays, or powders), Medicinal shampoos. Flea combs or lice combs, Environmental cleaning and disinfection. Treatments for ectoparasites include lindane, crotamiton, precipitated sulfur, benzyl benzoate, malathion, phoxim, carbaryl, permethrin, ivermectin, imidacloprid, phenol, and phenylpyrazole (Khalil et al., 2017, Mencke et al., 2004, Wright, 1999, Littlewood et al., 1995, Osman et al., 2006, Mencke et al., 2005, da Silva Mendes et al., 2011; French et al., 2016). However, resistance to these treatments often occurs (Martin et al., 2004). Resistance is caused by inappropriate drug prescription, mismatch with the dose prescribed, and no rotation of acaricides used (Chosidow and Scabies, 2006; Thullner et al., 2007). Since the use of acaricides is still the major curative and preventive strategy for ectoparasite infestations (Abbas et al., 2014). There is need to the development of plants-based alternative that are harmless, cheap and easily accessible to the poor farmers.

Prevalence of Lice

The goats within Toba Tek Singh District had a lice infection that ranged from 9.58% to 9.59% (Iqbal et al., 2014). *L. setosus,* a blood sucking louse, and *Trichodectes canis*, a biting louse, are reported from dogs. Dogs can also suffer from louse infestations, leading to symptoms like itching and hair loss (Mehlhorn et al., 2012). *Haematopinus tuberculatus* was reported in Buffalo (Shamim et al., 2015). According to research conducted in Faisalabad in 2006, roughly 18% of the total buffaloes had lice infestations (Hussain et al., 2006).

In August 2003 Prevalence of lice was 94.45% in pigeon in in India. It started declining in subsequently month i.e., September 2003 to December 2003 reached 58.8% (Ahmad et al., 2009). In the current study, 48% of domestic pigeons were infected with one or more lice species in Iraq (AL-badrani et al., 2023). In Ethiopia, the overall frequency of goat lice infection was 22.9% (Disasa, 2020). According to Azam et al. (2002), there were 34.7% more lice detected on buffalo in Quetta, Pakistan. More to 35.1% of Australian schools have reported having head lice (Speare et al., 2002). After conjunctivitis and diarrhea, head lice infestation is the 3rd most frequently reported outbreak in daycare facilities (Speare et al., 2002).

Life Cycle

There are three phases in the life cycle: nymph, adult, and egg (nit). Throughout her life, the female lays between 50 and 150 eggs, or between four and six nits every day. The oval-shaped eggs have a pale tan tint and resemble tiny sand particles in size. Usually on the top of the head and close to the ears, nits adhere to the bottom of hair shafts close to the scalp. Under typical circumstances, eggs hatch in 5 to 7 days (Figure 1). Nymphs that have just hatched are translucent. They can consume two or three blood meals a day, and they must consume a meal of blood within 24 hours in order to survive. Immature lice go through several nymphal stages in a span of around nine days, during which time they turn straw colored (Mumcuoglu, 2009).

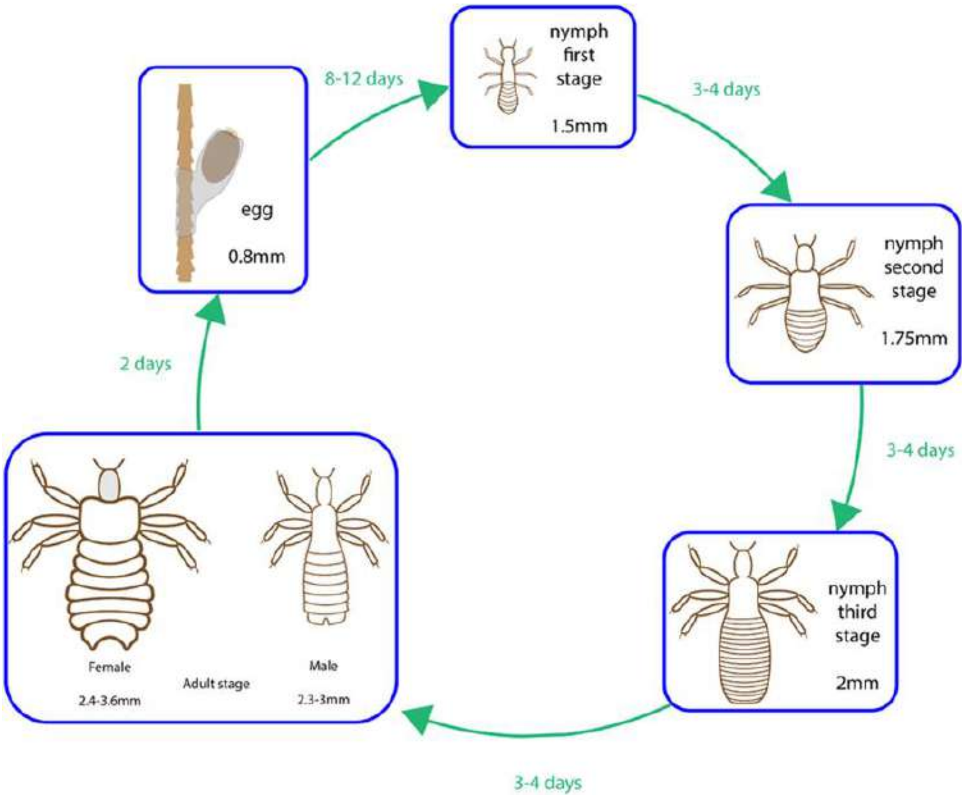

Fig. 1: Life cycle of lice.

Adults can survive a maximum of thirty days after completing their life cycle, which takes 15 to 21 days. It's not always the case that having nits indicates an active infestation. There could be nits from a past infestation. The location of nits along the scalp and hair the shaft can indicate whether an infestation is current or previous since eggs are affixed onto the hairline shaft at the scalp. Human hair grows roughly 1/4 inch and carries the louse egg with it in a week, the length of time that it requires for the egg to hatch. (Guillebeau and Van De Mark 2000). In her adult life, a female louse produces between 50 and 150 eggs. Initial nymphal stage emerges from the egg and, following three molts, develops into nymphs, and ultimately a male or female louse (Mumcuoglu, 2009).

Control of Lice

There is different method of controlling lice infestation in the animals. Lice infestation was control by using chemotherapy. Different drugs were used that shows the maximum output to the infestation i.e. ivermectin, albendazole and permethrin. Like the neurotoxic pediculicides (the drug that is used to kill the lice). Synergized pyrethrin or synthetic pyre thyroid are the active chemicals in the drug that directly affect the lice eventually the lice were kills. These drugs work by inhibiting neuronal sodium transport, leading to respiratory paralysis in larvae and adult lice (Coates et al., 2019). Due to the misuse and over use of the same chemicals to the lice, the lice developed resistance to these chemical drugs. It was difficult to cope with this condition so it is necessary to develop an alternative that show maximum output with neglected consequences, easily available and are cost effective. Plants based medication is considered as alternative as in ancient time plants were used to treat the disease in the ancient world that was most common in the Asian countries including India, Pakistan and China etc (Meinking et al., 2010; Burgess et al., 2013; Candy et al., 2018).

Use of Phytochemicals

Phytochemicals are natural bioactive substances obtained from plants that are added to animal feed to increase productivity. They are also known as phytobiotics or phytogenics (Gadde et al., 2017). The use of medicinal compound obtained from the plants for the treatment of diseases in known as Phytotherapy (Saeed and Alkheraije, 2023). Phytochemicals can be utilized in solid, dried, and grinding forms, as well as extracts (crude and concentrated). Depending on the method used to obtain the active constituents, they may also be categorized as essential oils, such as coconut oil, tea tree oil, olive oil, garlic oil, petroleum jelly, and mayonnaise (Gadde et al., 2017). Numerous remedies that can be sprayed to human hair and are supposed to prevent the spread of head lice contain natural oils and other substances. These products are sold over the counter by the majority of pharmacies, as well as health stores, beauty salons, and groceries. Garlic has an 8% percentage of ethanol, which makes it excellent for killing head lice. It has been demonstrated to be successful in controlling head lice infestation in 5 hours. Garlic is also frequently utilized for its antibacterial and antifungal qualities. Allicin, saponin, scordinin, and essential oil are found in garlic (Samiasih et al,.2023).

Use of Plants against Lices in vitro and in vivo

Medicinal platns was used against the lices infestation in different animals including humans. Here is the work done by some researcher to evaluate the efficacy of plants against lice infestation including humans is as follow;

The ovicidal activity of a neem seed extract preparation on skull and head lice larvae was assessed by Mehlhorn et al. (2011). The head and body lice species, *Pediculus humanus capitis* and *Pediculus humanus,* were incubated in neem seed extract for five, ten, twenty, 30, or 45 minutes. Neem seed extract has an effective capacity to eradicate head lice eggs and adults. The purpose of this study was to demonstrate that all larvae could be prevented from hatching with a modest 5-minute incubation period. Around 93±4% of the eggs from the untreated human lice measures and around 76% of the head lice controls hatched. This solution offers a complete remedy for lice on the head with just one dose if the head lice (eggs and movable stages) are fully coated for around ten minutes.

Semmler et al. (2012) conducted an evaluation on the importance of testing repellents for lice. It is difficult to restrict lice multiplication by treating affected heads alone because reinfections can happen as soon as a child's head has been completely cleared of lice with an active anti-louse drug. Because of this, many products have been developed with the goal of keeping lice away, however there isn't much hard proof of this.Repelling lice is significantly more challenging than repelling other kinds of insects or even ticks, as demonstrated by the current investigation, which comprised two louse insect repellents (Picksan® NoLice including Linicin® Preventive Spray) including three compounds (at a 10% dilution) acknowledged for their general repellent qualities action. Therefore, it is vital to be worried that some repellents available the market could not be as efficient as they claim since they might have been produced using an inaccurate testing method.

Comparative efficacy of new commercial pediculicides against adults and eggs of *Pediculus humanus capitis* (head lice) was studied by Gallardo, Anabella, et al. (2012). In controlling head louse infestations, the effectiveness of pyrethroids has significantly decreased due to resistance to these drugs. Since head lice treatments can be bought in Argentina, many of them have been produced in recent years. The purpose of this study was to compare the efficacy of both newly invented Argentinian items, Nopucid Qubit® or Nopucid Bio Citrus®, to two standard products, Nyda® and Hedrin®. Nopucid Qubit®, a two-phase lotion, contains ciclopentaxiloxane in phase two and geraniol and citronellol in phase one. Nopucid Bio Citrus®, conversely, ciclopentaxiloxane and dimethicone have been added. Furthermore, two laboratory experiments were employed to evaluate the sensitivity of the new formulations' insecticidal effectiveness. Both in the laboratory and in vivo, motile forms died before receiving exposure to a particular chemical for only a few minutes. Our research proved that official over-the-counter pediculicides have been successful against head lice eggs or motile stages for the first time in Argentina.

The Toxicity of Essential Oils from Three Origanum Species against *Pediculus humanus capitis*, the head louse, has been evaluated by Arserim et al. (2021). *Capitis humanus pediculus* Children of school age who have De Geer are at risk for the disease. Although a variety of chemical pediculicides have been used to eradicate lice, resistance has grown over the past few decades. As an alternate source of lice treatment chemicals, essential oils from plants have been employed. In this work, the pedalicidal activity of three Origanum species' essential oils against adult *P. humanus capitis* was investigated. Three Origanum species' aerial portions were hydrodistilled using a Clevenger-style device to extract the essential oils. The *P. humanus capitis* organisms that were utilized came from children who had been infected by combing at elementary schools. Applying the adult immersion test, human lice were subjected to three dilutions (1%, 0.5%, and 0.1 percent w/v) of tested oils for five minutes. The findings indicate that at 1% concentration, all Origanum oil constituents have been demonstrated to significantly reduce the rate of bowel, abdomen, and limb movements, resulting in more than 90 percent mortality within 12 hours. Our findings suggested that novel pediculicides towards head louse could be developed using essential oils from Origanum.

Al-Timimi et al. (2022) Assessing the effectiveness of Capparis spinosa Total flavonoids in the management of Menacanthusstramineus avian lice. This study included both in vitro and in vivo flavonid research on Capparis spinosa on chicken lice that were grown locally. All 115g of newly collected plant samples' flavonoids were extracted by reflex extraction. The necessary aglycon component was created by working nonstop for eight hours, and 600 milligrams of distilled water were mixed using 10% v/v HCl with ethyl acetate as the solvent for this purpose. The remaining material was weighed when the acetate layer dried and was examined qualitatively and quantitatively. In one hundred milliliters of distilled water, triple polyphenols (Capparis spinosa complete flavonoids) were compared to a positive control that included 0.5 mg/mL of permethrin. The use of distilled water is applied as a countermeasure. The study's findings demonstrated that the herb is rich in various flavonoids and has the ability to eradicate chicken lice from the skin at various phases of their life cycles. The impact on killing lice eggs and nymphs was larger when the percentage of the extract was increased; however, this difference was not statistically relevant in terms of killing adult lice.

The impact of COVID-19 and the delayed retrieval of lice prevalence in Cambridgeshire, UK, were assessed by Burgess et al. (2023). After adult and child interaction habits changed and schools were closed, there was a confirmed global decline in the prevalence of head lice. Concurrently, a decrease in therapeutic sales was seen, possibly as a result of product supply problems following the pandemic, but this did not appear to contribute to a rise in infestation cases. Examining schools close to Cambridge, UK, showed a significant drop in infection rates compared to surveys conducted prior to the COVID-19 pandemic, particularly in urban schools. In contrast to forecasts, the number of cases has gradually increased since schools started full-time operations in 2022–2023.

The prevalence of kid alterations resistance to insecticide in head lice *(Pediculus humanus capitis*) among elementary school pupils in Jeddah, Saudi Arabia, was assessed by Alsaady et al. in 2023.A growing body of evidence indicates that scalp lice (*Pediculus humanus capitis*), a serious global health concern, are becoming more common among Saudi children. The purpose of this study is to determine how frequently a mutation causing insecticidal resistance occurs in head lice collected from students. To find the location and frequency of the kdr T917I mutations in head lice, a polymerase chain reaction, or PCR, was used to ramp up the voltage-gated potassium channel gene component. Subsequently, two genotypic types were found using restriction fragment length polymorphism, or RFLP, patterns: homozygous-susceptible (SS) versus homozygous-resistant (RR) (Larkin et al., 2020).Of the forty-five samples, seventeen (37.80%) proved to be SS and twenty-eight (62.2%) to be RR. The RR sample's amino acid and nucleotide sequences were found to incorporate point mutations like T917I and L920F. Compared to other countries, Saudi Arabia's scalp louse population had a low prevalence of minoxidil resistance mutation. This study provides the first evidence of a permethrin sensitivity mutation in human lice living in Saudi Arabia. The findings of this investigation will show how the kdr mutation is increasingly affecting lice on the head in Saudi Arabia.

A study conducted in 2021 by Vigad, N., et al. examined the physical properties, chemical compositions, and insecticidal effectiveness of plant essential oils against parasites as well as chicken lice (Menopongallinae). It was decided to create an essential oil preparation to combat mites (Ornithonyssus bursa) and chicken lice (Menopongallinae). All the essential oils shown efficacy against lice and mites in vitro. Chicken lice died at a rate of 100% when citronella oil was used at the lowest dose of 0.208 µg/cm2, while cloves, ginger, lemongrass, Makwan oil (0.416 µg/cm2), and litsea oil (0.832 µg/cm2) were also shown to be effective at greater concentrations

Conclusion

Lice infestations are a common condition affecting millions of animals i.e. dog, sheep, buffalos, cow, and goats as well as humans each year. This Infestations can cause damage to physical and mental health and are difficult to control because of developing resistance to the currently used synthetic drugs in the developing countries. It is required to formulate the plant-based alternative to treat this infestation. It is cheap, less expensive and easily available to the farmers. However, Extensive research is required to solve the problem of resistance by using different plants and describe their phytochemicals that was more effective to the lice.

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Chapter 19

Moringa Oleifera as Plant Protein Source in Fish Meal

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ABSTRACT

The accessibility of affordable protein sources for formulating aqua feed is directly correlated to the prosperity of the aquaculture sector. Prices for fish diets would rise due to the fast fall in availability of fish meal (FM) caused by the high demand for aqua feed and the persistent and ongoing decrease in FM supply from various fisheries sectors, hence finding an alternate protein resource for aqua feed is essential. Since plant-based protein sources are always readily accessible, eco-friendly, sustainable, and inexpensive, they have largely replaced dietary FM in fish diets. *Moringa oleifera* is a member of the Moringaceae family, aquaculturists may consider it a viable plant-based protein substitute for dietary FM, on account of its distinctive nutritional attributes. Leaves of *M. oleifera* constituted a very high crude protein concentration. Several studies have demonstrated that *M. oleifera* can improve growth performance, digestibility coefficient, fish immunity, and resistance to illness, increase antioxidant capacity, and reduce symptoms of toxicity and physical stress in a variety of fish species when supplemented as a protein source in fish feed. In conclusion, moringa has the potential to serve as a sustainable, environmentally safe, cost-effective, and nutrient-dense feedstock for aqua feeds, thereby contributing significantly to the sustainable aquaculture sector.

KEYWORDS		
Moringa oleifera, Plant protein source, Fish meal, Cost effective, Growth enhancement, Antioxidant, Disease resistant.	Received: 09-Jun-2024 Revised: 03-Jul-2024 Accepted: 08-Aug-2204	A Publication of Unique Scientific Publishers

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INTRODUCTION

The accessibility of affordable protein sources for formulating aqua feed is directly correlated to the prosperity of the aquaculture sector (FAO, 2018). FM is unique primary protein sources, due to its balanced amino acid composition, excellent digestibility, and palatability, as well as its significance in improving the absorption, metabolism, and digestion of the various nutrients in fish diets. Prices for fish diets would rise due to the fast fall in availability of FM caused by the high demand for aqua feed and the persistent and ongoing decrease in FM supply from various fisheries sectors (Tacon and Metian, 2015). Finding an alternate protein resource for aqua feed is also important due to comparatively high costs, additionally inconsistent standards of FM throughout the prior decade (Turchini et al., 2019).

Plant Based Protein Source

Since plant-based protein sources are always readily accessible, eco-friendly, safe for the environment, sustainable, and inexpensive, they have largely replaced dietary FM in fish diets. Several studies have shown that other plants may be used to partially or fully replace FM in aqua feeds (Daniel, 2018). According to Hamed et al. (2021), "phytobiotics" are food additives derived from plants that include specific phytochemical constituents which can help fish wellbeing in many ways, including better development, stronger immunity, better antioxidant status, and overall health. Essential oils from these plants not only heal the fish, but they also kill germs and parasites (Dawood et al., 2021).

Moringa oleifera

The slim soft wood plant known as moringa (*M. oleifera*) is a member of the Moringaceae family. Pakistan, India, Sri Lanka, Madagascar, and parts of northeastern and southwestern Africa are among the main recipients. For all the good it does for organisms' health, diets, water supplies, and ecosystems, *M. oleifera* deserves the title "Tree of Life." Almost every component of this tree has a specific and useful function. This includes its roots, seeds, bark, gum, leaves, fruit, and flowers. A fast-growing tree native to tropical and subtropical regions, *M. oleifera* is recognized as "the drumstick tree" (Falowo et al., 2018). Moreover, due to its anti-inflammatory, antioxidant, hepato-protective, and antibacterial activities, moringa is sometimes mentioned equally "the miracle tree" for one's particular favorable medicinal qualities. Livestock and fish may eat all parts that make up the moringa tree, which includes pods, seeds, bark, roots, and flowers (Fig. 1). Goats, cattle, fowl, and fish, among many others, were shown to effectively consume meals made from *M. oleifera*, according to many publications (Abd Rani et al., 2018). Leaves of *M. oleifera* have a very high crude protein concentration of 260 gram per kilogram of dry matter (DM), and they all have the same configuration of essential amino acids (EAAs). This makes them nutritionally unique. Furthermore, the moringa foliage is loaded with many minerals and vitamins, including potassium, iron, as well as vitamins A, C, including E. Moringa has a large quantity of phytochemicals, including alkaloids, phenolic acids, terpenoids, carotenoids, and flavonoids (Ahmadifar et al., 2020), Research has demonstrated that *M. oleifera* can improve growth performance in a variety of fish species, including rohu and Nile tilapia, as well as Bocourti's catfish's feed utilization indices, as well as nutrient digestibility coefficients (Puycha et al., 2017). *M. oleifera* in the diet may improve fish immunity and resistance to illness, increase antioxidant capacity, and reduce symptoms of toxicity and physical stress (Elbad et al., 2019).

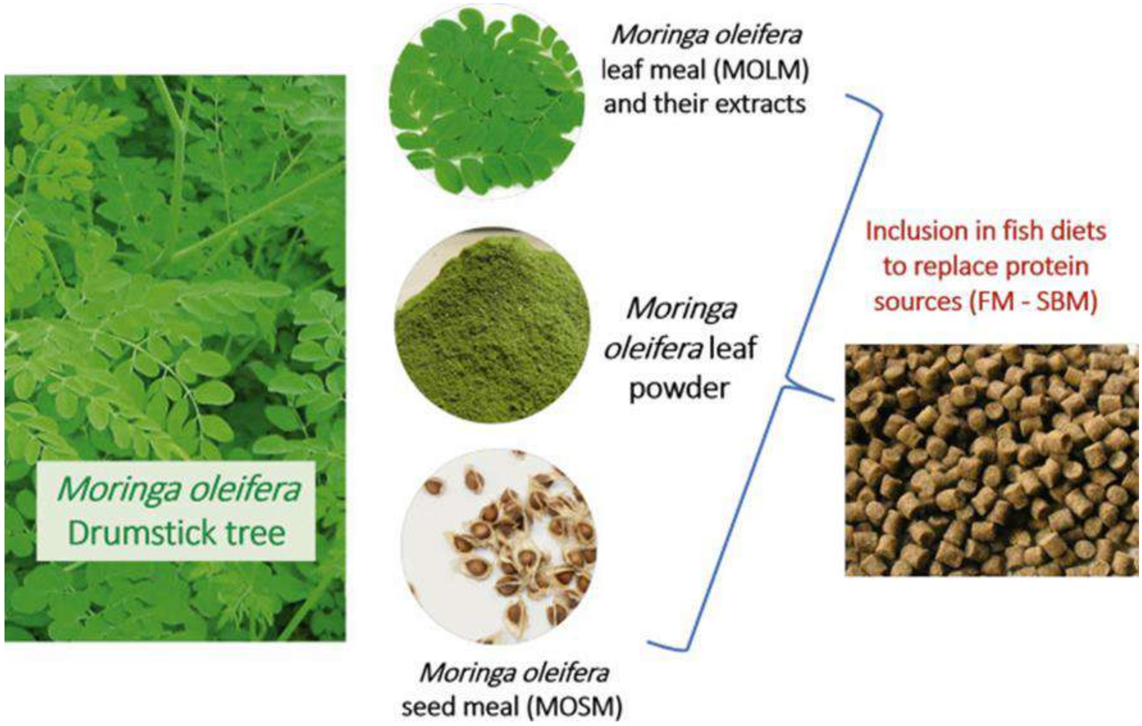

Fig. 1: Diverse formulations of *M. oleifera* used in fish feed (Abdel-Latif et al., 2022).

Nutritional and Chemical Organization of *M. oleifera*

Researchers in the fields of fish or cattle feeding and rearing have taken an interest in *M. oleifera* due to its antioxidant, immune-stimulating, and nutritionally diverse properties. Antioxidant polyphenols, microelements, fatty acids, vitamins, minerals, and crude protein levels are often quite high in *M. oleifera* leaves. In addition, numerous plant based chemicals, including alkaloids, carotenoids as well as proanthocyanidins, are abundant in *M. oleifera* roots, leaves, fruits, and seeds (Su and Chen, 2020). In-depth examination of the nutritious contents of *M. oleifera* foliage is shown in Table 2.

Crude Protein (CP) and Amino Acid Content

According to Wu et al. (2013), the CP concentration found in *M. oleifera* foliage varies between 23.0% and 30.3% on a dry matter basis. According to phytochemical research, all of ten EAAs are found in *M. oleifera*. An increase in the amounts of glutamine, and valine, there is also lysine, phenylalanine, as well as arginine was seen in *M. oleifera* (Busani et al., 2011). In Table 1 amino acid compositions of *M. oleifera* leaf meal (MOLM) in grams per 100 grams of protein are listed.

Crude Fiber (CF)

Comparing *M. oleifera* leaves to soybean meal (SBM), which has CF levels of 7.3%, the former has less than 5.9%. In general, fish and cattle find feeds with a low CF level to be more appetizing (Su and Chen, 2020).

Crude Lipids and Fatty Acid Contents

Compared to other woody plant forages, the lipid content of *M. oleifera* leaves is quite high, at about 7.09%. The unsaturated fatty acids make up around 57 percent from total fatty acid content of *M. oleifera* foliage, with the greatest amount being 44.57% of α-linolenic acid (Busani et al., 2011).

Mineral Content

Compared to maize, the mineral content of *M. oleifera* leaves is much greater, reaching up to 12.0% ash. Minerals such as calcium, iron, potassium, phosphorus, and zinc are rich in moringa foliage (Su and Chen, 2020). According to Teixeira et al. (2014), the dry weight of *M. oleifera* leaves is around 24,700 milligrams per kilogram of calcium, 4,400 milligrams per kilogram of phosphorus, 318.81-milligram milligrams per kilogram of iron, 190-milligram milligrams per kilogram of magnesium, as well as 22.05 milligram per kilogram of zinc.

Table 1: Amino acid composition (g/100g Protein) of *M. oleifera* leaf meal (MOLM) (Ganzon-Naret, 2014)

Amino acid	Composition (g/100g Protein)
Alanine [NEAA]	3.00
Arginine[EAA]	1.81
Aspartic acid [NEAA]	1.34
Cysteine [NEAA]	0.01
Glutamic acid [NEAA]	2.45
Glycine [NEAA]	1.526
Histidine[EAA]	0.697
Isoleucine[EAA]	1.181
Leucine[EAA]	1.948
Lysine[EAA]	1.629
Methionine[EAA]	0.302
Phenylalanine[EAA]	1.637
Proline [NEAA]	1.198
Serine [NEAA]	1.085
Threonine[EAA]	1.36
Tyrytophan[EAA]	0.491
Tyrosine [NEAA]	2.639
Valine[EAA]	1.409

*EAA (Essential amino acid), NEAA (Non-essential amino acid)

Phytochemicals

Phytochemicals are substances found in moringa plants which are having defensive and disease-prevention properties; they are not nutrients themselves. Zeatin, kaempferol, as well as isothiocyanates, are among several phytochemicals found in abundance in *M. oleifera*. In addition, kaempferol, quercetin, vanillin, gallic acid, chlorogenic acid, ellagic acid, ferulic acid, and kaempferol are all present in water-based extracts of moringa fruit, seeds, and leaves. The butanol component of *M. oleifera* is more abundant in the plant's leaves and fruits, while both contain polyphenols (Ahmadifar et al., 2020). Along with carotenoids, epicatechin, o-coumaric acid, niazirin, niaziminin A, 3-caffeoylquinic, and 5-caffeoylquinic acid, the leaves also contain niazirin. Chemical examination of *M. oleifera* seed ethanolic extracts revealed tannins, glycosides, alkaloids, and sterols. The main sterols found in the oil extracted from *M. oleifera* seeds are campesterol as well as clerosterol, with low concentrations of isoavenasterol. In addition, a synthetic polysaccharide including D-galactose, 6-O-Me-D-galactose, D-galacturonic acid, L-arabinose, and L-rhamnose was shown to be present in the water-soluble extract of *M. oleifera* (Roy et al., 2007). The blooms of *M. oleifera* comprise flavonoid peroxides including kaempferol, rhamnetin, isoquercitrin, and kaempferitrin (Muhammad et al., 2016). Furthermore, alkaloids, reducing sugars, triterpenoids, flavonoids, anthraquinones, catechol tannins, gallic tannins, and ether and water extracts of moringa leaves are present (Kasolo et al., 2010).

Table 2: Nutrient composition (% dry matter) of *M. oleifera* leaves (Ganzon-Naret, 2014)

Nutritional element	Compound percentage
Dry matter content	93.360
Crude protein content	29.100
Crude lipid content	8.500
CF content	8.100
Ash content	11.800
Nitrogen free extract	42.500
Metabolizable energy (Kcal/100g)	339.200
Calcium content	0.490
Phosphorus content	0.360
Potassium content	1.380

Anti-nutritional Factors

There are many health advantages of using woody plant leaves in fish diets regularly, there are also some potential downsides, such as the potential impact on feed palatability and digestibility because of the occurrence of anti-nutritional components (Su and Chen, 2020). Natural feed components may include anti-nutritional factors, which are compounds that disrupt digestive and metabolic functions in the body via different methods. These molecules are synthesized by plants in their regular metabolism. Soetan and Oyewole (2009) categorized anti-nutritional features based on their mode of action. These factors include those that inhibit the breakdown of proteins and utilization, those that inhibit energy consumption, those that accelerate the vitamin needs of organisms, in addition, those that interrupt the host's immune responses. When these anti-nutrients are present in high enough concentrations, they may impede protein digestion and prevent the body from absorbing trace elements from the diet. Reduced or delayed development performance and low feed efficiency are outcomes of using plant-derived protein sources in fish diets, which include anti-nutritional elements. Nile tilapia showed reduced growth indices and inadequate nutrient utilization when fed diets that replaced less than 10% of FM proteins by *M. oleifera* leaf with an amount of anti-nutritional elements (Richter et al., 2003).

Beneficial Uses and Dietary Applications of Moringa oleifera in Fish Nutrition

Fig. 2 shows the results of studies that looked at the usefulness of various *M. oleifera* extracts in aquafeeds, including MOLM (leaf meal), MOSM (seed meal), and aqueous, methanolic, and ethanolic extracts of *M. oleifera*.

Fig. 2: Broad remunerations of complementing fish feed with *M. oleifera* (Abdel-Latif et al., 2022)

Growth and Proximate Body Composition

There was no discernible effect on growth or fish health was recorded when 25% of the FM protein in a Tilapia diet was replaced with dietary moringa leaves (Hlophe and Moyo, 2014). The feed conversion ratio (FCR) and average daily gain (ADG) of Nile tilapia might be greatly enhanced by dietary supplements containing 15% MOLM (Ahmed et al., 2014). Tekle and Sahu (2015) found that Nile tilapia's growth indexes, such as weight gain (WG), FCR, specific growth rate (SGR), apparent protein utilization (APU), hepatosomatic index (HSI), and intestinal somatic index (ISI), could be greatly enhanced by supplementing their diet with a 0.25% ethanolic flower extract of *M. oleifera*. It is worth noting that Nile tilapia growth indices such as fish body mass gain (SGR), length gain rate (FCR), and fish somatic indices (ISI, HSI, and SSI) were significantly enhanced when food supplements containing 1.5 percent MOLM were administered (Elabd et al., 2019). The FCR as well as finalized body weight (FBW) for tilapia were significantly improved when they were supplemented with five percent *M. oleifera* leaf powder in their feed (El-Kassas et al., 2020). Research on rohu (*Labeo rohita*) found that growth metrics including FCR, WG, and SGR were significantly improved when 10% MOLM-based diets were used as FM protein (Masood et al., 2020). Similarly, Adeshina et al. (2018) discovered that *Cyprinus carpio* juveniles' FBW, WG, SGR, PER, and FCR were significantly enhanced when thirty percent of the dietary SBM protein was replaced with MOLM-based feed. Research by Kaleo et al. (2019) found that freshwater shrimp (*Macrobrachium rosenbergii*) had significantly higher WG, SGR, and PER, as well as enhanced FCR when supplemented with half percent MOLM in their diet.

Haemato-biochemical and Metabolic Indicators

When it comes to gauging the nutritional worth of fish diets, the physiological state of fish, and the impacts of harmful substances, haemato-biochemical indicators are invaluable biomarkers (Khafaga et al., 2020). Important parameters regarding fish overall wellbeing position include kidney and liver roles, which include hepatic enzymes like alanine transaminase (ALT), alkaline phosphatase, also known as (ALP), and aspartate transaminase (AST), as well as renal action indicators like urea, uric acid, and creatinine (Dawood et al., 2020). The circulatory system indicators of African catfish, including volume of packed cells (PCV), haemoglobin (Hb), total number of red blood cells (RBCs), as well as white blood cell count (WBCs), were found to be significantly higher in the group that supplemented their diet with *M. oleifera* leaves compared to the control population (Ezekiel et al., 2016).

Immunity Enhancement and Resistance to Disease

Ingesting *M. oleifera* being found to boost the susceptibility resistance of several fish species, including guppies (*Poecilia reticulata*), Mozambique tilapia, common carp, gibel carp, giant freshwater prawns, gilthead seabream, and *Oreochromis nilotics* (Bisht et al., 2020; Zhang et al., 2020). The results of a 45-day feeding experiment with *Aeromonas hydrophila* showed that *O. nilotics* increased its resistance, survivability, and immunological indices like serum lysozyme (LYZ) activity when supplemented with *M. oleifera* (Mbokane and Moyo, 2018). Incorporating 5% *M. oleifera* leaves into gilthead seabream diets significantly improved their systemic immunity. This was achieved by increasing protease as well as lysozyme and alternatives counterpart pathway action, as well as improving the phagocyte capability of the renal leucocytes as well as respiratory surge actions. In addition, Mansour et al. (2018) found that the dermis peroxidase, together with messenger RNA transcription intensities of lysozyme, while the TNF-α gene was significantly downregulated, in the intestinal mucosa of fish.

Antioxidative Capacity

Disruption of cell walls, membranes, proteins, DNA damage, and lipid peroxidation (LPO) are some of the harmful effects that can be inflicted on fish bodies as a result of oxidative stress, which is defined as an imbalance in the body's redox homeostasis caused by an excess of reactive oxygen species (ROS) like superoxide anion as well as hydroxyl radicals (Abdel-Daim et al., 2020). Furthermore, peroxynitrite (ONOO-) is a very reactive molecule that rapidly reacts to superoxide anion radicals to generate nitric oxide, yet an additional very irritable radical that has harmful effects on exposed tissues. Enzymatic antioxidant enzymes such as catalase (CAT), glutathione reductase (GR), superoxide dismutase (SOD), glutathione-S-transferase (GST), glutathione peroxidase (GPX), as well as selenium GPX (Se-GPX) can moderate ROS, while non-enzymatic mechanisms to maintain redox homeostasis include reduced glutathione (GSH) and lower intensities of malondialdehyde (MDA). One of the byproducts of LPO metabolism is MDA, which is why it is often used as a marker to indicate LPO. An efficient defense mechanism against the harmful effects of superoxide radicals is provided by the catalytic dismutation of these radicals becoming hydrogen peroxide (H_2O_2) as well as molecular oxygen (O_2). This is the primary and unique role of superoxide dismutase or SOD. The decomposition of H_2O_2 towards water and oxygen is aided by CAT and GPX (Abdel-Latif et al., 2022). Juvenile Nile tilapia, giant aquatic prawns, and gibel carp may have their antioxidant status strengthened by consuming *M. oleifera,* according to many studies (Zhang et al., 2020). In addition, a study conducted by Abd El-Gawad et al. (2020) demonstrated Nile tilapia supplementation with *M. oleifera* leaves significantly improved their tissue antioxidant status. This was achieved by increasing levels of SOD in addition to CAT regarding the hepatic as well as kidneys of the fish, while simultaneously reducing MDA values in these tissues compared to the control group. A current research through Zhang et al. (2020) found that young gibel carp supplemented with fermented *M. oleifera* leaves had a stronger antioxidant status in their blood. This was achieved by significantly increasing serum CAT, SOD, as well as GPX activities, and significantly lowering serum MDA along with protein carbonyl contents.

Attenuation of Toxicity Signs

Various studies have documented potent effectiveness of moringa in reducing toxic indicators associated with different substances. These include sodium fluoride in gilthead seabream (Abdulkareem et al., 2017), chlorpyrifos as well as pendimethalin within *O. nilotics* (Ahmed et al., 2020; Ibrahim et al., 2019). Furthermore, the detrimental effects of H_2O_2 on intestinal insusceptibility regarding the epidermis as well as gills of sea bream were effectively mitigated through nutritional supplementation with five percent *M. oleifera* (Mansour et al., 2020). Notably, when common carp were subjected to sublethal levels of CuONPs, dietary *M. oleifera* extract of seeds significantly reduced oxidative stress and histopathological modifications in hepatocytes as well as gills (Noureen et al., 2018).

Mitigation of Physical Stressors

Certain physical stresses can be mitigated by *M. oleifera*, including ammonia stress in *M. rosenbergii*, transportation as well as hyperthermia-mediated pressure in *O. nilotics* (Kazeem et al., 2017), incarceration trauma in *C. carpio* (Khalil and Korni, 2017), and undernourishment in *O. nilotics* (Elabd et al., 2019). Khalil and Korni (2017) documented the results of a sixty 60-the day feed experimental study wherein the inclusion of a water-based extract of the foliage of moringa in diets significantly reduced the 20-minute confinement period in common carp subsequent to the feeding experiment's conclusion. Additionally, it has been observed that Nile tilapia fed a dietary regimen enriched with one and half percent

MOLM for a duration of 90 days experienced a substantial reduction in 1-week starvation stress. This was demonstrated through notable enhancements in serum biochemical amounts including glucose, as well as cortisol concentrations, including CAT, SOD, and GPX activities (Elabd et al. 2019).

Final Remarks and Prospects for the Future

In general, the rising cost of FM and the escalating demand and scarcity for it have compelled aquaculture experts to investigate alternative sources. Interest has been significantly piqued in plant-based protein sources, such as moringa, among these alternatives. Aqua feeds may consider *M. oleifera* a viable plant-based protein substitute for dietary FM, either in part or in its entirety, on account of its distinctive nutritional attributes. Moreover, this "miracle tree" is replete with phytochemicals that have significant therapeutic, medicinal, and pharmacological applications. Numerous studies have examined the nutritional value of various *M. oleifera* preparations, including seed cake, liquid or methanolic extracts of leaves, entirety leaves, roots, seeds, floral products, as well as essential oils derived tough its seeds, when incorporated into aqua feed. Numerous studies have documented, fish whose feed were complemented through ideal inclusive dosage along with form of *M. oleifera* experienced greater weight gain and demonstrated enhanced growth performance, as well as improved biometrics and feeding utilization indices. Proximate carcass composition and haemato-biochemical parameters remained unaffected, and the hepatoprotective efficiency was found to be substantial. Certain studies have also demonstrated its potential to strengthen immune responses, improve resistance to bacterial pathogens, and enhance antioxidant status in fish. These effects are attributed to the distinctive phytochemical components of the substance, which possess notable antimicrobial, antioxidant, and immune-stimulating properties. In addition to the aforementioned beneficial properties for fish, the introduction of the wrong dose or form of nutritional moringa can result in adverse effects on fish health due to various anti-nutritional aspects. The adverse effects quite necessitate additional investigation. Subsequent investigations and research endeavors ought to be focused on addressing the issue regarding anti-nutritional aspects that are inherent in *M. oleifera*. This can be accomplished by implementing various processing techniques on the plant components, including fermentation, combining moringa foliage and exogenous enzymatic digestivity, or streamlining techniques involved in cultivation. In conclusion, moringa has the potential to serve as a sustainable, environmentally safe, cost-effective, and nutrient-dense feedstock for aqua feeds, thereby contributing significantly to the sustainable aquaculture sector.

Conclusion

In conclusion, the investigation into the potential of *M. oleifera* as a substitute for fishmeal in aqua nutrients exhibits considerable potential in promoting the sustainable growth of the aquaculture industry. The considerable body of research dedicated to examining the nutritional characteristics and health advantages of *M. oleifera* highlights its capacity to improve the growth, performance, and general well-being of fish. Nevertheless, it is critical to address potential negative consequences and anti-nutritional attributes by conducting additional research and employing processing methods. By doing so, the complete potential of moringa as a sustainable, ecologically sound and economically viable feedstock for aquaculture can be utilized, thereby enhancing the industry's durability and longevity and fostering the health of aquatic ecosystems.

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Chapter 20

Analysis of Medicinal Plants on Calcium Channel Activity in Rats for Cardiovascular Health

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ABSTRACT

Cardiovascular disease exists as a foremost reason of mortality all over globally. The situation encouraged the uses of medicinal plants for treatment of different ailments. This study emphases on the usage of *Solanum nigrum* extract to treat isoproterenol-induced myocardial infarction in rats. *Solanum nigrum* is acknowledged for its potent calcium ions into cells. This reduction in calcium ion influx leads to the vasodilation of heart blood vessels, therefore increasing myocardial infarction. By leveraging the natural properties of *Solanum nigrum* this research aims to provide a viable alternate for the treatment of cardiovascular diseases highlighting the plant's potential in mitigating the heart related ailments. This study underscores the importance of continued research into medicinal plants offering promising insights into alternative therapies for cardiovascular conditions. Through rigorous investigation *Solanum nigrum* may emerges as a significant therapeutic agent in the fight against cardiovascular disease, offering new hope for reducing mortality rates associated with heart ailments.

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INTRODUCTION

Medicinal Plants

Plants that have healing properties or provide positive pharmacological effects on human or animal bodies (Chekuri et al., 2020). Medicinal plants, often referred to as medicinal herbs, have been a fundamental part of traditional healthcare since antiquity (Giannenas et al., 2020). They generate a wide array of chemical substances that serve multiple functions, including protection against pests, diseases, and herbivores (Divekar et al., 2022). In numerous non-industrialized societies, medicinal plants are favored for their accessibility and affordability compared to modern pharmaceuticals (Bhandari, 2021).

Historical Context

In the Middle Ages the skills of healing, cultivation of medicinal plants and preparation of drugs moved to monasteries. In the 3500 BC the different countries' culture start using herbs for the purpose of therapeutic, aromatics, cosmetics and to prepare medicinal products.

Egyptians: Used plants extensively in their medical practices. The Ebers Papyrus (circa 1500 BCE) lists hundreds of medicinal remedies (Kurhekar, 2021). Greeks: Hippocrates and Dioscorides documented numerous herbal remedies. Chinese: Traditional Chinese Medicine (TCM) includes extensive use of plants. Indians: Ayurveda, dating back over 3000 years, employs a wide variety of herbs in treatments.

Significance of the Global Medicinal Plant Trade

The global trade in medicinal plants is substantial, with an estimated annual value of approximately $60 billion and growing steadily (Divekar et al., 2022). Despite minimal regulation in some regions, the World Health Organization works to promote safe and rational use of traditional medicine. However, concerns exist regarding the regulation of botanical herbal products with criticisms directed at the presence of unproven claims and pseudoscience (Giannenas et al., 2020).

Evolution and Challenges of Medicinal Plants in Modern Medicine

Medicinal plants confront various threats, such as climate change, habitat destruction, and over-harvesting to meet market demands (Rajasekharan and Wani, 2020). The role of plants in medicine underwent a profound shift in the 19th century with the advent of chemical analysis (Chekuri et al., 2020).

Cyclodextrin Composites

Cyclodextrin composites stay originate now in fruitlets, root vegetables as well as whole meals. It represents that the herbal plants are rich in bioactive compounds (Bhandari, 2021).

Examples

These contain enormously varied forms of complexes, such as:

- Phenolic acids
- Beta-Carotene
- Plant Steroids
- Thiols composites

Unveiling the Bioactive Components of Medicinal Plants

Therapeutic uses of plants have been part of traditional medicine practices for centuries. Primarily floras remained cast-off through individuals on the way to come across their nutritious necessities (Kurhekar, 2021). Common plants have become valuable for improving well-being and treating various ailments across many human societies. Numerous plant species are still used today in regions like Asia, South America and Africa for medicinal purposes against various diseases. (Howes et al., 2020).

Threats and Conservation

Therapeutic Floras (TFs) remain generally value foundations of vegetal foodstuffs in addition to they remain disappearing by the side of extraordinary proportion (Rajasekharan and Wani, 2020). The TFs assets exist below continuous danger of destruction for the reason that of inhabitants' expansion, overutilization, ecological devastation, unlawful employment as well as illogical reaping methods (Yan et al., 2018).

Efficient Therapeutic Plants

1. Gingko

Ginkgo devises extended antiquity regarding usage happening handling gore syndromes in addition to reminiscence concerns (Zaid, 2022). The situation exists finest identified currently by way of tactic towards hypothetically retain memorial shrill (Stableford, 2021). Research laboratory revisions take revealed that ginkgo recovers gore flow through initial active gore vessels in addition to production of a reduced amount of gluey blood. That one exists as well as quercetin (Rickels, 2020).

Potential Benefits

1. Dementia (loss of memory)
2. Magenta eyes (A pattern of abnormalities by birth that affects multiple organ systems of the body)
3. Soreness (A painful and uncomfortable condition because of injury)
4. Diabetes mellitus (condition in which the body losses its ability to produce insulin)
5. Nervousness (a state of being anxious)

Considerations

- Prolonged use might raise the risk of thyroid and liver cancer, as observed in rats.
- It could affect liver function, necessitating enzyme monitoring.
- It interacts through gore diluters.
- Its spores are toxic if consumed.
- Possible flank possessions comprise nuisance, distressed gastric, wooziness as well as sensitized reactions.
- Consult your doctor due to its numerous drug interactions (Ychanges, 2018)

2. Turmeric

Turmeric takes existed castoff now healing measures above the spans happening diverse portions in relation to the biosphere (Howes et al., 2020). Now in traditional medicines, turmeric remains assumed towards devising numerous therapeutic belongings as well as firming up generally dynamism of physique, releasing air, dispersing maggots, refining incorporation, modifiable menorrhoea, softening bilestone and discharging inflammation. Numerous south Asian republics expenditure the aforementioned by way of antibacterial used for wounds, injuries as well as bumps in addition to such as sterile mediator. Now in Pakistan, this one ensues castoff by way of inflammation reducer representative (McIntyre, 2019).

Potential Benefits

1. Relieve from arthritis
2. Cancer prevention
3. Preventing DNA mutations
4. Several skin diseases

Considerations

- Supplements may result in excessive intake, complicating dosage, and quality assurance.
- Prolonged use might lead to gastrointestinal discomfort.

Turmeric exhibits low bioavailability, combining it with pepper can improve absorption (McIntyre, 2019).

3. Tea Tree Oil

Tea tree oil, take out commencing the Australian native tea tree stays renowned for its effectiveness in treating various skin conditions such as bad skin conditions, sportsperson's base, injuries, dead skin flakes, bug bits also additional instigative issues (Abubakar et al., 2024). Research indicates it possesses antimicrobial properties, particularly beneficial for wound healing and infections. Often utilized as a potent essential oil, it should always be diluted with a carrier oil (Della Sala et al., 2022).

Potential Benefits

- Treating acne
- Alleviating athlete's foot
- Healing cuts
- Managing dandruff
- Soothing insect bites

Considerations

- Toxic if ingested
- Potential for skin allergic reactions
- Possible influence on hormone levels
- Long-term use is discouraged

4. Chamomile

Chamomile, characterized by its daisy-like flowers, is renowned for its anti-anxiety properties (Sah et al., 2022). It is commonly consumed as tea but also available in liquid, capsule, or tablet forms. Research supports chamomile's calming effects and its potential applications in cancer treatment (Dai et al., 2022).

Potential Benefits

- Alleviating anxiety
- Reducing stress
- Promoting better sleep
- Potential applications in cancer treatment

Considerations

- Can cause allergic reactions, including anaphylaxis
- Possible interactions with blood thinners (Candeloro et al., 2022)

Herbal Calcium Channel Antagonists

Medicinal plants with calcium channel blocking abilities are useful in addressing various conditions like high blood pressure, irregular heartbeats and chest pain (Ajebli and Eddouks, 2020). These plants have phytochemicals that affect calcium channels, reducing calcium influx into cells. This mechanism leads towards relaxation of visceral, non-striated muscles and encourages blood vessel dilation (Rzajew et al., 2020).

Phytotherapeutic Plants with Calcium Channel Blocking Benefits

Solanum nigrum, *Digitalis purpurea* (Foxglove), *Crataegus monogyna* (Hawthorn), *Olea europaea* (Olive tree), *Apocynum cannabinum* (Dogbane), *Lavandula angustifolia* (Lavender), *Valeriana officinalis* (Valerian) (Jia et al., 2019).

Ailments Treated by *Solanum nigrum*

1. Hypertension

Hypertension, or high blood pressure (140/90mmHg or higher), is a common condition that can become serious if left untreated (Abbas et al., 2024). It is a global health issue affecting people across developed, developing, and underdeveloped countries. Hypertension is categorized into primary hypertension, which accounts for 95% of cases, and secondary hypertension, which makes up the remaining 5% (Della Sala et al., 2022).

While FDA-approved synthetic drugs are available for treatment, they often have side effects (Schein, 2020). Herbal remedies, which are typically cheaper, safer, and more compatible with the human body, present a promising alternative (Dai et al., 2022). Calcium channels are effective targets for anti-hypertensive drugs, and Ca+2 network blockers stand powerful agents trendy the handling regarding hypertension (Jia et al., 2019).

Hypertension as a Silent Killer

The FDA calls hypertension a "silent killer" because many individuals are unaware, they have it (Sah et al., 2022). Hypertension is a serious condition marked by elevated systolic and diastolic blood pressure (Stableford, 2021). Regular body fluid compression remains around 120/80mmHg, whereas appraisals beyond 140/90mmHg require medical attention (Schein, 2020).

Types of Hypertensions

Hypertension remains distributed hooked on dual categories: prime or primary (or vital) hypertension as well as subordinate hypertension (Cheng et al., 2023).

Primary Hypertension

Primary hypertension which constitutes 95% of cases, has no identifiable secondary cause and includes subtypes like plexogenic arteriopathy, veno-occlusive disease and capillary hemangiomatosis (Al-Qadi et al., 2021).

Physiological Mechanisms Contribute to Primary Hypertension

Various physiological mechanisms contribute to primary hypertension, including:

- Genetic factors
- Sympathetic nervous system
- Over activity
- Renal dysfunction
- Obesity
- Oxidant stress
- Cardiovascular effects disruption
- Environmental factors

Primary Hypertension

Primary hypertension can cause cardiac changes, such as:

Thickening and stiffening of the heart walls, reduced cardiovascular contraction efficiency, Structural changes in large arteries and precapillary resistance vessels, atherosclerotic, thrombotic degeneration and left ventricular hypertrophy (Abbas et al., 2024).

Secondary Hypertension

Secondary hypertension, which comprises of five percent (5%) instances. It can be caused by:

Hyperparathyroidism, Thyrotoxicosis, Nocturnal as well as sustained increases voguish blood pressure, reduced femoral pulses, abdominal striate, pallor palpitations, increased carotid artery thickness. Secondary hypertension has known causes and is considered treatable (Al-Qadi et al., 2021).

FDA-approved Synthetic Drugs

FDA-approved synthetic drugs for hypertension include α-blockers, β-blockers, angiotensin receptor blockers, and diuretics (joshi and Shelke, 2021). However, aftereffects regarding these pills take driven the hunt in place of nontoxic herbal alternatives (Sharma et al., 2021). Herbal drugs, which are less expensive and further attuned through the humanoid physique, are gaining attention for their potential to treat hypertension (Stableford, 2021). Medicinal plants contain phyto-constituents that act on various hypertension drug targets and can be used in various forms, such as infusions, decoctions, fresh fruits or raw consumption (Verma et al., 2021). Calcium channels are proven drug targets for hypertension and various medicinal plants contain phyto-constituents capable of blocking these channels, suggesting their potential use in hypertension treatment. These medicinal plants can be considered for monotherapy (Ajebli and Eddouks, 2020).

Side Effects of Synthetic Antihypertensive Drugs

Synthetic antihypertensive drugs are widely used to manage Hypertension, but they can have various side effects such as:

- Electrolyte imbalances (e.g., low potassium, low sodium), Increased urination, Dehydration, Increased blood sugar levels, Muscle cramps, Dizziness, Fatigue, Depression, Bradycardia (slow heart rate), Cold hands and feet, Sleep disturbances, Sexual dysfunction, Cough (persistent dry wheeze), Raised plasma k^+ ranks, Truncated gore stress (hypotension), Wooziness, Angioedema (swelling of the tissues), Swelling in the ankles or feet.

Mechanism of Action of medicinal plants as calcium channel blockers is given in Fig. 1.

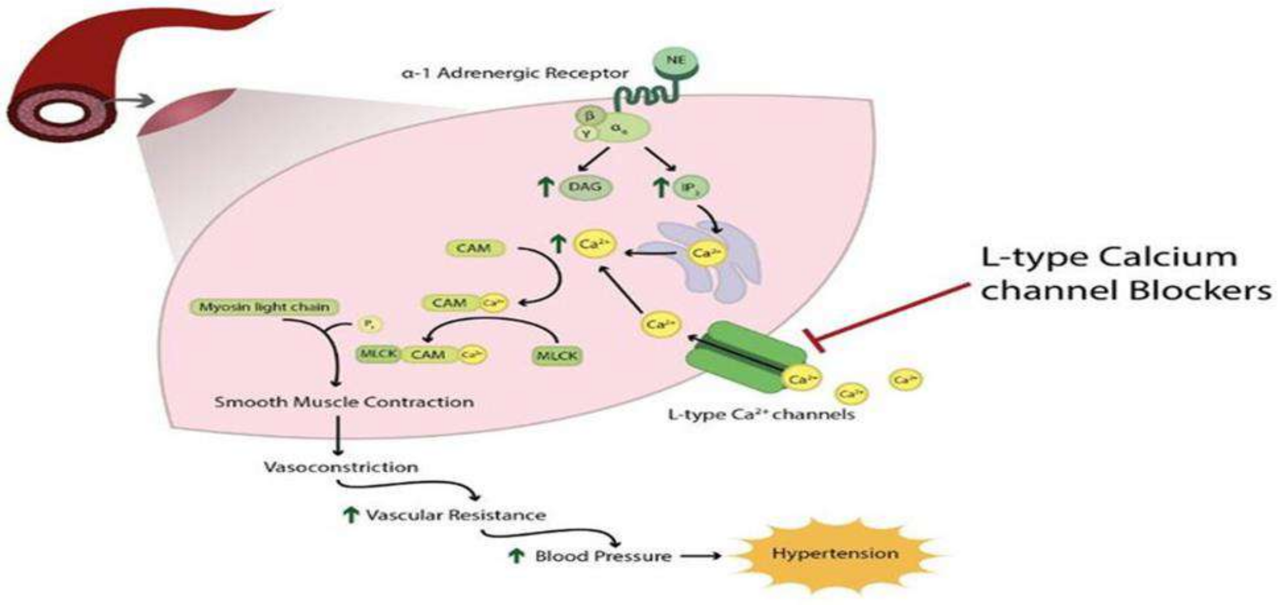

Fig. 1: Mechanism of Action of medicinal plants as calcium channel blockers

Herbal Medicines for Hypertension Treatment

Many antihypertensive drugs used to manage hypertension come with side effects. Consequently, scientific studies suggest adopting various lifestyle changes and incorporating appropriate therapeutic floras happening the handling regimen (joshi and Shelke, 2021). Subordinate bio-chemicals found in certain herbs and spices exhibit antihypertensive properties (Ajebli and Eddouks, 2020). Nineteen Subordinate bio-chemicals present in certain aromatic plant as well as seasonings show hypo tensor possessions (Hanxing et al., 2023).

Mechanism of Action of Herbal Medicines as Antihypertensive Agents

Utmost floral remedies manage as well as diminish hypertension through their antioxidant, ant leukotriene, as well as contra-apoptotic possessions (Verma et al., 2021). They also stimulate the eNOS-NO signaling alleyways in addition activate blood vessel formation (Xu et al., 2023). Procedure by which certain therapeutic floras and its extricate control in hypertension are illustrated in Fig. 2.

Calcium Channels

Calcium channels also known as L-type channels are part of high voltage-activated Ca^{+2} channel family (Tombesi, 2022). These channels are the primary pathway for Ca^{+2} influx within the skeletal and smooth muscle tissue, the heart as well as hormone producing cytes (Rzajew et al., 2020). They need significant loss of polarity to activate as well as have a lifelong effect. Recent concluded L-type ca^{+2} networks can be inhibited over dihydropyridines, phenylalkylamines, and Benzothiazepines (Landaw, 2019). The above-mentioned pills remain commonly castoff during the treatment of cardiac ailments.''

Calcium Channels Complexes

Calcium channels remain hetero-oligomeric centers composed of eight proteins:

1. α1 Subdivision: Comprises the ionic-regulating points, with four genes encoding the Alpha1 subunits of L-type ca^{+2} networks.
2. Selectivity filter
3. Voltage sensor
4. Obligatory positions**:** Intended for wholly identified ca^{+2} network blockers.
5. Ancillary subunits: Restrain the electro physical possessions of the network composite.
6. Within the β subdivision
7. Alpha2delta subunit: A dimer.
8. Trans membrane gamma subunit

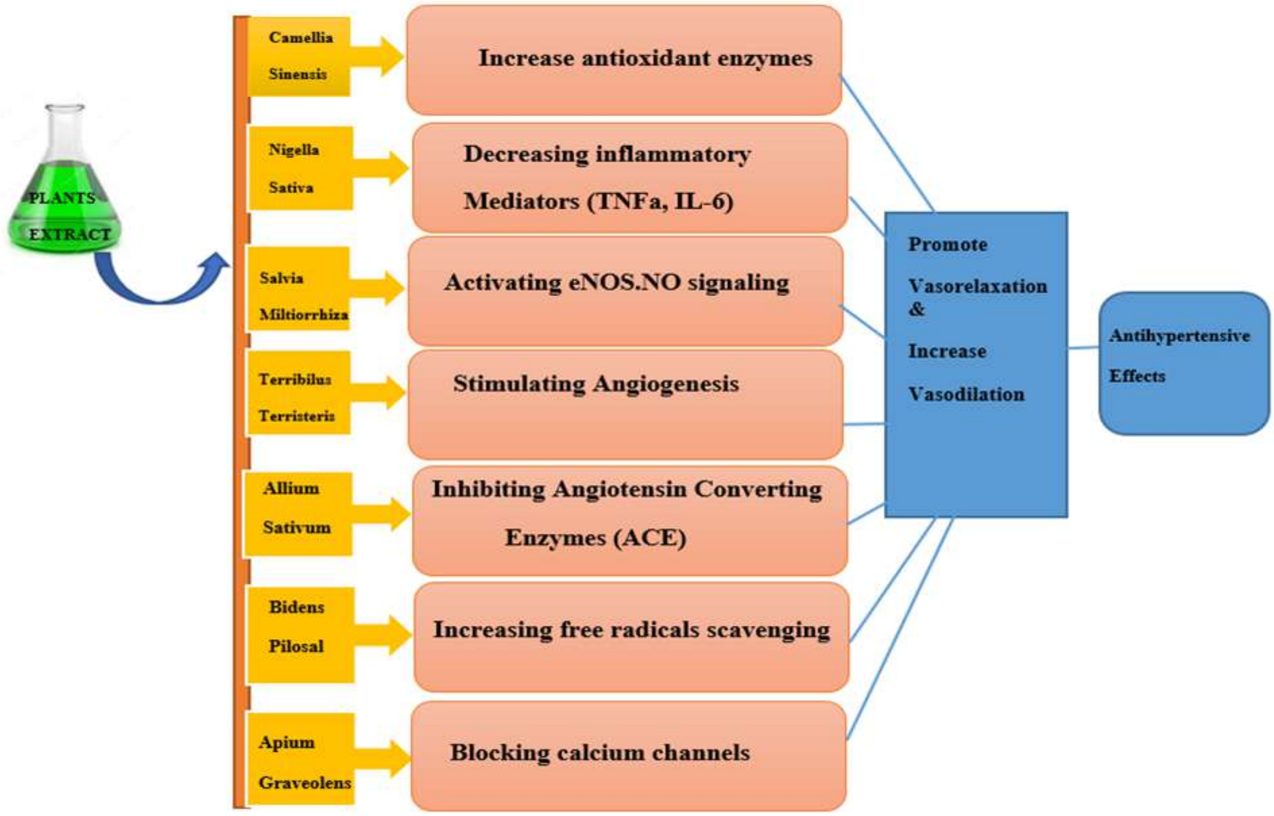

Fig. 2: Therapeutic floras and its Extricate control in hypertension

Expression of Calcium Channels in Various Tissues

Calcium channels are expressed in:

- Skeletal muscles, Cardiac muscles, Smooth muscles, Endocrine cells, Brain, sensory cells, Retina, Leukocytes.

Types of Calcium Channels

Calcium channels be present happening numerous arrangements (T, L, N, R, P, and Q) dependent on soft tissue forms (Stableford, 2021). Calcium channels are crucial for various biological procedures comprising tendon contraction, the body's chemical messengers discharge, and protein expression. The main types of ca^{+2} channels stand categorized grounded taking place in their biophysical and pharmaceutical belongings. Here are the primary types of calcium channels (Landaw, 2019).

1. L-Type Calcium Channels (Long-Lasting)

Function: Long- lasting -type networks are responsible for prolonged calcium entry into cells (Tombesi, 2022). The purpose Long lasting-form network remains to permit entrance of adequate Calcium on behalf of commencement of tightening through ca^{+2}- persuade intracellular ca^{+2} proclamation as of sarcoplasmic reticulum (Landaw, 2019).

Location: Found within heart and smooth and non-striated flesh cells, neurons, and hormone secreting cytes.

Pharmacology: These channels are sensitive to dihydropyridines drugs, such as amlodipine and nifedipine.

Key Role: They exist as a primary objective of ca^{+2} channel blockers (CCBs) cast-off to treat hypertension, angina, and arrhythmias (Chatki et al., 2021).

1. L-type (Long–lasting type)

The Long lasting-type ca^{+2} channel remains originate now vascular smooth muscle, in nonvascular smooth muscle within several soft tissue in addition to a numeral non-contractile soft tissue. Barricade of the Long lasting -type channel is blamable on behalf of the pharmaceutical activities of the existing Calcium channel blockers (To et al., 2020).

These channels are established drug targets for hypertension, and calcium channel blockers are effective antihypertensive agents (Waise et al., 2017).

2. N-Type Calcium Channels (Neuronal)

Function: It involved in Adrenaline release at neuronal junctions. (Jurkovicova, 2019). Location: Predominantly present in neurons. Pharmacology: Blocked by ω-conotoxins, from cone snail venom. Key Role: Crucial for neuronal conduction and potential pain management. (Antunes et al., 2022).

3. P/Q-Type Calcium Channels

Function: P/Q- form of networks remains essential for neurotransmitter release at central and peripheral synapses. Location: Found within the termini of presynaptic neurons. Pharmacology: Sensitive to ω-agatoxins from spider venom. Key Role: They perform noteworthy act within synaptic transmission then are involved within certain types of epilepsy and migraine disorders (Alehabib et al., 2021).

4. R-Type Calcium Channels (Resistant)

Purpose: It utilizes for neurotransmitter proclamation and neuronal dismissal. Location: Found in neurons and some types of endocrine cells. Pharmacology: Partially resistant to many calcium channel blockers, hence the name. Key Role: These channels are involved in fine-tuning synaptic transmission and neuronal activity (de Amorim et al., 2024).

5. T-Type Calcium Channels (Transient)

Function: Transient-form of channels mediate transient ca^{+2} currents, which are important for pacemaker activities in the heart and neurons. Transient network looks on further destructive potentials as compared to Long lasting form as well as perhaps the production of significant role within the primary depolarization of sinoatrial node and Atrioventricular node of tissue. Location: Originate within cardiac cytes, neurons also in a number of smooth muscle cells. Pharmacology: Blocked by mibefradil and certain antiepileptic drugs. Key Role: They are important for regulating heart rhythm, neuronal firing patterns, and are involved in sleep and epilepsy (Weiss and Zamponi, 2019).

Overview of Calcium Channel Types

L-Type: Prolonged calcium entry; targets for antihypertensive drugs.
N-Type: Neurotransmitter release; targets for pain management.
P/Q-Type: Synaptic transmission; involved in epilepsy and migraine.
R-Type: Neuronal firing and synaptic transmission.
Transient: Pacemaker actions; intricate within cardiac beats as well as mind convulsions.

Calcium Channel Blockers (CCBs)

''Calcium channel blockers exist as a group of treatments which inhibit ca^{+2} from inflowing into the cytes of the heart and blood vessel walls (Lee, 2023).

Mechanism of Action of Calcium Channel Blockers (CCBs)

The mechanism of the action of calcium channel blockers is illustrated in Fig. 3.

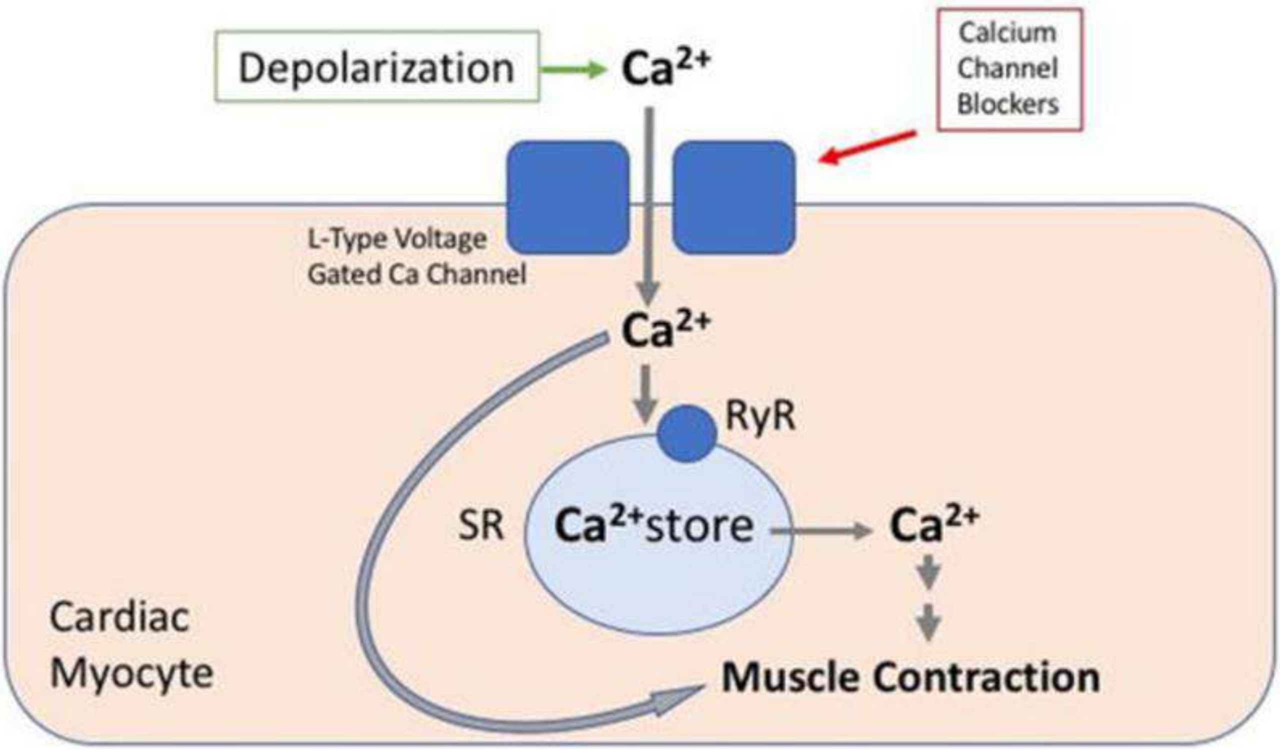

Fig. 3: Mechanism of Action of Calcium Channel Blockers (CCBs)

Categories of Calcium Channel Blockers

1. Dihydropyridines:

o Examples: Amlodipine and Nifedipine

o Prime Possessions: Mostly action going on non-striated muscle to increase the expansion of vessels. These exist as a mostly castoff to provide relief from anxiety and vasoconstriction (Miller, 2021).

2. Non-Dihydropyridines:

o Examples: Verapamil and Diltiazem

o Prime Possessions: Distress equally both in cardiac as well as haemo-vessels. This stay utilized for the treatment of over tension and vasoconstriction (Jentzer et al., 2018).

Indications

- Anxiety: Dropping the pressure of blood that reduce the chance of the risk of cardiac arrest.
- Heart attack: Releasing pain in the thoracic cavity through increasing the flow of blood towards the cardiac cavity.
- Arrhythmias: Treating certain types of abnormal heart rhythms, particularly those originating in the atria.

Common Side Effects

- Swelling (edema) of the ankles or feet, Headache, Dizziness or light-headedness, Flushing, Constipation, Palpitations

Clinical Considerations

- Patient Monitoring: Regular monitoring is required to adjust dosages and manage side effects.
- Interactions: CCBs can interact with other medications, necessitating careful management by healthcare providers.
- Lifestyle Adjustments: Patients may need to make lifestyle changes to optimize treatment outcomes and minimize side effects (Lee, 2023).

Calcium channel blockers act as an essential tool within the management of various cardiac conditions, providing relief from symptoms and improving patient outcomes through their vasodilatory and cardiac effects (de Amorim et al., 2024).

Voltage Dependency and Activation Characteristics of L-Type Channels

The primary calcium network within the cardiac organ remains in the Long-type ca^{+2} network, through a slight existence of Transit-form channels (Weiss and Zamponi, 2019). 10 genetic factors code the foremost Cavα1 subunit of voltage-gated calcium channels, divided into three main subdivisions: Cav1α1, Cav2α1, and Cav3α1. Nerve cells consists of N, P/Q, as well as R type networks (Huang, 2017).

The L-type channel remains immensely voltage-dependent and also includes Cav1α1 subunits. This one stimulates comparatively slow but then neutralizes quickly, exhibits feeble voltage-dependent deactivation, strong ca^{+2}-dependent deactivation as well as resistant to dihydropyridine ca^{+2} channel blockers (Rasmussen et al., 2020). Transmission through the Sinovial node and Atriovantricular nodes heavily relies on that calcium activation of L-type, does a combination of both agitation of vasoconstriction in heart cells (Shabalala and Ekolu, 2019).

The T-type channel, considered by means of less voltage-dependent activation, devours noticeable voltage-dependent deactivation, remains impervious towards dihydropyridines, also it is missing in ventricular tissue. However, exist within the cardiac cytes as well as in particular atrial cells (Huang, 2017). This one may participate in the pacemaking in the course of the minimal depolarization stage perceived in Sinoatrial nodes (Taiwo, 2023).

Calcium Activated and chloride Current (ICl (Ca))

Further forms of networks contain ca^{+2}-activated currents like ICl (Ca), that is a Ca^{2+} stimulated Chloride current as well as the Calcium activated nonselective cation current, INS(Ca) (Jiang et al., 2022). The Na+/Ca2+ exchanger creates INa/Ca current, which is be influenced by membrane potential as well as the amount of Ca2+ and Na+ (Taiwo, 2023). INa/Ca plays a crucial role in all heart cells, acting as a calcium transporter and contributing to the generation of both rhythmic and arrhythmic currents. (Rasmussen et al., 2020).

Calcium Channels in the Cardiovascular System

Ca^{+2} serves as universal intra-epithelial mediator that links resting membrane potential stimulus to cell proliferation (Asiedu, 2022). Within the cardiovascular (CV) system, elevated Ca+2 concentration within the cells that starts interaction between actin and myosin, leading to the muscle cells contraction (Zhu et al., 2019). Critical hypertension remains categorized through increased constriction in blood vessels, making crucial in hypertension and a viable target for antihypertensive treatments (Jentzer et al., 2018). Physiologically, there is a positive gradient of calcium ion concentration from the extracellular to intracellular space (Eisner et al., 2023).

ATP-Dependent Calcium Pump

Calcium removal out of cytes is controlled via ca^{+2}-Na altercation process, that transports a ca^{+2} ion from the cells in return on behalf of 3 Na ions towards the inside the cell (Sharma et al., 2021). Additionally, an adenosine triphosphate (ATP)-dependent calcium pump release ca^{+2} while converting ATP to adenosine diphosphate (ADP) (Shabalala and Ekolu, 2019).

Genetic Coding of the α1 Subunit in L-Type Channels

Receptor-operated channels are typically associated with receptors responsive to messenger molecules, primary objectives regarding pharmacological interventions stay the voltage-gated networks (Eisner et al., 2023). There are 5 chief subdivision that are: L, T, P/Q, N as well as R. In cardiovascular (CV) tissue, just L- and T-subdivisions exist. T-channels activate and inactivate reverse potentials, while long-lasting-type channels activate higher potentials of membrane (Taiwo, 2023). Functionally, the Long-lasting-type channel remains predominant within CV system, although the T-channel also plays a role, particularly in sinus node cells, kidney function, and aldosterone release (Asiedu, 2022). Voltage gated L-type calcium channels comprises four subdivisions—α1, α2, δ, β, as well as γ—but α1 subdivision predominates in CV tissue also it is coded almost ten variant genes (Gupta, 2018). Calcium channels of N- type are primarily found in nerve cells and, in its ending, influencing CV functions through their role in regulating sympathetic activity (Fedele and Brand, 2020).

Calcium Channel Subunits

Biochemically characterized ca^{+2} channels exist as intricate proteins consisting of 4 to 5 different subdivisions coded through numerous genes (Shabalala and Ekolu, 2019). The major subdivision Alpha 1 (α1) ranges from 190 to 250kDa and encompasses the conductivity aperture, sensors of voltage, apparatus for the gating, also the sites where the network is regulated through the secondary messengers, medications as well as poisons (Eisner et al., 2023).

α1 subdivision comprises amino acid residues that are almost 2000, which are systematized into tetra homological domains (I–IV), each containing hexa-segments of transmembrane (S1–S6) (Gupta, 2018). The voltage sensor module segments are from S1-S4. While the segments of transmembrane from S5 to S6 are present in every domain along with P loop among it,that will make pore module (Boonamnaj et al., 2021).
This subunit of Cav1 channel is illustrated in Fig. 4.

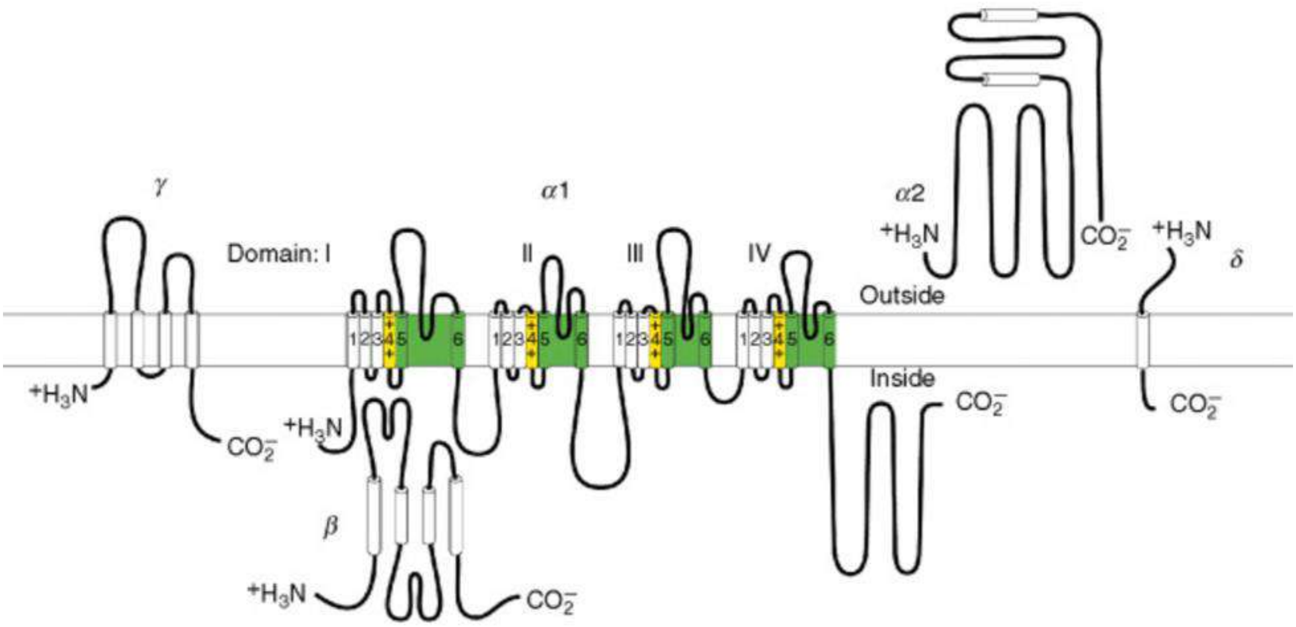

Fig. 4: Subunit structure of Cav1 channels. The subunit composition and structure of calcium channels purified from skeletal muscle are illustrated. Predicted helices are depicted as cylinders. The lengths of lines correspond approximately to the lengths of the polypeptide segments represented. Pore forming module, green; S4 voltage sensor, yellow.

Association of α1 Subunits with Auxiliary Subunits

α1 subunit is linked further with 4 auxiliary subunits that were initiated from three variant genes (Shabalala and Ekolu, 2019). β subunit that is present intracellularly is a protein that is highly hydrophilic, and the weight of this protein is varying between 50 to 65 kDa (Landaw, 2019). There is a complex of α2δ subunit, and this complex is connected through disulfide bond, this disulfide bond is encoded by a single gene (Gupta, 2018). After the translational process, the matured and covalently bonded α2 and δ subunits are formed (Asiedu, 2022).

Voltage-Gated Calcium Channels

Voltage-gated ca^{+2} networks ca+2 network as well as ca^{+2}-actuated K^+ network pairing neuromodulation (Pitt et al., 2021).

Animal Models in Biological Research

An animal model is a strategically designed framework used to investigate the structural and functional dynamics in humans (Paradiso et al., 2023). These models serve various purposes: explanatory models elucidate mechanisms in normal or abnormal biological functions, exploratory models tackle complex biological issues, and predictive models assess treatment effects (Fried, 2020).

Rat as an Animal Model

Laboratory rats are the most commonly used experimental animal (Fried, 2020). The reason is that its genetic makeup is most oftently matched with mammals as well as the rats is very useful in understanding the physiological and anatomical parameters (Paradiso et al., 2023).

Solanum nigrum

Solanum nigrum exists as a therapeutic herb also identified globally for its medicinal properties. *S. nigrum* cast-off for retrieving ruined land (Mandal et al., 2023). *S. nigrum* widely use as customarily for the cure of numerous diseases such as:

- Ache
- Swelling
- Illness

Phytochemical Investigation

Phytochemical investigation of the entire plant illustrates *S. nigrum* comprises of alkaloids, flavonoids, tannins, saponins, glycosides, proteins, carbohydrates, coumarins and phytosterols (Asraoui et al., 2021). As well as the fruits of *S. nigrum* devour valuable therapeutic properties, such as:

- Antioxidant
- Antiulcer
- Aerial parts of *S. nigrum* have antiulcer action
- Antitumor promoting agent in rats
- Potential CNS-depressant action

Cardiovascular Diseases

Cardiovascular disease is one of the most significant metabolic disorders that is leading towards the increased number of ailment and death all over the world (Mandal et al., 2023). The medicinal plants have anticipatory properties in curing of cardiovascular diseases (Asraoui et al., 2021). The main purpose of this study is to find out the cardioprotective effects of *S. nigrum* (hydro alcoholic extract) in isoproterenol induced myocardial infarction.

***Solanum nigrum* Cures Cardiovascular Diseases in Rats**

Solanum nigrum cures cardiovascular diseases by the following mechanism:

- *S. nigrum* is a strong calcium channel blocker. *Solanum nigrum* act by reducing the inflow of ca^{+2} electrons within the cells through this reduced influx regarding to calcium ions the blood vessels of heart relaxed and the patient get rid of myocardial infarction because his blood pressure normalizes and the workload on the heart reduces (Lin et al., 2022).
- *S. nigrum* extract contains many bioactive components, such as alkaloids, glycosides and flavonoids that aids in cardioprotective effects (Shenbagam and Sulthana, 2022).
- *S. nigrum* reduces the oxidative stress in a cardiovascular system by reducing the oxidative stress the vessels of both blood and heart relaxed and reduced the damage (Mozos et al., 2021).
- *S. nigrum* possesses an anti-inflammatory nature that aids in reducing the inflammation in the walls of heart (Ojo and Adanlawo, 2024).
- *S. nigrum extracts* have the capability of reducing cholesterol and triglycerides that ultimately reduces the cardiovascular diseases (Oner et al., 2023).
- *S. nigrum* has the capability to increase the production of nitric oxide because nitric oxide works as a vasodilator that widens the blood walls and improves the blood flow (Oluwagunwa, 2021).

Conclusion

This study highlights the impending effects of *Solanum nigrum* as therapeutic plant for the cure of cardiovascular diseases and hypertension and various other ailments. The primary aim is to enhance the usage of organic therapeutic herbs and plants as substitute to synthetic medicines. *S. nigrum* with its manifold medicinal properties offers a promising natural remedy for improving health and managing diseases. By focusing on natural plant-based treatments the study advocates for shift towards more sustainable and potentially safer options for managing health conditions. The findings suggest that incorporating *S. nigrum* into therapeutic practices could enhance the effectiveness of treatments and reduce reliance on synthetic drugs thereby minimizing associated side effects and promoting overall well-being. This approach aligns with a broader movement towards natural and holistic healthcare solutions. The key determination of this study is to use organic therapeutic herbs and plants to cure the various ailments instead of using synthetic medicines.

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Chapter 21

Antimicrobial and Antioxidant Potential of *Tamarindus indica* Plant Extracts against Microbial Infections

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ABSTRACT

Tamarindus indica belongs to the family Leguminosae, commonly known as tamarind (imli). This plant belongs to the tropical and subtropical regions. The extracts of leaves, fruits, stem and bark of this plant contain various chemical compounds or secondary metabolites such as flavonoids, glycosides, alkaloids, tannins, terpenoids, phenol, steroids, and proteins. The presence of these secondary metabolites confers the antimicrobial, anti-oxidative and laxative properties of this plant. It is used to treat the abdominal pain, infectious wound, diarrhea, constipation, severe malaria, pyrexia and the cardiovascular defects. Besides this, Tamarind plant is also used as anti-ulcerative, anti-inflammatory, anti-diabetic, anti-cancerous, hepatoprotective, anti-venom, and as an analgesic. Historically, the fruit and other extracts of this plant used as herbal drug for the treatment of wounds or for curing the abdominal pain. Today, as many microbes are getting resistant to a wide range of medicinal drugs, so we cannot overlook the importance of natural plants and their extracts. The purpose of writing a comprehensive chapter on Tamarindus indica plant is to explore the medicinal and pharmacological properties of this plant.

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INTRODUCTION

The use of plants and their preparations for medical purposes dates back to ancient times, virtually spoken word (Holt et al., 2023). Plants possess a number of medicinal and pharmacological properties because these plants have been used as an anti-venom (Ekele, 2023), anti-ulcerative (Malli et al., 2019), anti-cancerous (Singh et al., 2020), antidiabetic (Hung et al., 2012), antibacterial (Swamy et al., 2016), antiviral (Denaro et al., 2020), antifungal (Uma et al., 2017), insecticidal (Boulogne et al., 2012), antiparasitic (Wink, 2012), and as anthelmintics (Zaman et al., 2017). These properties of medicinal plants are due to the presence of numbers of secondary metabolites and chemical components. These are very beneficial for mankind in a variety of ways, including treatment of diseases (Souza-Fagundes et al., 2002; Sen and Samanta 2015). Recently, failure to treat and control infectious diseases along with resistant bacteria are well-established worldwide. Researchers are focused on natural plant products as an alternative for disease control. Plants have provided a variety of drug components used for medicinal purpose. Exploiting plants for medicinal purpose exclusively found in countries like China and Japan. Some African countries have also breakthrough in area of using plants as a potential source of new drugs. These countries include Egypt, Ghana, Faso, Burkina, Zimbabwe, Zambia, Nigeria, and South Africa (Abdullahi, 2011).

Tamarindus Indica commonly known as Tamarind, belongs to the dicotyledon family Leguminosae and the subfamily Caesalpiniaceae (Khanzada et al., 2008). The tamarind tree, used for medicinal purposes, is a long-lived evergreen tree found in different countries i.e., Egypt, Africa (tropical region), and Asia (Bhadoriya et al., 2011; Aly et al., 2023; Ghaly et al., 2023). Its extract obtained from pulp, seeds, and leaves of the tamarind tree, and its fruits are the most valuable parts and have been reported in several pharmacopoeias. The leaves have proven incredible to protective activity linked with the presence of polyhydroxylated compounds, many of them of flavonoid nature (Joyeux and Escalona et al, 1995). Leaves also contain rich sources of protein, fiber, fat, and vitamins i.e., thiamine, riboflavin, ascorbic acid, niacin, and B-carotene (El Siddig et al., 2006). Tartaric, citric, and maleic acids, Potassium bitartrate, pectin, water, gum, and parenchymatous fiber are rich in the pulp of the Tamarind tree (Nyadoi and Abdullahi, 2004). WHO (World Health Organization) report indicates that the fruit of Tamarind have most of the essential amino acids (Glew et al., 2005; Kuru, 2014). Reportedly, different parts of the Tamarind tree have shown anti-microbial, anti-viral, anti-fungal, anti-oxidant, anti-diabetic, anti-asthmatic, anti-venom, anti-malarial and anti-inflammatory activity (Bhadoriya et al., 2011; Kuru, 2014; Ghaly et al., 2023; Usman et al., 2023). However, not much information is available on peel and seed extract of Tamarind fruits.

Table 1: Antibiotic drugs, their mechanism of action and resistance developed against these antibiotics

Class	Example (and producing organism)	Molecule target	Resistance mechanism		Reference
			Endogenous resistance	Positive-function resistance	
Penicillin	Amoxicillin Semi-synthetic derivative of penicillin (*Penicillium crysogenum*)	Cell wall synthesis: penicillin binding proteins	Multiple changes in penicillin binding proteins, PBPs (*Streptococcus pneumoniae*)	Penicillinases, B-lactamase inhibitor	Truman, 2019 Silver et al., 1993
Cephalosporins	Cefacetrile Semi-synthetic derivative of cephalosporin C (Acremonium crysogenum)	Cell wall synthesis: penicillin binding proteins	Multiple changes in penicillin binding proteins, PBPs.	Cephalosporinase, B-lactamase inhibitor	Truman, 2019 Silver et al., 1993
Glycopeptides	Vancomycin (*Amycolatopsis orientalis*)	Cell wall synthesis: D-Ala-D-Ala termini of lipid II		Membrane protein: ligase with altered specificity	Truman, 2019 Silver et al., 1993
Macrolides	Erythromycin (*Saccharopolyspora erythraea*)	Protein synthesis: 50S ribosomal subunit		Methylation of 23S rRNA; inactivating enzymes; active efflux	Truman, 2019 Silver et al., 1993
Chloramphenicol	Chloramphenicol (*Streptomyces venezuelae*)	Protein synthesis: 50S ribosomal subunit		Antibiotic-inactivating enzymes; efflux system	Truman, 2019 Silver et al., 1993
Lincosamide	Clindamycin Semi-synthetic derivatives of lincomycin (*Streptomyces lincolnensis*)	Protein synthesis: 50S ribosomal subunit		Efflux and inactivating enzyme	Truman, 2019
Tetracyclines	Tetracycline (*Streptomyces aureofacians*)	Protein synthesis: 30S ribosomal subunit		Active efflux; ribosome "protection"	Truman, 2019 Silver et al., 1993
Aminoglycosides	Kanamycin (*Streptomyces kanamyceticus*)	Protein synthesis: 30S ribosomal subunit	Mutation linked to *nek* or *rpsQ* clinical relevance unknown	Antibiotic-inactivating and modifying enzymes	Truman, 2019 Silver et al., 1993
Quinolones	Norfloxacin	DNA synthesis: DNA gyrase, DNA complex	Single mutation in *gyrA* or *gyrB*; permeability changes		Truman, 2019 Silver et al., 1993
Fluroquinolones	Ciprofloxacin	DNA synthesis: inhibition of DNA gyrase and Topoisomerase IV	Target site gene mutations	Efflux pump, modifying enzymes	Truman, 2019 Mancuso et al., 2021
Diaminopyrimidines	Trimethoprim	Folate synthesis: inhibition of dihydrofolate reductase	Single mutation lowers affinity relative to substrate; derepression	Resistant dihydrofolate reductase; metabolic bypass	Truman, 2019 Silver et al., 1993
Sulfonamides	Mafenide	Folate synthesis: inhibition of dihydrofolate reductase		Resistant dihydrofolate reductase;	Truman, 2019 Mancuso et al., 2021

Flavonoids, Polyphenol, and other organic acid metabolites are found in the extract of Tamarind leaves, which contribute to its anti-microbial activity. These compounds have antimicrobial activity in many other plants (Chitra, 1999). Tamarind paste has an anti-microbial activity which is the reason why Tamarind paste is frequently used to treat wounds (Gupta et al., 2014). Due to its antimicrobial, anti-fungal, and anti-septic effects, it has extensive ethnobotanical uses in many areas of Latin America such as Puerto Rico, Mexico, and Trinidad and Tobago, and in other countries like Asia and Africa (Khare et al., 2004; Muthu et al., 2005; Melendez et al., 2006; Lans et al., 2007).

Keeping in view the significance and its role as an anti-bacterial, anti-viral, and anti-fungal along with other anti-inflammatory and anti-oxidative properties, the researcher begins to think about its use in medicinal drugs as in the modern era many bacteria develop anti-microbial resistance (AMR) against a wide range of antibiotics.

Chemical Drugs used against Bacteria and Resistance Develop against it

Bacteria, a natural foe of the humans and other animals since from the past, is the root cause of a number of diseases in animal as well as in humans. As knowledge expands and new discoveries are being made, humans become capable of dodging bacterial infections through the discovery of many chemical components that are being used to produce a number of chemical drugs called antibiotics. An antibiotic is defined as a substance used to kill or inhibit the growth of microorganisms. However, the development of new synthetic methods and techniques resulted in the modification of definition and now antibiotic is defined as a substance produced by microorganisms or similar substances that in low concentration inhibit the growth of microorganisms (Giguere et al., 2006; Szczepanowski et al., 2009). Among other classes of antimicrobials, antibiotics are comparatively less harmless to the host. They are small molecule having molecular weight less than 2000 (Kaiser, 2009). Antibiotic have both the bactericidal and bacteriostatic effect as well (Grenni et al., 2018). It can restrict the growth of bacteria by interacting with the cellular components of bacteria thus limiting the growth of bacteria. In general, antibiotics restrict the growth of bacteria in a variety of ways. Some of the antibiotics and their mechanism of action is discussed in the Table 1.

Discovery of antibiotics proves blessing for the mankind. It was used in the treatment of many diseases and infectious wound. As the knowledge about the antibiotics spread, people start using it blindly. Due to excessive misuse of antibiotics without understanding its mode of action, bacteria develop resistant against antibiotics (Muteeb et al., 2023). This phenomenon of bacterial resistance is also referred as antimicrobial resistance. Antimicrobial resistance (AMR) develops when microorganisms evolve to such extent that they become resistant to several antimicrobial medications, such as antibiotics, which are used for treatment (Tang et al., 2023). AMR is widely referred as “Silent Pandemic” and is a problem where immediate action should be taken and managed more effectively and should not be considered as future situation (Founou et al., 2021). If no preventive measure taken, it is estimated that by 2050, AMR could potentially become the world’s major cause of death (O’Neill, 2016). AMR is one of the leading causes of potential failure of several antibiotics. Some of the antibiotics against which bacteria develops resistance are discussed in the table 1.

Why there is a Need of *Tamarindus indica* Plant Extracts and its Antimicrobial Activity

As in the modern era of advancement in medicine field that leads to the development of many new antibiotics, the bacteria are also becoming quite resistant to certain antibiotics due to excessive misuse of antibiotics. AMR is becoming a major issue as many bacteria have developed a resistant mechanism to overcome the effect of certain antibiotics. They have developed certain degradation enzymes like β-lactamase that causes the lysis or breakdown of β-lactam ring, by active efflux of antibiotics, receptor modification, conjugation, transduction, transformation and mutation in the genetic makeup. AMR is a growing trend and it is uncertain to overlook the antimicrobial use in near future. Now the use of natural plants as an alternative source to treat certain bacterial infection is increasing. According to World Health Organization (WHO), the medicinal plant could be the best alternative to obtain a wider variety of drugs (Suntar, 2020). Since then, many plants are being discovered to treat bacterial infection.

Antimicrobial Activity

Antibacterial Activity

Tamarindus indicus phytochemical analysis indicates the presence of various chemical compounds like flavonoids, alkaloids, glycosides, terpenoids, tannins, steroids, phenol, proteins and various other compounds. It possesses antibacterial activity due to the presence of these chemical compounds that have shown broad spectrum antibiotic effect against wide range of harmful bacteria. Methanolic extracts of *Tamarindus indicus* leaves have potent antibacterial activity against *Burkholderia pseudomallei*. Its extracts (methanolic and acetonic extracts) have potential antibacterial effect against *Klebsiella pneumonia* (Parekh et al., 2006; Dhama et al., 2014). Its inhibitory activity is compared with standard antibiotic amikacin and piperacillin (Vaghasiya et al., 2009; Naeem et al., 2017). The antimicrobial activity of ethanolic, aqueous and acetonic extracts against gram positive and gram negative is analyzed by the inhibitory activity and measuring the zone of inhibition of extracts. They have latent antibacterial activity in opposition to *Staphylococcus aureus*, *Salmonella typhi*, *Salmonella paratyphi* and *Bacillus subtilis* (Doughari, 2006; Mehar and Dash, 2013). Some other studies reveals that the ether, water and ethanolic extracts of *Tamarindus indica* has strong antibacterial activity against gram positive and gram negative species (Mansingh et al., 2021). *Tamarindus indica* flowers extract (aqueous and methanol) possess antimicrobial activity (Fatimi et al., 2007; Ahmad et al., 2018). Pure essential oil and extracts (ethanol) from the fresh leaves of

Tamarindus indica has showed the strong antibacterial activity against the tested bacterial strains i.e., *Pseudomonas aeruginosa* and *Salmonella typhimurium* (Escalona-Arranz et al., 2010). The ethanolic extracts of *Tamarindus indica* leave and fruit was proven potent antibacterial agent against *shigella* spp. (Abdallah and Muhammad, 2018). The bark of *Tamarindus indica* also have the antimicrobial properties, its ethanolic extract was tested against gram positive (*B. cereus, S. aureus*) and gram negative bacteria (*K. pneumoniae, E. coli*) by well diffusion method. The large zone of inhibition is seen in case of *S. aureus* and *B. cereus* bacteria (Kapur and John, 2014). Furthermore, the ethanolic extract of fruit pulp is proven effective against *Escherichia coli* and *Pseudomonas aeruginosa* comparative to Gentamycin (Faisal, 2020).

General Mechanism of Action of *Tamarindus indica* against Bacteria

Tamarindus indica plant extracts possesses a strong anti-bacterial property that acts in one way or other, hence restricting the growth of bacterial cells by interfering with the host cell wall synthesis, interfere with DNA replication, inhibit the transcription and translational process results into the protein synthesis inhibition, and by the inhibition of synthesis of essential metabolites. The possible antibacterial mechanism of action is described in a picture below:

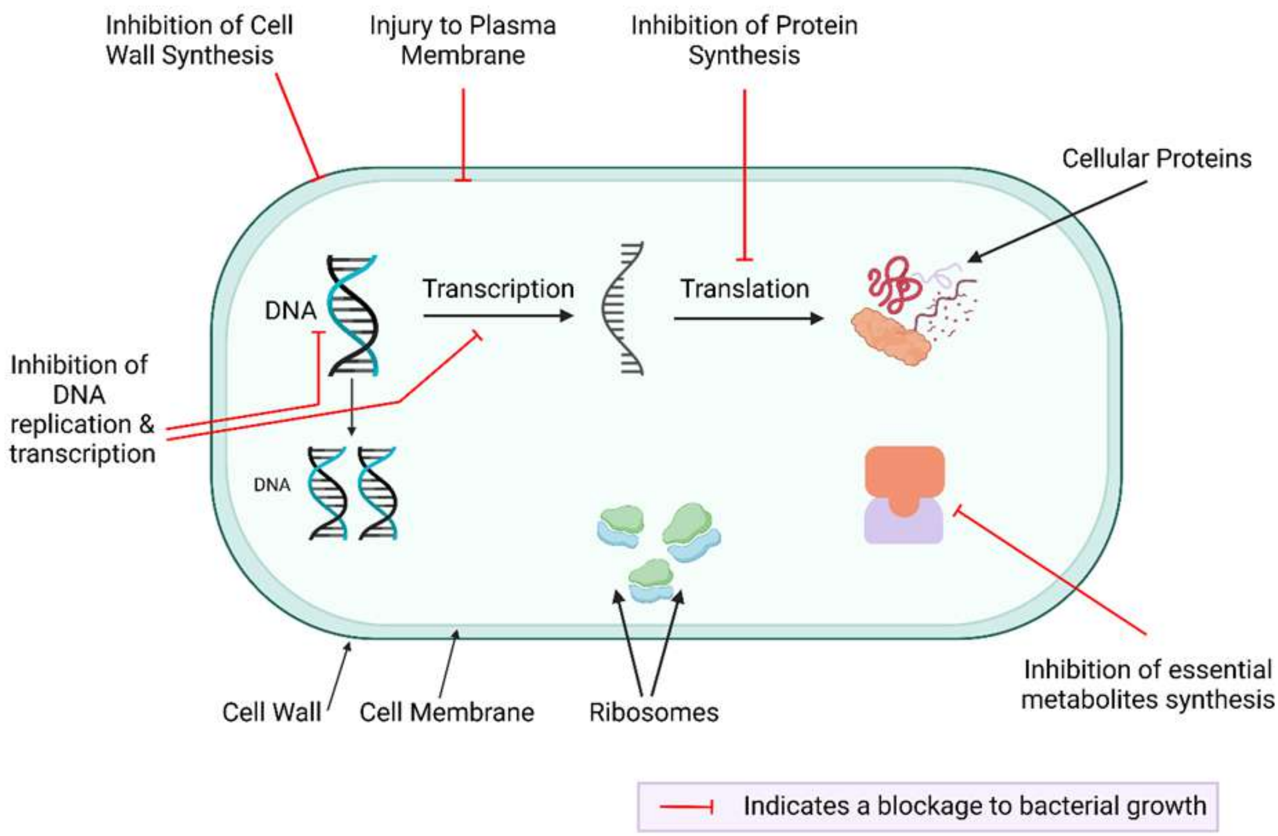

Fig. 1: The general antibacterial mechanism is illustrated in the diagram. Created with BioRender.com

Antiviral Activity

Tamarindus indica exhibit the anti-viral activity. The fruit extracts of *Tamarindus indica* have a potent antiviral activity against cow pea mosaic virus, watermelon mosaic virus and tobacco mosaic virus (Kuru, 2014). The crude ethanolic extracts of *Tamarindus indica* have inhibitory role against virus replication and results prove its inhibitory action against Newcastle disease virus (Perera et al., 2021).

Antifungal Activity

Tamarindus indica shows the antifungal activity. *Tamarindus indica* fruit extracts exhibit the antifungal activity against *Candida albicans* and *Aspergillus niger* (Kuru, 2014). Earlier studies of ethanolic extracts of leaves and mash proves the antifungal activity of *Tamarindus indica* against *Aspergillus flavus*, *Aspergillus niger* and *Fusarium oxysporum*. Bark of this plant can inhibit the growth of *A. flavus* and *F. oxysporum* up to some extent and growth of *A. niger* was not affected (Abubakar et al., 2010).

Some other Properties of *Tamarindus indica*

Anthelminthic Activity

The leaves of *Tamarindus indica* is used for Guinea worm (*Dracunculus medinensis*) extraction in Nigeria and its leave extract also used for wound treatment caused by parasites (Bhadoriya et al., 2011; Chimsah et al., 2020). The squash of seeds of *Tamarindus indica* is used as vermifuge in Ethiopia (Malathi et al., 2022) and fruit squash is used in Niger for this purpose (Havinga et al., 2010). In certain region of Tanzania, the leaf and root extract of *Tamarindus indica* is used as a treatment for Hook worm (ankylostomiasis) infestation (Chimsah et al., 2020). *Tamarindus indica* leaves and bark extracts (aqueous and ethanol) when tested against *Tubifex tubifex* and *Pheretima posthuma*, it paralyzes the worm and causes its death in much shorter time as compared to standard piperazine citrate (Soni and Singh, 2017; Khamesipour et al., 2021). Similar results were obtained in another study where the juicy extracts of *Tamarindus indica* leaves causes paralysis and quick death of *Pheretima posthuma* as compared to piperazine citrate, a standard drug (Mute et al., 2009; Manke et al., 2015). The anthelminthic activity of *Tamarindus indica* leaves extract (ethanol and aqueous) was also studied against earthworm infestation (Bondada et al., 2013). *Tamarindus indica* also have anti-nematodal against pine wood nematode, *Bursaphelencus xylphilus* (Meher et al., 2014).

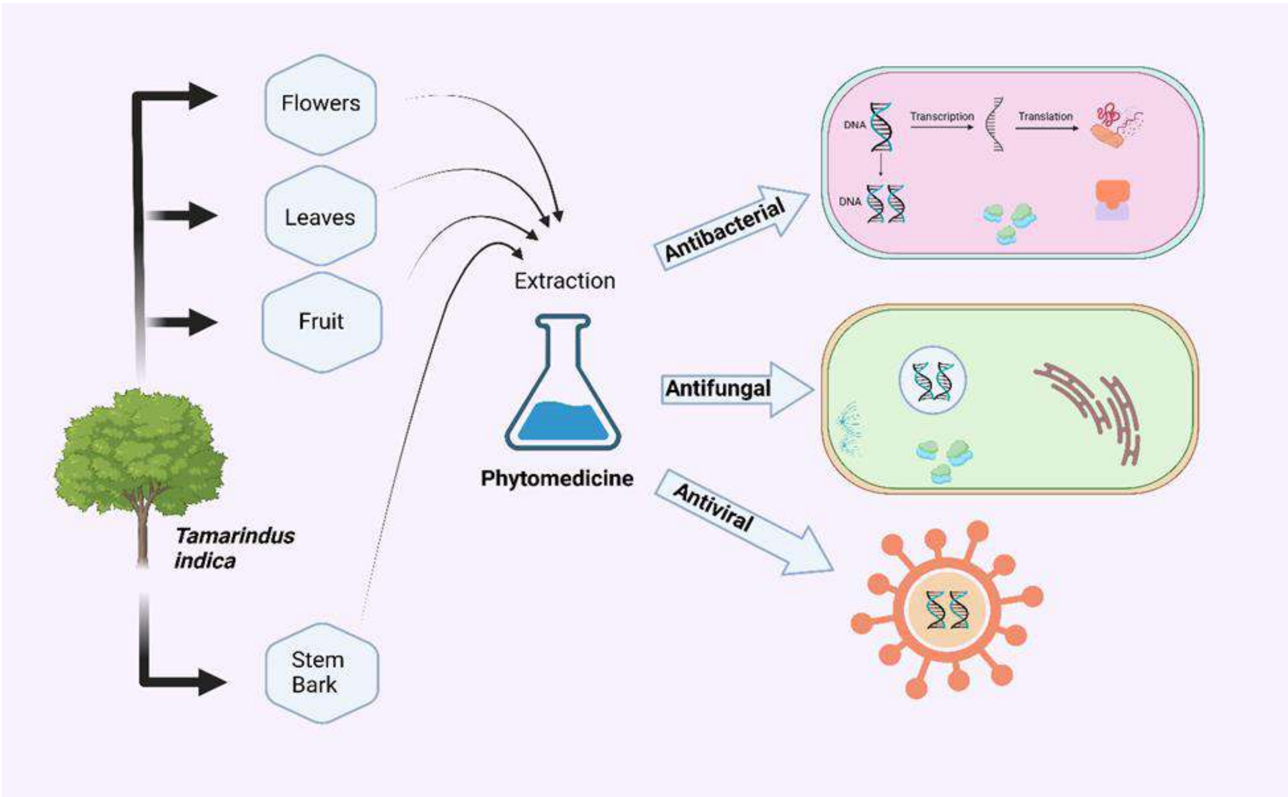

Fig. 2: The general antimicrobial effects of *Tamarindus indica* extracts. Created with BioRender.com

Anti-oxidant Activity

The good anti-oxidant activity of *Tamarindus indica* is due to the presence of phenolic compounds in its extracts primarily of seed and pericarp extracts (Sudjaroen et al., 2005). *Tamarindus indica* fruit pulp ethanolic extracts when exposed to the hamster, it shown noticeable anti-oxidant activity both in-vivo and in-vitro (Martinello et al., 2006; Atawodi et al., 2014). Furthermore, the ethanolic extracts of *Tamarindus indica* stem and roots have shown the strong anti-oxidant activity in DPPH radical, hydrogen peroxide scavenging assay and phospho-molybdenum assay (Borquaye et al., 2020). The seed coat ethyl acetate extracts also possess strong anti-oxidant activity (Luengthanaphol et al., 2004; Kahimbi et al., 2023). Aqueous acetonic extracts of *Tamarindus indica* exhibit highest anti-oxidant activity (Siddhuraja, 2007).

Anti-inflammatory and Analgesic Activity

The methanolic extracts of *Tamarindus indica* seeds causes the inhibition of human serine proteinase and neutrophils elastase thus exhibit a remarkable anti-inflammatory action in-vitro (Caluwe et al., 2010; Malathi et al., 2022). Furthermore, the seeds extract causes a significant decrease in IL-1β, IL-6 and TNF-α levels in arthritic rats (Sundaram et al., 2015; El-Gazzar, 2024). In another study a model of rat suffering from pleurisy caused by carrageenan is used to examine the anti-inflammatory activity of methanolic extracts of *Tamarindus indica* plant (Suralkar et al., 2012; Mans et al., 2019). Moreover, in male Wistar albino rat paw edema caused by carrageenan is reduced significantly by the ethanolic extracts of *Tamarindus indica* leaves (Bhadoriya et al., 2012). However, in another experimental investigation conducted on mice and rat models suffering from arachidonic acid and carrageenan induced ear edema, the results strongly convince the greater anti-inflammatory of both the ethanolic and chloroform extracts (Rimbau et al., 1999). *Tamarindus indica* also causes the inhibition of leukotriene production and activation of NF-B pathways, thus exhibiting a strong anti-inflammatory property (Komakech et al., 2019). Bronchitis is treated by the ginger juice extracts of *Tamarindus indica* leaves (Smruti, 2021). The dried bark is added to water and the resulting extracts used as a treatment for eye inflammation (Ajaiyeoba et al., 2001). Sterols and triterpenes present in the *Tamarindus indica* extracts have an analgesic effect (Dighe et al., 2009).

Anti-venom Activity

The extracts of seeds of *Tamarindus indica* plant is used to antagonize the effect of snake bite. Traditionally, it is used as folk medicine (More et al., 2021). *Tamarindus indica* seed extracts inhibit the protease, phospholipase A, 5′ nucleotidase enzymes, hyaluronidase and 1-amino acid oxidase activities of the venom in a dose dependent mode (Ushanandini et al., 2006; Fatimi et al., 2007). It inhibits the breakdown of β-chain of fibrinogen in human and thus preventing the hemolysis caused by venom hence prolonged the blood clotting process. The venom induced myotoxic effect like hemorrhage or edema is reduce markedly when extracts injected in a dose dependent mode. The results prove that the seed extracts of *Tamarindus indica* plant can be used as a serum therapy for the treatment of venom (Ushanandini et al., 2006; Bhadoriya et al., 2011).

Anti-cancerous Activity

Tamarindus indica has potential to treat the cancer thus having the anticancer effect. The strong antioxidant activity of *Tamarindus indica* seed extracts aid in the treatment of cancer. (Afzaal et al., 2023). The methanolic extracts of *Tamarindus indica* seed and inspect its cytotoxic potential on human lymphoma cell lines and rhabdomyosarcoma cancer. Results prove that the extracts of seed possess the strong anticancer effect on the cancer cell lines (Soni and Singh, 2019; Arshad et al., 2019). Anticancer effects of *Tamarindus indica* bark in the ethanol extract was observed on the human colorectal adenocarcinoma cell line (HT29). The evidence shows that the ethanolic extracts of the bark possess the anticancer activity against the human cancer cell line (Rini and Saini, 2022).

Anti-diabetic Effect

The anti-diabetic activity of aqueous extracts of seeds of *Tamarindus indica* plant is proven experimentally by the streptozotocin induced diabetes in an experimental model rat, the results showed the strong anti-diabetic activity of extract (Maiti et al., 2005). Furthermore, the ethanolic extract display the strong anti-diabetic activity in the alloxan induced diabetes in the rat (Bhadoriya et al., 2018).

Anti-ulcer Activity

Tamarindus indica plant possess ulcer healing character. A study proposes that the anti-ulcerative property is due to strong anti-oxidant activity (Raja et al., 2008; Singh et al., 2023). The methanolic extract of *Tamarindus indica* seed coat remarkably reduce the total acidity and volume of gastric juice in experimental pylorus ligated subject in comparison with ranitidine, a standard drug. It proves the anti-ulcerative effect of Tamarind (Kalra et al., 2011).

Hepatoprotective Activity

The aqueous extracts of *Tamarindus indica* unroasted seeds, fruits and leaves had a noticeable hepatoprotective effects in rats exposed to paracetamol induced hepatotoxicity (Pimple et al., 2007). However, the ethanolic extracts of bark showed strong protective functions in Sprague Dawley rats which are exposed to chemotherapy thus preventing the hepatic damage (Meena et al., 2019). Another study confirms the hepatoprotective activity of *Tamarindus indica* flower, the results confirmed that the Rifampicin and Isoniazid induced hepatotoxicity in Wistar albino rats is prevented by the ethanolic extracts of the *Tamarindus indica* flower (Ramirez-Maroquin et al., 2019). *Tamarindus indica* show hepatoprotective effect in case of alcohol induced liver toxicity, thus preventing the apoptosis of liver cells. *Tamarindus indica* causes stabilization of membranes and decreases the consumption of Glutathione. Additionally, it causes the fragmentation of DNA and activation of CASP-3 and causes histopathologic amelioration (Caluw et al., 2010; Kuru, 2014).

Effect on Cardiovascular System

In Bangladesh, the effect of *Tamarindus indica* fruit was evaluated on the Systolic and diastolic blood pressure, lipid profile and the human body weight (Xie et al., 2021). In a study on the hypercholesterolemic hamster, the *Tamarindus indica* extracts was examine on the atherosclerosis lesion and the lipid serum level. *Tamarindus indica* extracts have a greater potential of decreasing the risk of atherosclerosis in human (Arshad et al., 2019).

Abdominal Pain, Diarrhea and Constipation

Abdominal pain is a non-specific disorder of abdomen resulting in a pain in the abdomen which may be caused by the Diarrhea or Constipation. In Nigeria, the rural Fulani eats soaked fruits to relieve pain resulting from constipation (Lockett et al., 2000; Havinga et al., 2010). Although treatment with *Tamarindus indica* relieve pain but it makes it difficult to determine the cause of disease. In East Africa abdominal pain maybe due to Diarrhea. *Tamarindus indica* squash of young fresh bark is used as laxative to relieve abdominal pain (Fandohan et al., 2007). Similarly in Benin the young stem squash for 24 h and taken orally to treat abdominal pain. In East Africa, root extract is used to treat abdominal pain or stomach ache (Geissler et al., 2002; Chimsah et al., 2020). It is also used in Burkina Faso for the treatment of abdominal pain and other related complains (Kristensen et al., 2003). *Tamarindus indica* leaves are used for diarrheal treatment, for constipation fruit of *Tamarindus indica* is used and for abdominal pain roots and soft parts of bark can be used (Havinga et al., 2010).

Wound Healing

Tamarindus indica has great efficiency of wound healing, its leaves and bark when applied on the wound either in the form of concentrated extract, powder form or as a plaster (Malabadi et al., 2021). Its fruit is also used as medicine for wound healing (Vuyyala et al., 2020). The wound healing potential of seed and cork ash of *Tamarindus indica* was studied against Wistar albino rat, the results showed that it has a greater wound healing potential caused by tissue injury (Naik et al., 2017). The *Tamarindus indica* leaves extract are used to treat wound caused by Guinea worm (*Dracunculus medinensi*) in Nigeria and also for treatment of other parasitic wounds (Chimsah et al., 2020). In Dakar, the bark of *Tamarindus indica* plant is sold for wound treatment, other parts of the *Tamarindus indica* is used in medicine like pod husks, fruits or gum (Bhadoriya et al., 2011).

Malaria and Fever or Anti-pyretic

In Madagascar, the *Tamarindus indica* fruit is known as febrifuge (Baiyeri et al., 2019). In Ghana, *Tamarindus indica* leaves are used as a treatment for malaria (Asase et al., 2005). The pulp of tamarind fruit is used as laxative and febrifuge (Naeem et al., 2017). In a study conducted on rat, the experimentally induced pyrexia in rat due to yeast and lipopolysaccharides, the strong anti-pyretic activity of *Tamarindus indica* fruit pulp is proven (Izquierdo et al., 2007).

Laxative Properties

The *Tamarindus indica* fruit used conventionally as a laxative because of the presence of higher amount of tartaric acid, maleic acid and potassium acid (Chimsah et al., 2020). In Madagascar, the fruit of *Tamarindus indica* is given to the children to treat constipation. In Bamako, the *Tamarindus indica* pulps are used to prepare drinks and in Burkina Faso, the *Tamarindus indica* fruit is chopped and soaked in water with salt for half times a day before consumption. In Northern Nigeria, the *Tamarindus indica* leaves mash along with potash is used and also the fruit is used as laxative (Naeem et al., 2017).

Conclusion

Tamarindus indica, a Leguminosae family plant, found in the Africa, Egypt, Asia and other tropical and subtropical regions. The importance of this plant is due to its medicinal as well as the pharmacological properties. In ancient time, it is used for wound treatment and for abdominal pain. The extracts of different parts of this plant such as seed, leaves, fruit, and bark are used for the treatment of diabetes, ulcer, wounds, abdominal disorders, diarrhea, constipation, and even as a laxative, antipyretic, anti-inflammatory and as an analgesic. Its antimicrobial such as antibacterial, antiviral and antifungal properties are truly explained due to the presence of phytochemical compounds such as alkaloids, flavonoids, glycosides, terpenoids, tannins, steroids, phenol and proteins. It also possesses the anti-oxidative, laxative, hepatoprotective and anti-cancerous properties. A detailed information about the medicinal usage of *Tamarindus indica* plant and its extracts is discussed in this chapter. However, more experimental work should be done to explore the beneficial uses of natural extracts of this plant.

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Chapter 22

Alternative Use of Plant-based Diet for Tilapia

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ABSTRACT

For growth and well-being, tilapia, an omnivore fish that is extensively farmed, needs proteins, fats, carbs, and vital minerals. While fats especially essential fatty acids are important for growth and health, the quality of proteins has a big influence on metabolic efficiency and growth. Because fish meal is becoming more and more expensive and has a negative environmental impact, aquaculture is looking into alternate protein sources. The nutritional profiles and palatability of plant-based alternatives such as soybean meal, insects, and animal proteins are gaining popularity. Insects are highlighted because of their high protein content and capacity to break down organic waste. Fish meal substitutes for Nile tilapia benefit from the vast research conducted on soybean meal because it is inexpensive and has a balanced amino acid profile. Plant-based diets have potential despite obstacles such as shortages in amino acids and antinutritional elements. Methods such as substituting soybean meal (SBM) can preserve tilapia development performance and enhance intestinal health. Subsequent investigations will focus on improving sustainability and effectiveness using better nutrient use and functional feed additives.

KEYWORDS		
Tilapia, Alternatives, Proteins, Fats, Nutrition	Received: 12-Jun-2024 Revised: 11-Jul-2024 Accepted: 07-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

The fastest-growing food industry in agriculture is aquaculture, which will eventually supply the majority of the world's food needs (Khieokhajonkhet et al., 2021). Aquaculture is the growing of aquatic organisms in regulated or semi-controlled conditions, such as freshwater or saltwater, including plants, invertebrates, and vertebrates. This technique provides a better way to grow selected aquatic species for use in food production (Stickney and Gatlin, 2022). Aquaculture has now become an important contributor to the seafood supply (Wu et al., 2021). Due to the decline in wild fish sources due to anthropogenic activities, aquaculture has become an essential means of fulfilling the increasing demand for seafood worldwide.

Aquatic farming nowadays is expanding at a faster rate than other traditional livestock industries, such as poultry, and this presents an encouraging development for food security. However as it develops, the effects on society and the environment must be carefully considered for better growth of fish industries (Little et al., 2016). The development of workable feeding plans to promise quicker and healthier fish growth is a growing area of interest for the fisheries industry (do Nascimento et al., 2020).

Ineffective policies related to fisheries and aquaculture are sometimes caused by the lack of knowledge about the complex problems these sectors face. Better administration requires acknowledging the real cause of the complexities faced by the fisheries sector so they can develop solutions appropriately (Jentoft and Chuenpagdee, 2013). The fish industry addresses concern about the environment, safety, and food security to enhance their habitat and to make sure the provision of seafood. Furthermore, it is noted that successful health care, breeding grounds and initiatives with proper feeding strategies would raise the world's fish production (Furuya et al., 2023).

Fisheries have grown at an exponential rate becoming a significant source of animal protein due to high polyunsaturated fats (PUFA) (Hua et al., 2019). Tilapia, an omnivorous versatile freshwater fish known for its fast growth and ability to thrive on plant-based diets, emerges as a key player in meeting the rising global demand for seafood (Prabu et al., 2019). They have been purposefully introduced all over the world (Makwinja and Geremew, 2020). Tilapia can withstand stress better than the majority of other fish species (Lv et al., 2021).

Fish from the cichlid family, tilapia, are omnivores that are native to Africa. They have been inadvertently or purposefully introduced all over the world. Because of its special benefits, tilapia stands out among other commercially farmed fish as a possible contender for aquaculture in the future. Hardy freshwater fish native to Africa and the Middle East, tilapia develop quickly and reproduce prolifically. Because they can adapt to a wide range of meal sources and are herbivorous, tilapia can live at a lower trophic level than many carnivorous fish that must eat fish. This dietary characteristic makes tilapia production less detrimental to the environment, more significant, and less taxing on wild fish populations. In addition, tilapia are a commercially appealing aquaculture option due to their mildly flavored flesh and quick market size attainment (Yue et al., 2016) Tilapia can survive in unfavorable environmental conditions that other fish species would typically not be able to, such as low dissolved oxygen and high ammonia levels. *O.niloticus,* the Nile tilapia, is undoubtedly the most widely cultivated fish (Magbanua and Ragaza, 2024).

The heavily farmed Nile tilapia has achieved success, but now it must strike a balance between fish health and affordability. Although issues with growth and adaptability were addressed through selective breeding, increased demand is driving up feed prices. Fish meal is the ideal feed (Munir et al., 2023) due to its nutrient-rich nature, but it is not cheap and non-sustainable. An alternative that is more affordable and sustainable is plant-based protein (derived from plants), such as soybean meal and maize gluten. Therefore, employing the appropriate processing techniques and amino acid supplementation to create a cost-effective balance that increases fish health is the key to successful plant-based tilapia diets (Magbanua and Ragaza, 2024).

Nutritional Needs of Tilapia

With its superior nutritional profile and ease of use, fish meal has emerged as a viable alternative to all animal protein sources. Because fish meal is in short supply right now, the cost is rising daily. Given that the majority of commercial fish species are either omnivorous or carnivorous, it is therefore vital to identify an appropriate, affordable, and environmentally acceptable replacement protein source (Bera et al., 2022). A successful feed management strategy is essential for tilapia farming. Innovations in aquaculture make it possible to build feeds that are customized to meet certain requirements and even let farmers use locally available items to make feed. As a result, assessing these components is crucial to creating diets that are ideal for different aquaculture species and carrying out accurate nutritional studies (Gule and Geremew, 2022). The omnivorous fish tilapia may be fed a variety of plant-based foods (Yang et al., 2021).

Tilapia needs proteins, fats, carbohydrates, vitamins, and minerals for its normal growth. In the fish body, macro minerals like Ca, K, Mg, Na, and P and microminerals like Zn, Mn, Cu, Fe, Se, and I have distinct functions that include skeletal system development and homeostasis (El-Sayed et al., 2023). While trace elements such as copper, iron, chromium, zinc, iodine molybdenum, etc. are also essential for its health, excessive concentrations can be hazardous to fish (Makwinja and Geremew, 2020). Proteins, lipids (L), and carbohydrates (Gurunathan et al.) These are the main energy sources used in aquaculture-formulated meals. Fish require a greater amount of protein—the most expensive nutrient—than terrestrial animals do to maintain proper growth and health (Xie et al., 2017).

Proteins

The primary organic substance found in fish tissue is protein. An important portion of the fish's total body weight, around 65–75% dry weight, was made up of protein (Subandiyono and Hastuti, 2020). Dietary protein content has a major effect on fish growth and development. Although an increase or shortage of protein can retard growth, the effects are usually different. While high protein can result in inadequate nutritional absorption and increased ammonia excretion, which can have detrimental effects on fish health, growth, and the environment, low protein lowers digestive enzyme function retarding its growth (Yang et al., 2021).

The nutritional value of fish diets generated is known to be influenced by the quality of the protein source used in feed composition (Luthada-Raswiswi et al., 2021). Feed is the most significant expense for the productive growing of tilapia in closed aquaculture systems, particularly the feed's protein component. Numerous investigations on various feed additives that could complement the protein supply in fish feed have been conducted by different researchers (Nguyen et al., 2021).

Fish need essential amino acids for the formation of proteins, as other animals do. The fish have to get these essential amino acids from their surroundings because they are not able to make them on their essential amino acids to get them from their diet. Fish health and growth are traditionally associated with 10 essential amino acids (EAAs), which include methionine, arginine, and lysine etc. Any of these EAA deficiencies can restrict the synthesis of proteins and have a detrimental effect on fish development and decreases its growth and health (Furuya et al., 2023). Plant-based protein diets like fish meal are inferior to those including maize gluten feed and cottonseed meal (Magbanua and Ragaza, 2024).

Fats

Lipids are just as important to aquatic species' diets as protein. Fish health depends on essential fatty acids (FAs), which have an impact on immunological response, development, and reproduction. They also influence the health and functionality of cell membranes through elements such as phospholipids (Nakharuthai et al., 2020). Lipids perform essential and dynamic role in growth and health, neural and visual development (de Oliveira Coutinho et al., 2018).

Essential fatty acids and other important lipid groups are provided by these non-protein energy sources, supporting general health and development (Jia et al., 2020). Because high-fat diets (HFDs) are economical and help fish retain protein, they are widely used in contemporary aquaculture (Qian et al., 2021). Omega-3 and omega-6 PUFAs, among other important fatty acids, can be found in Tilapia i.e., The main n-3 PUFAs are α-linolenic acid (ALA), docosahexaenoic acids (DHA), eicosapentaenoic acid (Ravindran et al.) and docosapentaenoic (DPA) (Chepkirui et al., 2021).

Carbohydrates

Although carbohydrates are not considered necessary development products for fish, fish feed contains carbs since they are less expensive energy sources (de Oliveira Coutinho et al., 2018). A large amount of carbohydrates (30–70%, depending on age) can be used by Nile Tilapia in their diet. A recent study investigated the effects of different dietary carbohydrate amounts (0–50%) on adult Nile Tilapia metabolism (Oonanuntanasarn et al., 2018).The content of carbohydrates has a major impact on how easily carbohydrates can be digested and eliminated overall in the diet (Maas et al., 2020). Unsuitable or excessive carbs may spike glucose levels in fish might impair immunological response, development, and general health (Azaza et al., 2020).

Reduce tilapia's capacity for nutritional digestion, results in poor assimilation of nutrients which results in nutrients like protein ending up as metabolic waste (Bashar et al., 2021). Fish growth is highly dependent on how well they are able to convert food into nutrients that they can use known as FCR (Food Conversion Ration), especially in the early stages of development (Santo et al., 2020). It has been suggested that probiotic dietary supplements improve fish health and illness resistance. Additionally, research shows that dietary probiotics can improve aquatic animals and nutrient digestibility by activating their digestive enzymes which increases fish health and metabolism (Maas et al., 2021). Probiotics for aquaculture can be made from the intestinal microbes present in fish (Reda et al., 2018). Aquaculture is increasing day by day and hence there is a rise in the use of probiotics, which are live bacteria living in fish gut with health advantages. By improving digestion, eliminating dangerous germs, and strengthening the immune system, the dietary supplements can encourage fish growth, development and illness resistance (Liu et al., 2017).

Protein Alternative Sources

Animal

Animal protein sources have long been thought of as the best replacement protein sources for fish meal in fish diet formulation because of their higher protein and fat content, improved essential amino acid profile, and exceptional palatability which increases the digestion and results in better assimilation (Luthada-Raswiswi et al., 2021).

Fish meal substitutes are becoming more popular; because of their high nutrient content and palatability, animal protein sources are especially appealing. However, a possible obstacle to its long-term use in fish feed is the growing need for animal protein worldwide across all industries (Luthada-Raswiswi et al., 2021). The comparatively high levels of protein, fatty acids, energy, well-balanced amino acids, and minerals (sodium, iron, potassium, and zinc) found in insects have been linked to their sustainable use as feed (Wachira et al., 2021).

In general, insects are thought to be a good source of EAAs. The EAA concentration is frequently raised in insect species in comparison to soy protein (milligrams per gram of protein) (Hawkey et al., 2021). The adult crickets, mealworms, grasshoppers, and pupae of the black army fly have demonstrated superior outcomes among all insect larvae and pupae (Bera et al., 2022). Black soldier fly larvae (BSFL) have the highest potential being the most effective converter of organic waste into valuable biomass of high protein value (Magbanua and Ragaza, 2024). Insect meals have been identified as a potential feed element because they are high in protein (40–45%) and fat (26–35%), particularly in BSFL (Fawole et al., 2021).

Several aqua feeds have effectively exploited alternative insect protein to lessen dependency on the expensive and rare fish meal used in fish diets. The impact of insect-based feed on tilapia growth as a food source is also astonishing (Wachira et al., 2021). They can develop on relatively low-quality diets and ingest high-quality protein and a variety of other critical elements, insects have attracted a lot of attention due to their high levels of protein. Insects have different nutritional values according to their species, diet, and developmental stage. They provide a variety of easily obtainable vitamins and minerals, as well as high-quality protein, PUFA, and energy (Hawkey et al., 2021).

In order to create insect meals, the typical procedure is as follows:

1. First, we must confirm the availability of the specific insect abundance within that region
2. Next, decontamination is accomplished with the use of radiation or heat treatments.
3. The third phase involves using radiation or convection to dry the entire insect, pupae, or maggot.
4. Then, insects are ground into tiny fragments using a grinder. Some insects (like yellow-low mealworms) require the defattening process to obtain their fat during this period.
5. Next, using microorganisms to aid in the fermentation process, chitin needs to be extracted from the insect meal.

Insects require regulated environmental conditions for optimal growth during mass raising and breeding (Bera et al., 2022).

Periphyton

To increase the productivity of fish farming in ponds, waterbodies and cage systems, periphyton-based aquaculture grows periphyton on artificial surfaces as a natural food source for fish. Periphyton is comprised of invertebrates such as zooplankton, bacteria, fungi, and algae. Naturally, periphyton grows on submerged substrates that are added to the water bodies. Moreover, because periphyton is largely composed of green microalgae, it has frequently been stated to be the primary producer in pond systems (Khieokhajonkhet et al., 2021).

Plants

Plant-based refers to a broader range of foods that are predominantly derived from plants, such as fruits, vegetables, nuts, oil, whole grains, and legumes (Alcorta et al., 2021). The production of fish that are appropriate for a plant-based diet has expanded, thanks to aquaculture. The nutrition of fish has been improved, which has reduced feed waste and, as a result, increased industrial profitability. The output, survivability, and quality of farmed fish have all increased with a diet high in beneficial components such as prebiotic compounds, antioxidants, and omega-3 fatty acids (Nagappan et al., 2021).

The more costly fish meals are replaced by many plant and single-cell protein sources (Luthada-Raswiswi et al., 2021). Single-cell proteins are isolated from the cells of microorganisms with a high protein ratio, such as fungi and bacteria (Aragão et al., 2022).

One of the significant ingredients that may be used in a variety of meal preparations is vegetable protein. They provide sustenance, but they also serve as sources of energy and amino acids, which control the chemical and physical characteristics (Etemadian et al., 2021). In the past, vegetable protein sources have been a convenient, affordable, and beneficial substitute for fish meal in aquafeed composition. Soybean meal (SBM) is the most widely utilised vegetable protein source in aquafeed formulation because of its high protein content, ideal amino acid profile, and digestibility. However, because of its high non-digestible carbohydrate content, SBM is known to have detrimental side effects on the intestinal health and fish welfare of some species of carnivorous fish (Randazzo et al., 2021).

Due to its high protein content (40–51%), affordability, and widespread availability, soybeans are a popular choice for replacing fish meal. Raw soybeans, however, have anti-nutritional elements that may prevent fish from growing. These elements can be eliminated during processing by using techniques like solvent extraction or mechanical pressing, which results in soybean meal (SBM), a common ingredient in fish diets. Soybean protein concentrate (SPC), a different processed form, has an even better digestibility and protein content (65–67%) than soybean buttermilk (SBM) (Magbanua and Ragaza, 2024). The value of soybean meal for fish, especially Nile tilapia, when it comes to aquaculture diets where fish meal is substituted:

Using Fermented Soybean Meal (FSBM) in Place of Fish Meal

The study looks into using fermented soybean meal, or FSBM, in place of fish meal in tilapia diets.

Maintains Growth Performance

The growth performance of fish on a diet containing 7% FSBM was comparable to that of fish meal, suggesting that FSBM has the potential to be used in place of other feed.

Enhanced Plant-Based Diets

The addition of FSBM increased the tilapia's overall efficiency in using plant-based diets.

Enhances Gut Health

By raising the height of the intestinal villi and the quantity of goblet cells, higher FSBM inclusion levels (over 21%) enhanced gut health.

Overall, the results of this study indicate that fermented soybean meal may be a useful substitute for fish meal in tilapia (Picoli et al., 2022).

In the actual scenario of producing fish feed, the primary plant protein is soybean meal (SBM). This feedstock has a fairly well-balanced amino acid profile among the plant by-product meals, is produced in large quantities, is affordable, and has a moderate protein content (Wattanakul et al., 2021).

In aquaculture, soybean meal (SBM) is a viable source of protein that substitutes for fish meal for a number of reasons.

High Protein Content for Fish and Balanced Amino Acid Profile

Soybean plant have a greater amount of protein in it. SBM provides a better complete amino acid profile which result in better growth, development and results in a comparatively higher amount of usable protein for fish than other plant-based choices, both of which are critical for fish growth.

Stable Supply and Fair Price

SBM provides reliable availability at a lower cost than fish meal, which is subject to supply constraints and price swings.

Success with Particular Fish Species (Tilapia)

Research has shown that herbivorous fish species, such as Nile tilapia *Oreochromis niloticus,* can successfully substitute fish meal in part or in full with SBM without sacrificing growth or health (Peng et al., 2022).

Diets denoted by D1, D2, D3, D4, and D5 contain 0, 25, 50, 75, and 100% of SBM, respectively, given gram/kg. According to this study, *O. niloticus* can grow well when up to 75% of its FM is replaced with SBM. When SBM was used in place of 100% FM (D5), it produced a decline in fish growth. Lower growth rates were the result of the higher SBM content. In the experiment of 180-day testing period, the fish group fed the diet (D4) containing 75% soybean meal (SBM) instead of fishmeal (FM) displayed increased length and weight hence better growth of the fish (Pervin et al., 2020).

The proper plant-based feed formulation in tilapia is due to the following reasons:

Relevance of Feed Management

The financial viability of tilapia farming depends on the effective use of plant-based feed ingredients which are economical and profitable as well.

Problems with Plant-Based Diets

Although plant-based diets provide a sustainable substitute for fish, they frequently include anti-nutrients that obstruct and hinders the assimilation and digestion resulting in improper growth of fish hence population growth declines.

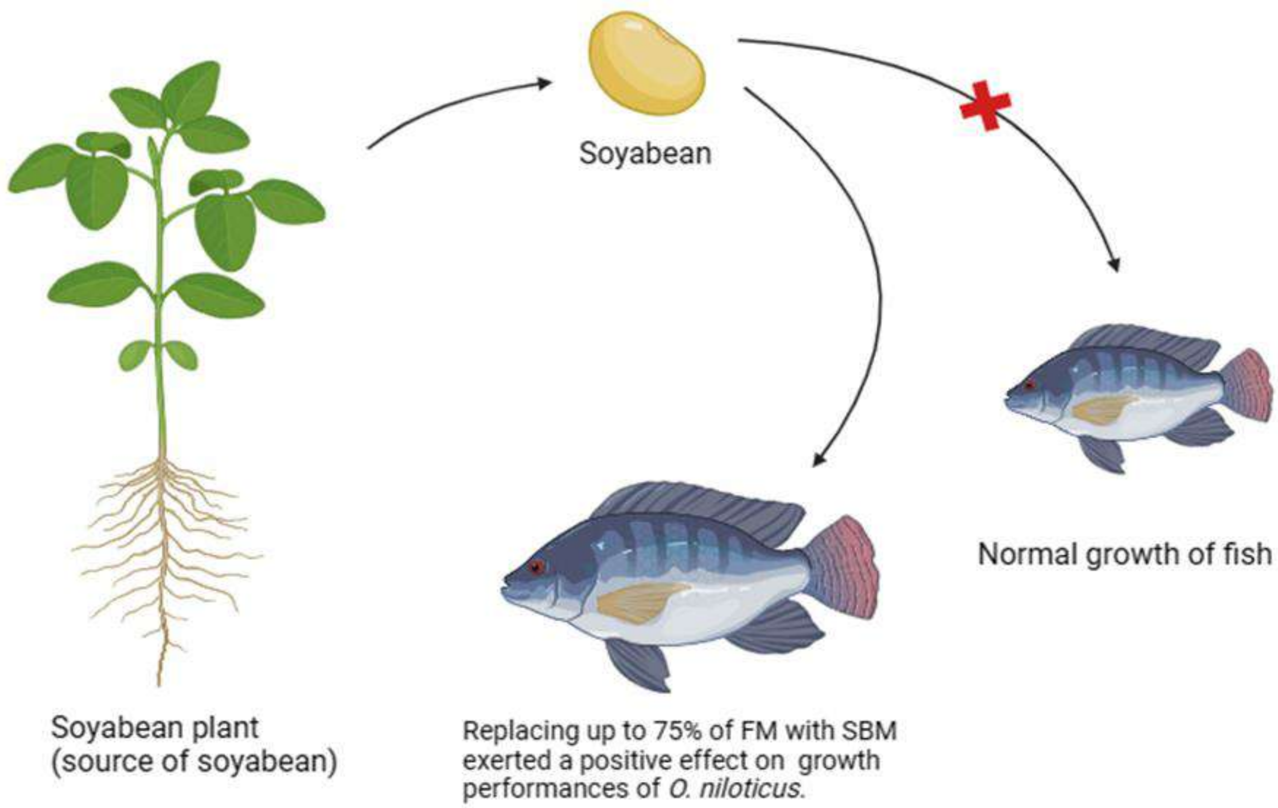

Fig. 1: Replacing upto 75% of Fish Meal with Soybean Meal exerted a positive effect on growth performances of Nile Tilapia. Created with biorender.com

Table 1: Formulation of Supplemental Diet with replacing Fish meal with Soybean meal.

Ingredients (I)	Diet 1 (D1)	Diet 2 (D2)	Diet 3 (D3)	Diet 4 (D4)	Diet 5 (D5)	References
Wheat Flour	100	100	100	100	100	(Pervin et al., 2020)
Wheat Bran	150	150	150	150	150	(Pervin et al., 2020)
Maize Meal	200	200	200	200	200	(Pervin et al., 2020)
Fish Meal	400	300	200	100	0	(Pervin et al., 2020)
Soybean Meal	0	100	200	300	400	(Pervin et al., 2020)
Vitamin B	5	5	5	5	5	(Pervin et al., 2020)
Cod Liver Oil	10	10	10	10	10	(Pervin et al., 2020)

Formulation procedures

To address and overcome these issues, the review examines a number of feed formulation procedures, including heat treatment, fermentation, and enzyme supplementation to maximize nutrient quality and availability for fish and to stop or minimize the procedures which reduces anti-nutritional effects.

Emphasis on Nutrient Utilization

The importance of further study to enhance the absorption and assimilation of nutrients from plant-based diets is essential for productive tilapia farming and enhanced growth and reproduction as well as normal metabolism. Nutrients are properly utilized by the body only when they are properly digested and assimilated efficiently.

In general, the text emphasizes the need for appropriate formulation methods to fully realize the benefits of plant-based diets (Salavatian et al., 2022).

Although substitutes made of terrestrial plants are being investigated, fish health may be compromised by the anti-nutritional elements which are responsible for decreased growth and these anti nutritional elements are frequently present in them. While research on plant-based proteins is still ongoing, other novel ingredients such as insects and microalgae are receiving more attention because of their potential nutritional profiles and benefits for sustainability (Aragão et al., 2022).

Creating the ideal tilapia feed is crucial to ensure optimal nutrition and balanced diet particularly when using plant-based alternatives. This study shows how to combine chicken manure (dropping) with inexpensive, locally available plant components like bran. It's critical to examine the nutritional makeup and profile of these plant-based compounds which form diets for optimum growth of fishes. The section describes a typical technique for employing these substitutes, which frequently have a different protein composition than fish meal, to balance the protein levels in formulated feed. With plant-based diets, proper feed composition guarantees tilapia receive the nutrients they need for healthy growth, supporting a more economical and sustainable aquaculture industry (Hailu et al., 2019).

Strategies to Overcome Feed Challenges for Fish Health

Phytate is a challenge to tilapia's plant-based diets. When removed, this anti nutrient damages the ecosystem because it binds vital phosphorus, decreasing its availability which results in improper growth of fish and decreases its immune system. Since they were created for cold-water fish, current phytases—enzymes that break down phytate—might not be the best choice for tilapia due to their pH range. Furthermore, phytase efficacy is influenced by a number of circumstances (Manikandan et al., 2020).

This investigation of the use of herbal supplements (mint, basil, and lemongrass) in Nile tilapia fry feed revealed the advantages and disadvantages of plant-based diets. While fish development was improved by basil and lemongrass etc, mint had the opposite effect resulting in improper growth. The nutritional profile of the fish was similarly affected by plant preservatives. The results emphasize the necessity of choosing carefully which plants to use in tilapia aquaculture and which to not use. To find the best plant-based diet that support tilapia growth while maintaining their nutritional value and efficiency, more research is necessary (Ndour et al., 2020).

There were particular challenges even if total substitution with plant-based alternatives appeared promising. Some plant meals, such as soybean meal, were more successful and promising in promoting healthy growth than others, such as linseed meal. Furthermore, fish on plant-based diets often digested less efficiently results in less efficiency of the meal. Scientists recommend combining several plant sources to create a more balanced diet or adding vital amino acids to get over these restrictions. Another way to increase plant proteins' digestibility for tilapia is by fermentation. Through investigation of these approaches, scientists hope to create plant-based diets that support tilapia growth in a healthy manner and lessen reliance on fish meal (Gaber, 2006).

Impact of Plant based Diet on Tilapia

The increasing demand for tilapia aquaculture is due to population growth and declining fish stocks due to their high demand. It highlights the limitations of fish meal as a feed source and explores plant-based proteins as a substitute because feed sources have nutrition but fish meal also have drawbacks. The emphasis is on the need for cost-effective, locally available plant ingredients like rice polish to formulate tilapia feed and assess its impact on growth performance. Plant based diet is essential for plants due to high nutritional value and great impact on gut health and growth. (Rahman et al., 2023).

There is evidence which suggests that a plant based diet is good for fish health. In comparison to the control group, Nile tilapia that were fed particular plant extracts—namely, Asparagus racemosus and Basella alba—exhibited better growth performance.

Additionally, Plant based extracts showed immunostimulatory properties, which may have improved the fish's general health and growth. Increased immune system results in better adaptability and survivability of fish in harsh environments. These results imply that food supplements made of plants may help tilapia grow and stay healthy due to improved nutrition (Ghosal et al., 2021).

Research Findings Related to Plant-based Tilapia Diets

Fish meal and plant-based diets for Nile tilapia were examined in the study, they are compared to investigate the better feed for Tilapia. Fish fed the plant-based diet showed worse growth performance (weight gain, specific growth rate) and feed efficiency (feed conversion ratio) compared to fish meal-fed fish, even though the plant-based diet was more economical per kilogram of feed. Hence, not all plant based diets are essential for Tilapia (Jatta et al., 2022).

A fermented soybean meal (FSBM) as a fish meal replacement in tilapia diets. Replacing 7% of fish meal with FSBM maintained similar growth performance, while higher FSBM inclusions (over 21%) improved gut health in tilapia (Khan et al., 2023). These findings suggest FSBM as a potential fish meal alternative for tilapia aquaculture increasing its growth and promoting better immune response (Picoli et al., 2022).

Recent research indicates potential, despite the fact that plant-based diets for tilapia were once thought to be inferior because of things like anti-nutritional components and amino acid profiles. Fish meal can be partially replaced with certain plant proteins (such as fermented Moringa oleifera leaves or dephytinized canola meal) to keep tilapia growing well and possibly even boost their immune systems (Magbanua and Ragaza, 2024).

Future Directions and Research Needs and Ongoing efforts and research on Tilapia Diet

Adding bile and cholesterol acids to tilapia diets that are plant-based. When compared to a plant-based diet alone, this combination can enhance the growth performance and liver health of tilapia. These nutrient additions maximize tilapia's plant-based diets (Jiang et al., 2024). Researchers are investigating the methods, including probiotics and enzymes, to enhance the metabolism and assimilation in these diets (Gule and Geremew, 2022).

To enhance nutrient utilization and overall fish production and growth, researchers are investigating the use of functional feed additives (such as probiotics and prebiotics) in plant-based tilapia diets. Probiotics are basically good bacteria and prebiotics non digestible plant fibres. This is in addition to initiatives to lower the price of these additives and look into their possible health benefits for fish growth (Neves et al., 2024).

There are trade-offs associated with plant-based diets for tilapia fish aquaculture, which is becoming more and more important. Future developments are probably going to center on two things:

1) Plant based diets are often affordable ones, hence finding more affordable and readily available plant-based foods for tilapia.

2) Making these diets more sustainable hence environmentally friendly, socially acceptable, and economically profitable. This indicates that more study should be done to create affordable plant-based ingredients and optimize their formulation for balanced nutrition and low environmental impact of food (Mitra, 2021).

The use of aquatic plants for tilapia as tilapia feed holds potential for sustainable aquaculture in the future. It offers two advantages:

1) Economical as it Lower costs by substituting cheap and plentiful aquatic plants for fish meal

2) Better environmental outcomes by limiting the spread of potentially harmful aquatic weeds, as food is readily available for tilapia in its own habitat. This implies that more investigation into the most economical methods of adding aquatic plants and weeds to tilapia diets that could be a major step towards sustainable aquaculture (Naseem et al., 2021).

A Two-pronged Strategy is Probably in Order for Sustainable Plant-based Tilapia Diets in the Future

Studies on FuFAs have shown promise in enhancing fish performance on plant-based diets by improving nutrient utilization, much like probiotics and enzymes do. Gaining an understanding of the mechanisms underlying FuFA additions will enable targeted enhancements through the application of biochemical and molecular approaches (Hossain et al., 2024).

Conclusion

To sum up all about alternative plant based diets, tilapia are ideally suited for sustainable aquaculture due to their innate capacity to flourish on plant-based diets. Although fish meal is still the best feed for fish, there are alternatives such as soybean meal, but the fish alternative diets must need to be investigated due to their drawbacks in terms of price, availability, accessibility, assimilation and environmental effect. Plant-based proteins are a viable alternative for fish diets, but formulation strategies for fish diets must address issues like non-assimilation and anti-nutritional factors which can be treated. One such strategy is fermented soybean meal. *O. niloticus* can grow well when up to 75% of its fish meal is replaced with SBM. To ensure a sustainable and productive aquaculture sector, future studies on functional feed additives, inexpensive plant sources, and improving nutrient absorption are essential to realizing the full potential of plant-based diets for tilapia.

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Chapter 23

The Role of Plant-Based Therapies in Modern Veterinary Practice

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ABSTRACT

In the animal health care industry, plant-based medications are used for therapeutic, prophylactic, or diagnostic reasons. Many ailments, such as toxicity, digestive issues, dermatitis, foot and mouth illness, burning, stomach pains, respiratory distress, mange, bone fractures, and skin disorders, are treated using phytotherapy. Because of their natural nature, plant-based medicines are believed to be more secure, non-toxic, and more inexpensive than allopathic treatments. Conversely, synthetic medications may have adverse effects and are often expensive. In addition, they have been in use for many generations. Plants are thought to be the source of over 25% of all prescription medications worldwide. It is known that synthetic medications are hazardous and may cause major issues. Herbal remedies, on the other hand, are more affordable, environmentally friendly, and largely harmless. In addition, they have been in use for many generations. They have also been used to routine animal healthcare issues. In the globe, 25% of prescription medications are derived from plants. Numerous animal maladies, including poisoning, coughing, constipation, foot and mouth disease, dermatitis, cataract, burning, pneumonia, bone fractures, snake bites, stomach aches, skin problems, etc., are known to be treated by these herbs. Herbal medications are viable options for animal therapy, offering natural and comprehensive methods for controlling diverse health issues. Their effectiveness, along with a reduced occurrence of adverse reactions in comparison to traditional medications, makes them very important in the field of veterinary medicine. Nevertheless, it is important for veterinarians and pet owners to possess comprehensive knowledge about the appropriate use, dose, and possible hazards associated with these therapies. Continual study and standardization of herbal products are essential to guarantee their safety and efficacy, promoting a more comprehensive approach to animal healthcare. Important medicinal plant species that are beneficial to animal health are included in this chapter.

KEYWORDS		
Herbal Medication, Phytotherapy, Non-toxic, Inexpensive, Synthetic Medications, Environmental Friendliness, Affordable, Safety and Efficacy, Standardization	Received: 09-May-2024 Revised: 04-Jul-2024 Accepted: 08-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Botanical Plant Properties

Now-a-days, herbal medicine is the most widely acknowledged and approved type of medication worldwide. Herbal pharmaceutical products are mostly obtained from the plant's production of diverse secondary metabolites, which are biosynthetically formed from primary metabolites (Ghosh et al., 2019). Various phytochemical compounds that have specific physiological effects on humans are what give plants their therapeutic and nutritional value (Essiett and Okoko, 2013). The World Health Organization reports that a significant portion of the population currently uses phytomedicine to advance healthcare. Plant parts are utilized by humans to make medication, which serves as a cure-all for the ills of contemporary society (Ghosh et al., 2019). A variety of medicinal plants would be the most effective way to obtain high-quality herbal medications for both the prevention and treatment of numerous diseases. Thus, to better comprehend a botanical attribute like morphology, anatomy, or physiology, as well as to learn about the chemical qualities, safety, and efficacy of these medicinal plants, thorough investigation is necessary (Mohammed et al., 2010).

Traditionally, people have used medicinal plants to heal illnesses, reduce symptoms, and extend life. It's anticipated that nature may provide cutting-edge therapeutic remedies for diseases like cancer. Extracts of plants have been shown to have anticancer properties, and some of these byproducts include Vincristine is derived from the periwinkle plant (*Catharanthus roseus* (L.) G. Don), taxanes are obtained from the bark of the Pacific Yew tree (*Taxus brevifolia* Nutt.), epipodophyllotoxin is extracted from the mandrake root of *Podophyllum peltatum* L., and camptothecin is derived from the bark and stem of *Camptotheca acuminata Decne*. Current studies may be able to locate, describe, and assess novel plant derivatives that combat disease (Fig 1). Moreover, compared to modern anticancer medication, there might be fewer adverse effects due to their natural source (Berrada et al., 2005).

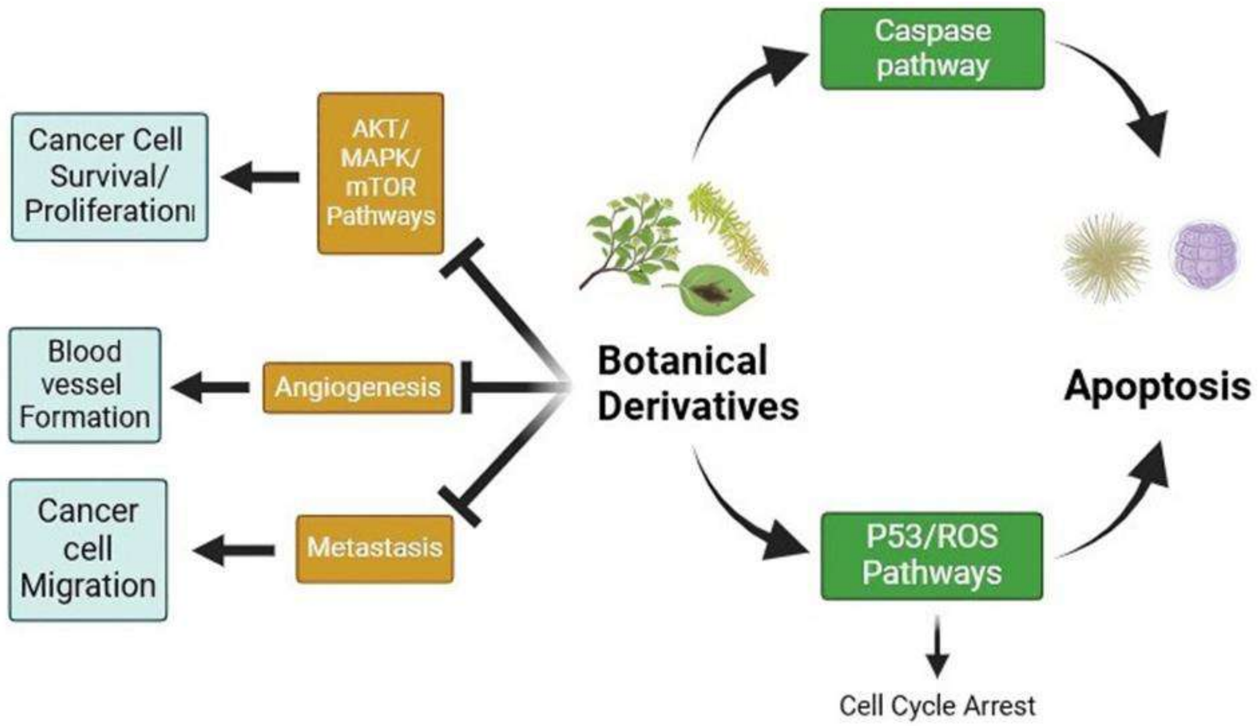

Fig. 1: Botanical compounds trigger programmed cell death and halt the cell cycle via activating caspase- and p53/ROS-dependent pathways. Botanical compounds inhibit cell survival, cell growth, angiogenesis, and metastasis.

The allomorphic pistillate flowers and fruits of *Euphorbia hirta* are one of its characteristics. Worldwide in distribution, *Euphorbia hirta* is also known by the popular names like milk weed and asthma weed. In Bangladesh and West Bengal, it is referred to as "Boro Keruie" locally. It can be found in lowlands, gardens, waste areas, roadsides, and paddy fields in temperate or tropical regions of India, Asia, Australia, and Africa (Ghosh et al., 2019). *Euphorbia hirta's* ethanol extract exhibited strong antianaphylactic qualities. Ethanol extract shown significant efficacy in preventing both the early and late phases of allergic responses (Kow et al., 2023).

Moench, *Helichrysum arenarium* (L.) synthetic medications that are used to treat liver, dyspeptic, and gallbladder issues. *Helichrysi flos*, derived from the plant *Helichrysum arenarium* (L.) Moench, is utilized in traditional medicine for its choleretic, diuretic, moderate spasmolytic, hepatoprotective, and detoxifying properties. Additionally, it is employed as a cholagogue for the management of dyspeptic ailments (WHO, 2015).

Botanical Therapeutic Protocols for Veterinary Practice

One of the main reasons for subpar livestock performance and significant financial losses in the nation is animal illness (Wondimu et al., 2007). The nation still lacks a sufficient infrastructure for animal health, veterinary clinics, and veterinarians, making conventional veterinary care less developed. Moreover, the majority of farmers and pastoralists cannot afford the high cost of the majority of modern medications (Yineger and Yewhalaw, 2007). Integrative oncology combines evidence-based complementary medicines with conventional therapy in a multidisciplinary approach to evaluate and treat the entire individual. It places a strong emphasis on being aware of and sensitive to a patient's mental, emotional, and spiritual needs (Cassileth et al., 2005). In order to promote health, the SIO suggests these guidelines for a range of methods that work in conjunction with traditional cancer therapies such radiation, chemotherapy, surgery, and molecular therapies (Sagar, 2008). These guidelines include a healthy diet, dietary supplements, mind-body modalities, massage therapy, physical activity, energy therapies, acupuncture (Deng et al., 2009).

Current Status of Botanical Medicine

Between 75 and 80% of the global population, especially in developing countries, continues to rely on herbal medicine for primary treatment (Kamboj, 2000). Even after the recent chemical synthesis of the active constituents contained in these plants emerged, the toxicity of plants has been known for centuries, and the history of these toxic plants alongside medicinal ones is very old and well-known worldwide. They are still regarded as the primary natural source of folk medication and toxication (Yuan et al., 2016).

In order to discover novel treatments for a wide range of illnesses, research on plant resources was stepped up in traditional medicine during the 20th century (Benzie and Wachtel-Galor, 2011). This contributed to focusing research on phytotherapy and herbal medicine in the continual pursuit of new drugs. (Weldegerima, 2009). Three methods exist for integrating herbal medicine with other types of traditional medicine (TM): 1. it may be incorporated as a vital element of a country's official healthcare system, with each specialty being recognized separately as acceptable medical fields within the same structure.2. Individual medical professionals may use it into their practice in conjunction with contemporary medicine. 3. Two branches of medical research, traditional and modern techniques can be combined, eventually incorporating aspects of each to create a new branch (WHO, 2000).

The People of China has long bragged about its medical education system, which mandates that practitioners of modern medicine complete some formal training in traditional Chinese medicine so they can apply appropriate TCM techniques when practicing Western medicine (Matos et al., 2021). Nevertheless, there is a dearth of evidence supporting its effective incorporation in clinical practice (Giordano et al., 2004). The extensive utilization of botanical products as complementary and alternative medicine (CAM) or phytomedicine in Western countries such as the US, Australia, Canada, and EU members has led to the emergence of a multinational, multibillion dollar industry (Yen et al., 2013). The industry has led to professional associations, conferences, integrated medicine practices, pain management clinics, and research funding agencies, integrating complementary and alternative medicine into traditional medical colleges. These advancements have led to continuous international discussions over the past several years on the integration of CAM, including herbal preparations (Tsai et al., 2024).

The primary difference between therapy classified as "alternative" and "complementary." As supplements to conventional therapies, complementary therapies consist of supporting measures that improve overall patient care, regulate symptoms, and improve well-being (Deng et al., 2004). Certain complementary therapies have been shown to be safe and successful over time. These can then be included into mainstream medicine as a component of an integrative medicine programme and, in actuality, become the norm for care. On the other side, fraudulent and scientifically dubious alternative therapies are promoted as alternatives to traditional medical care. Delays in therapy might reduce the chances of remission and cure, which is particularly problematic in the field of cancer (Cassileth and Deng, 2004). According to studies, depending on the parameters used, CAM use ranges from 10 to >60% in cancer patients (Navo et al., 2004). Certain signs point to a rise in CAM use among cancer patients in the last few years. According to a statewide survey conducted in Japan, CAM use was more common among patients with lung cancer (53%) compared to patients with other types of cancer (Hyodo et al., 2005). Various data are reported by European surveys (Molassiotis et al., 2005). All polls, however, consistently reveal that CAM users are younger, better educated, and wealthier, indicating that they constitute a health-conscious population willing and able to actively participate in personal care. According to a more recent survey, up to 40% of American cancer patients use complementary and alternative medicine (CAM) during the survival phase after receiving acute cancer therapy (Gansler et al., 2008).

Veterinary Clinical Trials and Controlled Studies; Commonly used Medicine in Veterinary Practice

Accurate scientific evidence must be readily available in order for veterinary medicine to be practiced in an evidence-based manner that is complete, trustworthy, and not deceptive. The most reliable way to evaluate the effectiveness of therapeutic interventions is through randomized controlled trials (RCTs), which are also a great source of data for making clinical decisions when combined with their synthesis in the form of systematic reviews (Balshem et al., 2011). But a variety of biases, such as those related to reporting, performance, detection, attrition, and selection, might skew the results of randomized controlled trials (RCTs) (Higgins et al., 2011). When bias is present, it can mislead physicians in applying the evidence to treatment decisions and cause misinterpretations of treatment benefits or harms. When evaluating the validity of RCTs, another potential issue is sponsorship bias, which is the impact of the source of funding on trial outcomes reporting. There are conflicting reports in the medical literature on the potential impact of financial conflicts of interest on trial results. According to some research, there is a higher chance of positive outcomes for trials funded by the industry (Flacco et al., 2015), however according to other research, there is no difference between trials sponsored by the industry and those not (Pang et al., 2015).

Clinical trials for veterinarians may look into medications, herbal remedies, medical technologies, surgical methods, nutraceuticals, and behavioural therapies. NSAIDs are among the prescription medications that people use the most frequently worldwide. They are widely available, frequently over-the-counter medications with popular uses, allowing them to be present in a variety of environmental contexts (Bori et al., 2009). Ketoprofen, naproxen, diclofenac, and ibuprofen are the most often used NSAIDs; although they have distinct chemical structures, they have many of the same qualities and attributes (Weigel et al., 2004).

Numerous internal and external parasites can be found in companion animals, particularly dogs and cats (Selzer and Epe, 2021). One of the most important parasites in the field of companion animal health, both in terms of pathology and economics, is *Dirofilaria immitis*, a parasitic filarial nematode that causes heartworm disease. The condition in dogs is caused by young adult and adult parasites that generate pathology in the pulmonary arteries. Dogs serve as the primary host for microfilariae, which enter the circulation and undergo sexual reproduction in the pulmonary arteries (Selzer and

Epe, 2021). The current approach to controlling heartworm illness is therefore prevention, which makes use of a single family of medications known as macrocyclic lactones (MLs), such as moxidectin, milbemycin oxime, and ivermectin (Wolstenholme et al., 2016). The World Health Organization (WHO, 2019) regards ivermectin as a necessary medication due to its effectiveness in treating human filarial parasites. Four of the six endemic nations have eliminated onchocerciasis as a result of the drug's successful application in the Americas (Lakwo et al., 2020; Sauerbrey et al., 2018). According to ivermectin has played a significant role in large-scale drug administration campaigns aimed at controlling human pathogenic filarial infections in Africa (Lakwo et al., 2020).

Strong anti-inflammatory medications known as corticosteroids are frequently prescribed in standard clinical practice, particularly to treat sports-related injuries. Their role is still unclear and their application in treating overloaded injuries is still debatable (Khan et al., 2000). In addition to being detrimental to a patient's mental health, behavioural distress can also have an impact on a patient's general health, compliance with treatment plans, diagnosis, and course of therapy (Lloyd, 2016). Negative veterinary visit experiences increase the likelihood that a pet may be afraid and disturbed on their subsequent visit, which will hinder the provision of care (Edwards et al., 2019). While handling and low stress conditions would not be enough to dramatically reduce anxiety, adding behavioural medicines might help lessen fear and anxiety related to receiving veterinary care. Reducing patient anxiety and dread enhances the quality of veterinary visits for patients, clients, and the veterinary team while lowering the risk that patients may represent to the staff (Overall, 2013). Developed as an anticonvulsant, gabapentin is a gabapentinoid that also has analgesic and anxiolytic properties (Mnigaux et al., 2005). Before surgery, it is commonly administered as a single dose (Tirault et al., 2010). Since gabapentin is anxiolytic in cats, it should only be used extra-label in both cats and dogs. Despite the growing usage of gabapentin to treat anxiety (Siao and Pypendop, 2010).

Safety of Botanical Medicine

Many nations, including the United States, South Africa, South America, Canada, Norway, and the United Kingdom, use the phrases herbal medicine, botanical goods, flavouring pharmaceuticals, and phytotherapy interchangeably (Capasso et al., 2000). Plants have been the main resource for managing diseases by man during human pre-history, and for many thousands of years the knowledge about plants with presumed medicinal properties has been handed down through generations. Only recently have plant-, animal- and synthetic medications added to mineral-derived medications of non-natural origin, and currently by engineered protein and gene therapy. However, in most of the world's countries, especially those in the African continent, Asia and South and Central America, most of the population still relies mostly on plant-derived medicine. A recent World Health Organization (WHO) survey estimates that up to 81% of the population in Africa depend on traditional medicine for their health (WHO, 2003).

Herbs are thought to have a high probability of negative consequences (Talalay, 2001). Moreover, adverse effects that are fatal have been caused by adulteration, insufficient formulations, ignorance of herbs, and drug combinations (Elwin-Lewis, 2001). Before any plant is commercialized as a medication, appropriate clinical trials must be conducted to ascertain its safety and effectiveness (Vickers, 2007). Consumers typically have the taboo belief that herbal remedies are always safe due to their "natural" nature. However, because synthetic pharmaceuticals and plant medicines may combine or require different effects from one another, they may induce toxic indications in the patient. The United States does not require the standardization of purity and dose; nonetheless, due to biochemical variability among plant species, even products synthesized to equivalent specifications may change (Newmaster et al., 2013).

Quality control is a vital role of the pharmaceutical sector. Medications must be marketed in formulations that are both safe and therapeutically efficacious, with reliable outcomes. The development of enhanced and novel medications is gaining momentum. Concurrently, there is a growing development of more rigorous and sophisticated analytical methods to evaluate them. The main goals of quality control, that are often carried out at the conclusion of an operation, are material and product. A more thorough approach like quality assurance, which focuses on the material, product, and process and is an online activity, is required due to the growing demand for quality. However, TQM is more extensive, including all processes, materials, and products, and it begins even before operations begin (Shinde et al., 2009). The use of suitable analytical techniques to guarantee the quality, safety, and purity of botanical medicines through adherence to good manufacturing procedures (GMPs) is fundamental to their manufacturing. The majority of the time, GMPs are required in accordance with national regulatory models that differ based on whether botanical preparations are classified as "traditional medicines" (in the EU, Asia, and India), "natural health products" (in Canada), or, in the US, as "dietary supplements" or "botanical drugs." A range of analytical tools, each with unique strengths and limitations, are available in all circumstances where regulatory models exist (Dijkstra et al. 2012).

Hepatotoxicity is the term for liver damage brought on by drugs, chemicals, herbal remedies, or nutritional supplements. In ancient Greek, "Hepar" means liver and "Toxicon" means poison. The primary signs of the injury are fever, weakness, recurrent exhaustion, vomiting, nausea, changes in the colour of the urine and stool, rash, jaundice, and stomach discomfort. Certain laboratory tests for liver function that are conducted on blood samples enable the detection of hepatotoxicity. The normal ranges for these tests are as follows: 3.5–5.0 g/dl for albumin, 8–48 U/l for aspartate transaminase, 0.1–1.2 mg/dl for bilirubin, and 7–55 U/l for alanine transaminase and 45–115 U/l for alkaline phosphatase. Hepatotoxicity is indicated by elevated ALT, ALP, AST, and bilirubin and decreased albumin levels. Pregnancy also causes a rise in ALP levels (Nudrat and Naira, 2016). In nature, no chemical exists that has no impact. As a result, this diversity raises the likelihood of contact while also expanding the range of products. There is an interaction between two pharmaceuticals if another substance (herbal medicine, product, ingredient) modifies the effects of one drug either qualitatively or quantitatively. As a general rule, for an interaction to happen, two medications need to be in the body at the same moment, especially in the location of interaction. However, interactions can occasionally happen even when a medicine is not present in the body if it has a long-lasting effect on the body, Useful interactions can occasionally be purposefully generated to lessen a drug's negative effects or boost a drug's therapeutic benefit when combined with another drug. In other situations, the patient may be initiating therapy with a particular prescription, or the interaction may happen unintentionally due to misuse of medication (See figure 2). Unpredictable medication interactions can occasionally happen. Interactions between medications and herbal remedies can be caused by both drug-related and disease-related factors (Tatli, 2013).

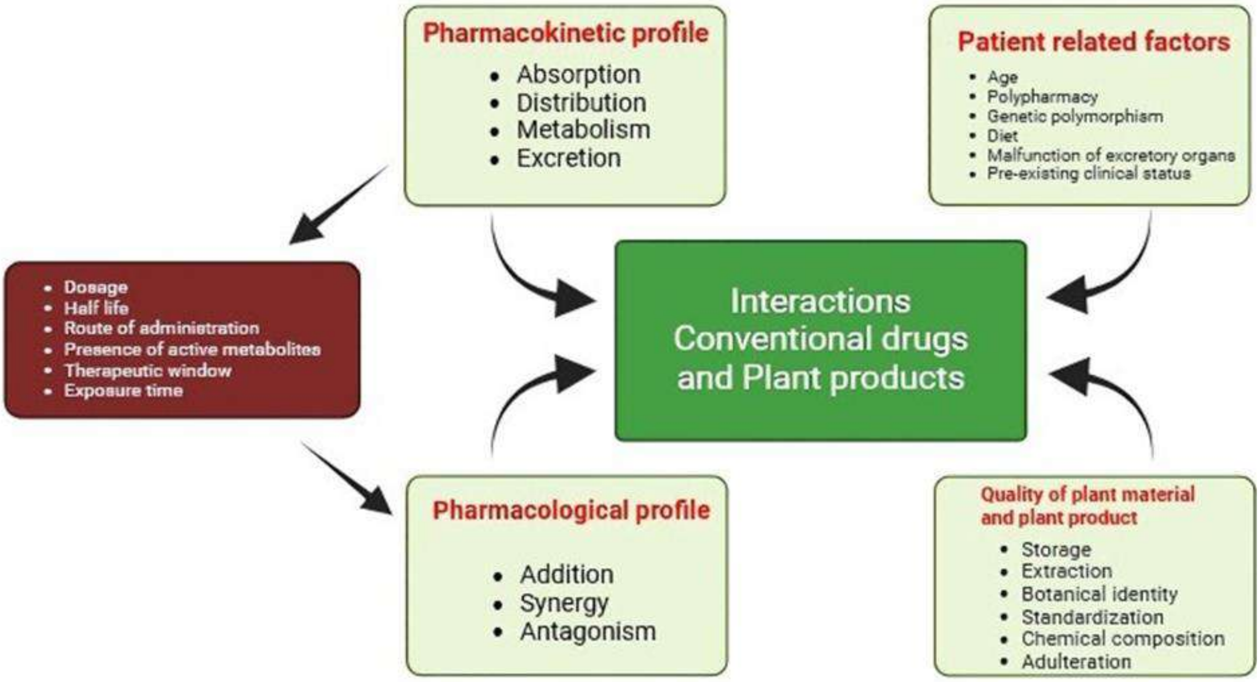

Fig. 2: Interactions between herbal products and conventional drugs

Herbs are not prescription drugs. Herbs are not individual substances; rather, they are a part of entire plants. Herbal effects are a result of nature's concoction working in concert with one another. Herbs and drugs are utilized differently, but when used properly, both can be very helpful. Maternal drug consumption during pregnancy might result in adverse consequences for both the mother and the developing fetus. These effects can include congenital deformity and other negative outcomes. Certain herbs might produce uterine contractions that could result in miscarriage, an early birth, or harm to the developing fetus, making them dangerous to take while pregnant. Certain herbs are dangerous to consume while pregnant since they can result in hypertension, congenital abnormalities, or even death. While herbs have been used for ages as natural medicines and seasonings, there are certain herbs that should not be used while pregnant because they may be detrimental to expectant mothers and their unborn children (WHO, 2000). While not all pregnant women require the use of herbs, the following plants have been successfully used by women for millennia and are suggested by skilled herbalists (Bensky and Dan, 2004). Black haw (*Viburnm prunifolium*) relieves tension that leads to uterine contractions, relaxes uterine muscle, and prevents miscarriages. *Clinicus benedicuts*, or blessed milk-thistle boost and improve the flow of milk by stimulating blood flow to the mammary glands. *Viburnum opulus*, or crampbark, can stop miscarriages. *Taraxacum officinale*, or dandelion Rich in calcium, iron, and vitamin A; promotes energy, tones the liver, helps with digestion, and has diuretic properties, squaw vine (*Mitchella repens*) tones and nourishes the uterus (Shinde et al., 2012).

The main reason for the problems associated with traditional and herbal therapies is that in certain countries, these products are classified as food or nutritional supplements. Thus, prior to commercialization, it is not necessary to furnish evidence of the efficacy, safety, or quality of these herbal treatments. Similarly, the production standards and quality inspections are generally less strict or controlled, and traditional health practitioners may not always possess a license or certification. Consequently, both the general public and national health authorities are currently deeply worried about the safety of conventional and herbal treatments (Kasilo and Trapsida, 2011). In many other regions of the world, particularly the developing nations, this is not the case, since many unregistered and inadequately controlled herbal items are freely offered on the market with little to no restriction. In addition, the widespread misperception that natural goods are safe and free of side effects frequently results in incorrect usage and excessive consumption, which has also brought about serious poisoning and urgent medical issues. This false belief is not exclusive to underdeveloped nations. It also occurs in highly developed nations, where people frequently turn to "natural" products without being properly informed about the risks involved, especially when using them excessively or chronically (UNESCO, 2013). Herbal drugs are subject to varying definitions and classifications across different countries. A single medicinal plant may be classified in different nations as a food, functional food, dietary supplement, or herbal medicine, depending on the laws governing foods and medicines. This leads to confusion among patients and customers, making it exceedingly challenging to establish a clear definition of "herbal medicines" for the purpose of national drug regulation (WHO, 2005). It is erroneous and misleading to have the belief that medicines or herbal remedies are entirely safe and devoid of any adverse effects. Studies have shown that herbs can cause a range of negative or harmful effects, some of which can lead to death, serious injuries, or other situations that pose a threat to life. There is a substantial body of literature including indisputable accounts of poisoning (Ernst, 2002).

In summary, botanical medicine can be safe and effective when used judiciously and under the guidance of a qualified healthcare provider. It's essential to consider factors such as quality, drug interactions, toxicity, allergies, pregnancy, regulation, individual variability, and potential adverse effects when using botanical products. Consulting with a healthcare professional can help ensure the safe and appropriate use of botanical medicine for your specific health needs.

International Bias against Botanical Medicine Diseases, Canine 'itch' or Mange and Diarrhea in Cattle

Plants have been employed by humans for a multitude of purposes since the dawn of civilization, most notably as food and medicines for both human and animal health and nutrition, respectively. They have been depended upon for numerous millennia to maintain, enhance, and restore human health. They are utilized in all civilizations worldwide. All African societies utilize them regularly to maintain health and well-being, and they are an essential part of traditional medicine (TM). They are employed as treatments for a wide range of illnesses, including relatively recent ones like HIV/AIDS, as well as for their maintenance and prevention (Langlois-Klassen et al., 2007). Drugs (allopathic treatments) and herbs (herbal medicines) can interact to change the pharmacological or toxicological effects of each ingredient. As a result, synergistic therapeutic effects may make it more difficult to provide medications for chronic illnesses. For instance, taking herbs that are typically used to treat diabetes along with traditional antihyperglycemic medications may theoretically result in hypoglycemia.

Before allopathic or conventional medicine was introduced, traditional medicine was the only healthcare system accessible to the entire African people (Abdullahi, 2011). Due to their extensive history of use in treating illnesses and the knowledge they have amassed over many generations, plants utilized in traditional medicines are generally thought to be harmless. Toxic fatalities have been uncommon in many cultural contexts because medicinal plants have been carefully chosen for use. Even the US National Poison Control Centers do not have a category for adverse reactions to herbs in their database, despite the fact that thousands of people die every year from even seemingly "safe" over-the-counter remedies. Instead, deaths or hospitalizations caused by herbs are extremely uncommon. (Nasri and Shirzad, 2013).

Numerous pharmacologically active substances found in botanicals have either antagonistic or synergistic biological effects. The possibility of interactions is increased by the presence of numerous substances, and it is thought that interactions between herbs and drugs may be more prominent than those between drugs. These interactions may function to increase or decrease the consequences related to pharmacology or toxicology. The pharmacokinetic interaction between two xenobiotics, encompassing metabolism, excretion, absorption, and so forth, mediates such interactions. Each of these occurrences would alter the apparent dosage response as well as any beneficial or harmful consequences (Cohen and Ernst, 2010). However, encounters could be neutral, hostile, or favourable (Cheng et al., 2010). The ingestion of substandard and contaminated products has resulted in numerous adverse consequences that range in severity from mild to severe. Chronic conditions can cause various symptoms, including allergic reactions, respiratory issues, pain, fatigue, gastrointestinal disturbances, mood swings, seizures, and even death (Ekor, 2013).

In order to ensure the efficient use of high-quality botanicals, rigorous pre- and post-market evaluation is required. Manufacturers, packers, distributors, sellers, and other dealers of herbal goods ought to be forced to adhere to certain regulatory criteria, such GMP and ADR, that are related to the usage of their HMPs. There is no question that the quality of HMP is influenced by the beginning material. As a result, GMP and good agricultural practices (GAP) ought to coexist. Although growers and manufacturers are not legally required to follow GAP, several countries require their manufacturers to comply with GMP before granting a license for the production of HMP. It should be mandatory to comply with GMP and GAP in order to guarantee the high quality of HMPs. Contract farming for the growing of medicinal plants would guarantee product quality, reduce variability in plant preparations, and maintain high-quality output (Wah et al., 2012).

Swimmer's itch and sea bather's itch have similar symptoms. They are both caused by the juvenile nematocysts of larval cnidarians found in thimble jellyfish or sea anemones. This causes a hypersensitive reaction that results in extreme itching. However, the development of tiny red papules on the skin beneath swimwear or in between hairs is the distinguishing feature of sea bather's itch compared to cercarial dermatitis (Freudenthal and Barbagallo, 2002).

Several mite species that are found globally, including *Chorioptes bovis*, *Sarcoptes scabiei*, *Demodex bovis*, and Psoroptes ovis, can infest cattle. Although *Demodex bovis* can exist as a commensal on the skin, it may also produce tiny cutaneous nodules that can harm hide (Taylor et al., 2007). *Demodex bovis* is found in hair follicles and sebaceous glands. Cattle in Belgium are no longer commonly infected with *Sarcoptes scabiei* (S. scabiei), a mite that burrows into the epidermis and causes hair loss and thickened skin. The comparatively benign ailment known as *Chorioptes bovis* (C. bovis) mange mostly affects dairy cattle, specifically Holstein Friesians (HF), and is frequently found at the legs, tail base, and udder (Mitchell et al., 2012).

Regarding specific ailments like canine itch or mange and diarrhea in cattle, botanical remedies have been traditionally used to address these issues in various cultures. However, the acceptance and efficacy of botanical treatments for these conditions may vary widely depending on factors such as the severity of the condition, the specific botanical remedies used, and individual variations in response to treatment. In veterinary medicine, there is growing interest in exploring alternative and complementary therapies, including botanical medicine, but the evidence base supporting their efficacy and safety in treating specific conditions may still be limited compared to conventional treatments. As such, biases against botanical remedies in veterinary medicine may also exist, reflecting similar concerns about efficacy, safety, and standardization.

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Chapter 24

Elucidating the Anthelmintic Efficacy and Phytochemical Profile of *Citrullus colocynthis* (Linnaeus) Schrader

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ABSTRACT

Citrullus colocynthis is beneficially being used as a medicinal plant for the management of animal parasites. This botanical entity is commonly referred to as bitter apple or colocynth, it belongs to the Cucurbitaceae plant family and has a historical record of being used for several centuries for the management of various ailments. This study highlights the phytochemical components present in the plant and particularly focuses on the terpenoids, flavonoids, alkaloids, and cucurbitacins as the major bioactive compounds having medicinal properties. Keeping in view the emerging concern of the development of drug resistance to traditional anthelmintic medications, this chapter examines the potential of *C. colocynthis* as a supplementary natural intervention for the management of parasitic infections. The chapter examines the challenges and potential future opportunities pertaining to the utilization of a certain substance as an anthelmintic. The authors advocate for additional research efforts to comprehensively exploit its therapeutic efficacy. Drawing on both traditional knowledge and scientific evidence, it is determined in the article that *C. colocynthis* possesses the capability to impede worm muscle activity and hinder the hatching of eggs, thereby establishing its efficacy as a natural remedy for parasitic worms.

KEYWORDS	Dates	Publisher
Citrullus colocynthis; Parasite control; Traditional uses; Herbal remedies; Ethnomedicine	Received: 04-Jun-2024 Revised: 01-Jul-2024 Accepted: 05-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Agricultural sustainability in rural areas is largely dependent on livestock production, particularly when the financial returns from crop production are inadequate (Khajuria et al., 2013; Ahmed et al., 2020). However, parasitism has historically posed significant challenges in maximizing the yield generated by livestock production systems (Batool et al., 2019). *Haemonchus* is a primary barrier to small ruminant production and causes an estimated ten billion dollar loss to veterinary production (Roeber et al., 2013). Each parasite consumes about 0.05 mL of blood daily (Alim et al., 2016), resulting in severe damage to the gastrointestinal mucosa (Singh et al., 2015). Continuous blood loss resulting from *H. contortus* produces anorexia, anemia, diarrhea, edema, emaciation, and hypoproteinemia, eventually leading to the animal's death (Githigia et al., 2001). Severe illness significantly impacts meat, milk, and wool production, reduces weight gain by 23-63%, and leads to death in 25% of cases before weaning (Singh et al., 2015). The economy of rural communities heavily relies on domestic ruminants such as cows, buffaloes, goats, and sheep. Amphistome parasites are highly prevalent among domestic ruminants worldwide (Khan et al., 2023). These parasites cause severe and acute fluke infections, resulting in debilitation, reduced productivity, slow growth, and poor production of milk, meat, skin, and wool. Consequently, the livestock industry suffers significant economic losses every year (Menaria et al., 2020). The use of synthetic chemicals to combat nematode pests has been widely and commonly applied; however, these chemicals pose negative environmental and biodiversity impacts increasing the urgency for developing a biosafe alternative. Researchers have studied phytopesticides as an alternative to synthetic chemicals due to their eco-friendly nature, easy availability, and biodegradability in soil. This review article emphasizes the significance of *Citrullus colocynthis* L. Schrad as a potential biological and pesticidal agent. It can be utilized for treating medicinal ailments and controlling pests that negatively impact animal growth. The article also highlights the importance of harnessing the beneficial properties of this plant against nematodes (Khatri et al., 2021). The *Cucurbitaceae* family is renowned for its remarkable genetic diversity among food plants (Zaini et al., 2011). These plants are usually drought-tolerant but sensitive to wet, poorly drained soils and frost. Prominent members of this family include bitter apple, bitter gourd, cucumber, pumpkin and melon (Bisognin, 2002). *C. colocynthis* a perennial herb with trailing characteristics, is commonly found in the wild in sandy regions of the Punjab, Sind, North West, southern and central India, the Coromandel coast, Arabia, Tropical Africa, West Asia and the Mediterranean region (Hussain et al., 2014). *C. colocynthis* also known as bitter cucumber, bitter apple, Indravaruni or Gavakshi, is a viny plant native to the Asia and Mediterranean basin, particularly Nubia, Turkey, the desert areas of Pakistan and India. Its fruit extracts have shown antibacterial and antimicrobial effects against *Pseudomonas* and *Staphylococcus*. The application of medicinal plants to prevent and treat gastrointestinal parasitism originated from ethnoveterinary medicine. Medicinal plant-based remedies serve as alternatives to synthetic antihelmintic or anthelminthic drugs.

Botanical Description

C. *colocynthis* is a long-lasting plant with persistent roots and sturdy, rough, vine-like stems that spread horizontally on the ground and can also ascend upwards. It produces a singular yellow blossom at the intersection of takes off. The plant is monoecious, with long stalks and a tuberous rootstock that grows long trailing or climbing stems (Li et al., 2022). The roots are lasting, whereas the stems are precise, intense, and harsh vine-like structures that spread on a level plane on the ground and can too climb upwards. The seeds are smooth in surface, oval in shape, and extend in color from yellow to brown.

A single yellow bloom is created at the intersection of clears out. The plant is monoecious and has long stalks. The takes off are precise and degree roughly 5–10 cm in length. They have a triangular shape, unpleasant surface, and are green in color. The plant produces 15-30 natural products, which are almost 7–10 cm in breadth. The color of the natural product may vary from yellow or green with yellow stripes. The natural product mash contains oval seeds (Hussain et al., 2014).

They are rough on both sides and have 5-7 lobes. *C. colocynthis* produces both male and female flowers. The fruit is globular, slightly flattened, with a diameter of 5-7cm. When ripe, the fruit turns white and smooth, but initially, it is green in color. The fruit contains a dry spongy pulp that is extremely bitter. The seeds are pale brown and measure 4-6mm in length (Pravin et al., 2013).

Geographically Distribution of *Citrullus colocynthis*

Geographically, *C. colocynthis* is found in West Pakistan, barren areas of India, Arabia and Ceylon, primarily in the region west of the Mediterranean (Jafri, 1966). Among the reported 17 genera and 32 species, Pakistan records 25 medicinal plants of the *Citrullus* genus (Jafri, 1966; Nazimuddin and Naqvi, 1984).

Table 1: Taxonomic account of *Citrullus colocynthis* (Linnaeus) Schrader

Sr.No	Classification	
1	Kingdom	Plantae
2	Division	Magnoliphtya
3	Class	Magnolipsida
4	Order	Cucurbitales
5	Family	Cucurbitaceae
6	Genus	*Citrullus*
7	Species	*colocynthis*
References	(Khatri et al., 2021)	

Plant Part Value and Mode of Administration

According to research conducted by Mazher et al., 2023 the fruit of the *C. colocynthis* plant, including its rind, pulp, and seeds, is commonly used by local people for ethnomedicinal and ethnoveterinary purposes. For whole fruit and seeds the highest plant part value (PPV) was found to be 90. Second and third highest PPVs were of rind and pulp as 83.3 and 80, respectively. Lower PPVs of 26.7, 20, and 6.7 was found for leaves, stem and roots respectively. According to the ethnobotanical survery findings the Traditional Ethnomedicines use various methods for preparation of *C. colocynthis*, including cooking the fruits, consuming it as a powder with water, applying it as a paste or poultice, ingesting different parts, making decoctions with water, or making it into tea.

Traditional uses of *Citrullus colocynthis*

Plants have been utilized for therapeutic purposes since antiquated times, and there's presently a developing interest in plant-based medicines resulting from a stronger understanding of the side effects of synthetic drugs. This expanded request for restorative plants has put weight on species like *C. colocynthis*. This specie is broadly utilized around globally for the treatment of different maladies, counting obstruction, asthma, diabetes, joint torment, bronchitis, jaundice, mastitis and cancer (Abo et al., 2008; Sultan et al., 2010; Pravin et al., 2013).

Table 2: Names of *Citrullus colocynthis* in different Languages

Sr. No	Languages	Common names of plant
1	English	Colocynth, Bitter- gourd, Bitter- apple, Bitter- cucumber
2	German	Koloquinthe
3	French	Coloquinte
4	Sanskrit	Indravaruni
5	Arabic	Handhal
6	Punjabi	Ghurunba or Kortuma
7	Bengali	Makhal
8	Tamil	PaedikariAttutummatt-i
9	Marathi	Kaduindravani
10	Gujarati	Indrayan
11	Malyalam	Paikummatti
12	Hindi	Indrayan
13	Pashto	Maraghonae
References	(De Smet, 1997; Pravin et al., 2013; Elltayeib et al., 2020)	

In subtropical and tropical nations, it is commonly utilized as an antidiabetic medicine. In Pakistan and India, the natural products are utilized to treat intestinal clutters, bacterial diseases, diabetes, and cancer in both people and animals. Different parts of *C. colocynthis* have been utilized for different illnesses. For illustration, the dried natural product mash is successful in treating acid reflux and gastroenteritis, whereas the natural product itself has antioxidant, antimicrobial, and anti-inflammatory properties (Marzouk et al., 2010; Hameed et al., 2020).

Moreover, *C. colocynthis* has appeared potential in treating diabetes, anthelmintic contaminations, torment, sensitivities, and cancer. *C. colocynthis* is also effective in treating gastrointestinal conditions, pulmonary and skin infections, constipation, diabetes and edema. The dried mash of the natural product is utilized for gastrointestinal disarranges, whereas the plant entirely is utilized for diabetes, liver issues, bowel developments, and intestinal issues. Besides, the natural product extricate is utilized for pain relieving. The natural product of *C. colocynthis* has blood filtering properties and can be utilized as a cure for extension of the spleen and tumors. Furthermore, the seeds of this plant are used to manage diabetes, and the leaves are utilized to treat jaundice and asthma (Baquar and Tasnif, 1967; Qureshi et al., 2010).

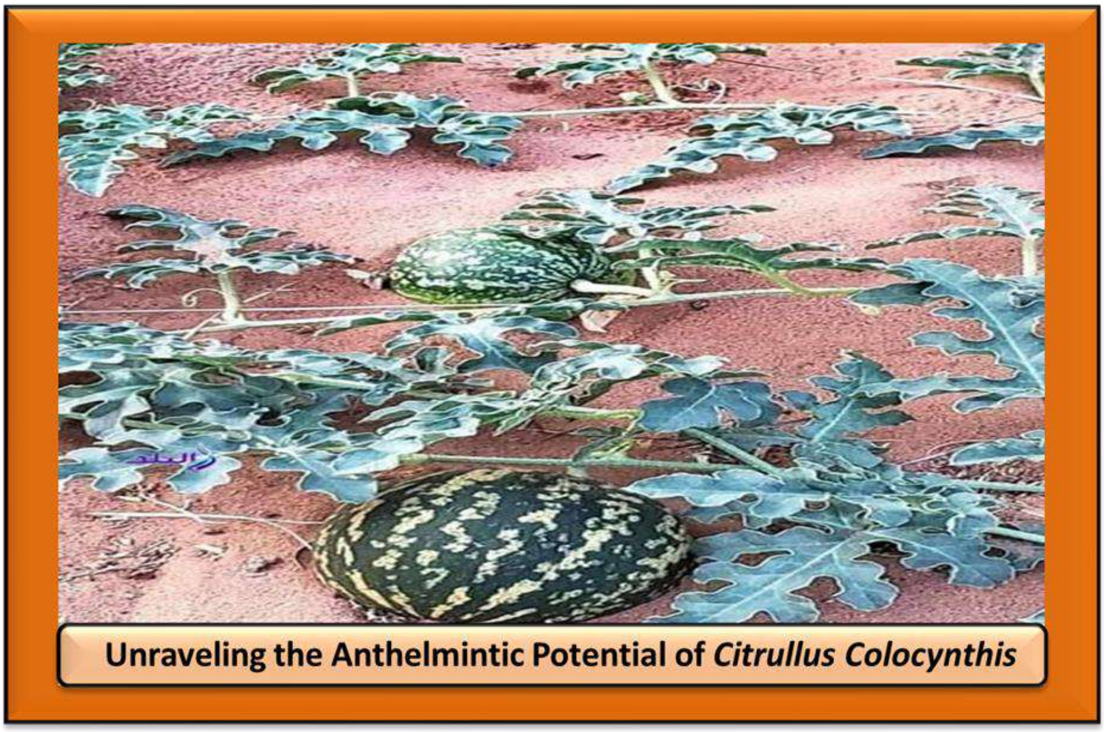

Fig. 1: Unraveling the Anthelmintic Potential of *Citrullus Colocynthis*

Proximate Composition of *Citrullus colocynthis*

The composition of the seeds and natural products of *C. colocynthis* shifts depends on the nation of beginning. The proximate investigation of *C. colocynthis* uncovered 56.1% fat, 24.7% protein, 10.8% carbohydrate, 3.8% dampness, 3.5% fiery remains and 1.1% fiber. The seed parts contain around 50% oil, 30% protein, 10% carbohydrate, 4% fiery debris, and 3% fiber. It is imperative to note that these values may change due to the wide range of agro-ecological conditions and rural hones in each nation (Ogundele et al., 2012).

Phytochemistry of *Citrullus colocynthis*

C. colocynthis contains a wide extend of bioactive compounds, counting little hydrocarbons, flavonoids, terpenoids, amino acids, hydrocarbons, alcohols, esters, greasy acids, and cucurbitacins. Phytochemical screening of the natural products has uncovered the nearness of glycosides, flavonoids, alkaloids, phenols, carbohydrates, greasy acids, and basic oils (Dhakad et al., 2017).

Glycosides, Phenolic Acids and Flavonoids of *Citrullus colocynthis*

The antioxidant action and phenolic profile of distinctive extricates from *C. colocynthis* have been considered and detailed the locally developed natural products of *C. colocynthis*, two cucurbitacin glucosides (glucopyranosyl cucurbitacin and 2-glucopyranosyl-cucurbitacin L) and three flavone glucosides (isoorientin, isosaponarin and isovitexin) were extricated and distinguished. These flavonoids have critical antioxidant impacts, which are advantageous for treating different disarranges related with receptive oxygen species, such as aggravation, cancer, tissue harm, and other maladies. Within the ethanol extricate of *C. colocynthis* natural products, four flavonoids (quercetin, kaempferol, catechin and myricetin) eight phenolic acids (vanillic corrosive, ferulic corrosive, gallic corrosive, sinapic corrosive, chlorogenic corrosive, p-hydroxy-benzoic corrosive, caffeic corrosive, and p-coumaric corrosive) were recognized (Hussain et al., 2014).

Table 3: Pharmacological activities of *Citrullus colocynthis* and its medicinal use safety and efficacy

Sr. No	Pharmacological Activity	
1	Anti-inflammatory Activity	Potential to reduce inflammation
2	Antioxidant Properties	Exhibits antioxidant effects, Helping to neutralize free radicals
3	Antidiabetic Effects	Potential blood sugar regulation
4	Antimicrobial Activity	Antimicrobial effects against certain bacteria and fungi
5	Gastrointestinal Effects	Laxative properties, possibly linked to compounds stimulating bowel movements

Cucurbitacins of *Citrullus colocynthis*

Various preparations of *C. colocynthis* contain proteins, amino acids, carbohydrates, phenolic compounds, tannins, steroids, alkaloids, terpenoids, glycosides and cucurbitacins A, B, C, D, E, J, and L. From the natural material of *C. colocynthis*, colocynthosides A, cucurbitacin L, and cucurbitacin B were extracted and purified. The most abundant cucurbitane-type triterpene glycoside, Cucurbitacin E 2-O-D-glucopyranoside, and its aglycon, cucurbitacin E, displayed anti-allergic properties (Yoshikawa et al., 2007).

Fatty Acids

The seed oil of *C. colocynthis* contains two major immersed greasy acids (SFAs), palmitic corrosive and stearic corrosive, inside the extend of 8%-17% and 6%-10%, individually. Oleic corrosive and linoleic corrosive are the major monounsaturated greasy acids (MUFAs) show within the oil. Linoleic acid is found within the extent of 50%-60%, which is higher than other oils. *C. colocynthis* seeds contain linolenic, myristic, palmitic, oleic and stearic acid. A few greasy acids found in *C. colocynthis* have been studied for their nematicidal exercises. Oleic corrosive, the foremost common greasy corrosive in nature, has appeared to be showing beneficial action against *Bursaphelenchus lignicolus*. Hexadecanoic, lauric, caprylic, and myristic corrosive have been found successful against the phytonematode *Meloidogyne incognita* (Zhang et al., 2012).

Alkaloids

A few things about it have detailed the nearness of alkaloids, particularly choline and unidentified alkaloids, in *C. colocynthis* natural product, which require assist examination (Ali et al., 2013).

Minerals

The natural product and seeds of *C. colocynthis* contain a wealthy sum of minerals. Specifically, the seeds are a potential source of calcium, potassium, zinc, and phosphorus. The concentration of calcium is 569mg per 100g, whereas potassium is displayed at a concentration of 465mg per 100g (Sadou et al., 2007).

In Vitro Anthelmintic Effect of *Citrullus colocynthis*

Different innate plants have been found to have an anthelmintic impact against cestodes, trematodes, and nematode parasites. A particular plant, *C. colocynthis*, is considered to show antileishmanial and antitumor properties. It is also effective against *Leishmania major* (a protozoan parasite) and show molluscicidal properties against *Biomphalaria Arabica*

(Nizam et al., 2013; Zaid et al., 2013). Additionally, *C. colocynthis* has shown beneficial anthelmintic efficacy against *Haemonchus contortus*, which results in a reduction in the egg count, and also cause the paralysis of the worm *Pheretima posthuman* (Talole et al., 2013; Ullah et al., 2013).

In vitro Assessment of the Anthelmintic Properties of *Citrullus colocynthis* (L.) Schrad on *Haemonchus contortus*.

Haemonchus contortus which is the causative agent of haemonchosis, is a major obstacle in small ruminant production. It causes significant economic losses in the veterinary market, estimated at around ten billion dollars annually. This parasite feeds on approximately 0.5mL of blood per day, resulting in damage to the gastrointestinal mucosa. The continuous blood loss leads to diarrhea, anemia, edema, anorexia, emaciation and hypoproteinemia, eventually causing the animal's death. Severe infections have a substantial impact on wool, meat and milk production, Resulting in a 23-63% drop in weight gain and causing death in 25% of cases prior to weaning. Therefore, there is an urgent need to control infections caused by *H. contortus* in ruminants (Rehman et al., 2021). The same procedure was repeated for the ethyl acetate extract. The extracts were stored as pastes at 4°C. Flavonoids and phenolic compounds in the aqueous methanolic extract were identified through high-performance liquid chromatography (HPLC) analysis. At regular intervals, the worms' motility was examined with an inverted microscope. Worms that did not show any motility were considered alive only if their motility revived after being placed in lukewarm PBS. Egg hatch assays were performed to assess the efficacy of the extracts. Female worms were triturated to release the eggs, which were then diluted to a concentration of 200 eggs per milliliter. The assays included four doses of each extract and three concentrations of oxfendazole (a synthetic drug). Post-incubation, unhatched eggs were counted using an inverted microscope, and their percentage was calculated. The results showed that at a dose rate of 25mg/mL after 4 and 8 hours of exposure of ethyl acetate and aqueous methanolic extracts respectively, paralyzed all adult worms. 83.7% and 80.7% of *H. contortus* eggs remained unhatched in the egg hatch assay, when the same dose of ethyl acetate and aqueous methanolic extracts was used, respectively. These findings suggested that *C. colocynthis* fruit extracts have a promising potential as an alternative to synthetic drugs for controlling *H. contortus* infections.

Orthocoelium scoliocoelium

Swarnakar and Kumawat, 2014 conducted a study and investigated the effects of *C. colocynthis* fruit extracts on amphistome parasites, putting their main focus on *Orthocoelium scoliocoelium*. Although previous research had tested the alcoholic fruit pulp extract of *C. colocynthis* in vitro against these parasites but no studies had examined the anthelmintic effects of the fruit extracts by using a light microscope. In their materials and methods section, Menaria et al., 2020 described the collection of live amphistome parasites from freshly slaughtered domestic ruminants' rumen (buffaloes, sheep, and goats) at the local zoo abattoir in Udaipur. The parasites were thoroughly washed with a saline solution (0.9% NaCl) and then divided into three groups. Following the method of Dutt, 1980, whole mount preparation was carried out to identify the species of amphistomes for the first group. The second group was referred as the untreated control and the the third group was treated in vitro with fruit extracts of *C. colocynthis*. Bouin's fixative was used for fixation of both the control and treated amphistomes for histological examination by using a light microscope. For preparation of the fruit extracts, fresh *C. colocynthis* fruits were recieved from the desert areas of Shriganganagar, Jaisalmer, and Barmer in Rajasthan. The fruit pulp was then dried after separating the seeds and was ground to a powder by using a grinder. The results of the study evaluated that the *C. colocynthis* fruit extract had significant anthelmintic effects on *Orthocoelium scoliocoelium*. Under the light microscope he treated amphistomes showed extensive damage to their structures as compared to the untreated control group. This included disruption of the tegument and internal tissues, indicating the potential of *C. colocynthis* as an effective treatment against intestinal worm infections in ruminants.

Plants used for Treating Intestinal Worms

This ponder centers on the utilization of plants in Ibadan, Nigeria for treating intestinal worms (Afolayan et al., 2022). One of the plants commonly utilized is *C. colocynthis* (L. Schrad. frequently combined with other plants such as *Curculigo Pilosa*, *Securidiata longepedunculata*, *Laganaria breviflorus* and *Anthocleista djalonensis* A. Chev. *C. colocynthis* (L. Schrad) seeds are utilized in treatment by washed and bubbled for 30 minutes together with diced *Laganaria breviflorus*. Alternatively, the roots of *Anthocleista djalonensis* A. Chev., *Securidiata longepedunculata*, the seeds of *C. colocynthis* (L. Schrad) and the bark of *Curculigo pilosa* are thoroughly rinsed and cooked. To address intestinal worm infections, adults are advised to take this treatment once daily, prepared as a decoction. Intestinal worm infections are a significant global health issue, especially in subtropical and tropical regions. Traditionally, three classes of anthelmintics, namely cholinergic agonists, macrocyclic lactones and benzimidazoles have been used to control these worms. However, the emergence of anthelmintic resistance calls for new approaches. One potential avenue that offers natural and cost-effective remedies for parasitic infections (including those caused by intestinal parasites), is the use of medicinal plants and traditional medicine. This research recorded the medicinal herbs utilizatoin in treating intestinal worm infections within the Ibadan metropolis, using an ethnobotanical survey. The main focus of the survey are the three main traditional herb markets in Ibadan: Oba, Oja and Oje, and Iwo Road. Structured questionnaires interviewed herb sellers and got information regarding the demographic details, names of the plants used, the components of plants, dosage, and the methods of preparation. Data collected was analyzed by descriptive statistics and calculations were made for Relative Frequency Citation (RFC), Use Value (UV), and Informant Consensus Factor (ICF) for the cited plants. The survey put forth that 45 plants from 31 families were used for treating intestinal worms in Ibadan. *Cryptolepis sanguinoleta* (Lindl.) Schltr and *Aristolochia albida* Duch were the most frequently reported, each with an RFC of 0.9. Plants from the Apocynaceae and Euphorbiaceae families were commonly used. The leaves (18.5%) and roots (25%) were the most commonly utilized plant parts.

Ethnoveterinary Practices in Cholistan Desert, Pakistan

An analysis was conducted to record the conventional ethnoveterinary restorative hones utilized by nearby shepherds within the treatment of parasitic illnesses in animals. The analysts conducted a starting study to distinguish conventional healers and collected data through organized surveys and interviews. They found that the parasitic illnesses detailed in animals included lice and tick invasion, helminthiasis, myiasis, and mange. A total of 77 ethnoveterinary remedies were documented, with 49 derived from plant usage and 28 from dairy products, chemicals, and other organic substances. Eighteen plant species belonging to 14 families were identified among the reported remedies for treating parasitic diseases. For case, *C. colocynthis* (Linn.) Schrader was utilized for lice invasion by bubbling 500g of its natural product with 1L of water and applying it topically. For helminthes treatment a mixture of 500g of *C. colocynthis* fruit with 250g each of black and common salt was given orally at a dose of 50-100g per day for 2-3 days. The recorded remedies were used for various domesticated animals in this area, including cattle, goats, sheep, and camels. Different doses were used for small and large animals. It was found that the majority of the remedies were plant-based. Out of the 118 plant species native to the Cholistan desert, only 10 (8%) were used for treating parasitic diseases in animals. However, a total of 64 plant species including herbs, shrubs, grasses and trees have also been reported for their uses as medicine in the desert. Some of the indigenous plants found in the sand dunes and sandy soils of Cholistan desert were *Aizoon carariense, Aerva javanica, Capparis decidua, Cyperus rotundus, Haloxylon salicornicum, Calligonum polygonoides, Pinus roxburghii, C. colocynthis, Salsola baryosma, and Solanum surratens* (Farooq et al., 2008)

Ethnoveterinary Practices for Mastitis

Mastitis could be a exorbitant illness within the dairy industry around the world. It happens when dairy animals like buffaloes and other creatures associated with microorganisms in their environment (Muhammad et al., 2008). In Pakistan, mastitis has been recognized as a major problem for animals. To address this issue, ethnoveterinary medication can be a more reasonable and feasible elective to engineered medications. EVM includes utilizing home grown arrangements that have been customarily utilized by pastoralists and agriculturists for treating animal’s maladies. One particular herb, *C. colocynthis* (L.) Schrad, has been detailed to be utilized for controlling mastitis. In India, it has been utilized as a galactagogue. The plant species most commonly reported include *Citrullus colocynthis* (L.) Schrad, *Lepidium sativum* L., *Allium sativum* L., *Sesamum indicum* L., *Capsicum annuum* L., *Citrus limon* (L.) Burm.f, *Zingiber officinale* Roscoe, *Curcuma longa* L., *Cuminum cyminum* L., *Triticum aestivum* L., *Rosa indica* L., *Centratherum anthelminticum* L., *Peganum harmala* L., and *Nigella sativa* L. (Takhar et al., 2004).

Antioxidant and Free Radical Scavenging Potential

Cancer prevention agents are substances that prevent against harm caused by reactive oxygen species (ROS), which are included in different maladies. These ROS, such as hydrogen peroxide and superoxide anions, can lead to oxidative stress and contribute to the betterment of various conditions like atherosclerosis, stroke, Alzheimer's diseaes, diabetes, and cancer. Furthermore, there has been increasing interest in normal cancer prevention agents, especially compounds found in plants like flavonoids and phenolic, due to their potential therapeutuc benefits. One plant of interest is *C. colocynthis*, particularly its seeds and natural products. Ponders have examined the antioxidant properties of diverse extricates from *C. colocynthis* seeds. The extricates were tried at a concentration of 2,000µg/ml employing a 1,1-diphenyl-2-picrylhydrazyl measure. The ethyl acetic acid derivation extricate appeared to be showing the most noteworthy antioxidant action with a lessening rate of 88%, taken after by the hydromethanolic extricate (HM) with 74%, and the rough watery extricate (E1) with 66%. Ascorbic corrosive, a known antioxidant, had an IC50 of 1µg/ml. These discoveries propose that *C. colocynthis* seeds have potential as a common antioxidant source (Gill et al., 2011).

Antiparasitic Insecticidal and Antiscorpion Effects

A study conducted from the Office of Pharmacology at Thi qar College in Nasiriyah, Iraq, pointed to examine the impacts *C. colocynthis* on creepy crawlies and scorpions. The analysts tried different extricates of *C. colocynthis* clears out against *Culex quinquefasciatus* hatchlings. The extricates included unrefined acetone, hexane, ethyl acetic acid derivation, methanol, and petroleum ether. After 24 hours of presentation, the petroleum ether extricate appeared the most noteworthy larval mortality. Advance investigation of this extricate driven to the distinguishing proof of two greasy acids, linoleic corrosive and oleic corrosive which displayed powerful larvicidal action against *Anopheles stephensi*, *Aedesaegypti* and *Culex quinquefasciatus* hatchlings. In expansion, the analysts tried diverse extricates of *C. colocynthis* natural products against *Aphis craccivora*. The ethanol extricate showed the most noteworthy insecticidal effect, and the extraction of the recognizable compound, 2-O-β-D glucopyranosylcucurbitacin E, was encouraged, which shows the most extreme insecticidal impact (Torkey et al., 2009).

Moreover, *C. colocynthis* was evaulated as a promising preventive approach for scorpion envenomation, particularly against *Androctonus australis* hector poison. The analysis found that pretreating mice with *C. colocynthis* provide some time recently poison infusion given security against poison harmfulness. It decreased paw edema, cell relocation, exudation, hyperglycemia, and oxidative stretch. *C. colocynthis* too diminished certain incendiary markers and kept up the levels of particular proteins. A study proposes that *C. colocynthis* has antiparasitic, insecticidal, and antiscorpion impacts, making it a potential device for decreasing the pathophysiological impacts initiated by envenomation (Fatima et al., 2014).

Conclusion

This book chapter is about studying the nutrients and possible health benefits of *C. colocynthis* by looking at information from different academic sources. The study shows that *C. colocynthis* is a healthy fruit with many good effects on health. This fruit is really healthy having various benefits including antivenemous, antibacterial and several other properties as mentioned in the article in various sections. Its benefits are very vast but this is not well known among the people. So there is a need to improve the studies and spread the knowledge of the defectiveness of this plant.

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Chapter 25

The Pharmacological Potential of *Moringa oleifera* Reviews of its Bioactive Compounds and Therapeutic Effects

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ABSTRACT

The tropical periodic deciduous plant *Moringa oleifera*, which is a member of the Moringaceae family, is abundant in biologically active compounds like phytochemicals, vitamins, electrolytes, and minerals. Every part of *Moringa* has a different composition but most commonly powder of dried leaves of moringa is used as functional ingredients in our food. Moringa is also thought to be a treatment for malnutrition and many other disorders. It has numerous pharmacological qualities, including antioxidant, anti-inflammatory, anti-anemic, antibacterial, anti-diabetic, and anti-cancer effects. It improves liver and brain health. Probably, the presence of flavonoids and other bioactive chemicals in moringa is directly related to the plant's pharmacological qualities. To serve as a reference for Moringa's possible use as a functional food, this chapter will include a summary of its bioactive chemicals and therapeutic qualities.

KEYWORDS *Moringa oleifera*, Phytochemicals, Therapeutic, Nutritional, Bioactive compounds	Received: 07-Jun-2024 Revised: 24-Jul-2024 Accepted: 15-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Among the monogenetic family Moringaceae, *Moringa oleifera* Lam (syn. M. ptreygosperma Gaertn.) is one of the most well-known, extensively distributed, and naturally occurring species. It is incredibly useful so there has been a lot of research done on this plant, one of the 13 species of the Moringaceae family (Boopathi and Abubakar, 2021). And as the "kelor tree" in others. Shagara al Rauwaq, which translates to "tree for purifying," is the name of the tree in the Nile Valley while it is cultivated and grown throughout Pakistan under the native name "Sohanjna." The tree is between five and ten meters tall. The tropical *Moringa oleifera* is local to Asia Minor, Africa, Arabia, India, Pakistan, and the western and sub-Himalayan areas. It can tolerate poor soil conditions, grows well in hot, dry, and humid tropical climates, and is not greatly affected by drought. With an estimated yearly demand of between 250 and over 3000 mm, it can tolerate various rainfall. *Moringa oleifera* can be found in Central America, the Caribbean Islands, South and North America, Cambodia, and the Philippines (Anwar et al., 2007).

M. oleifera ranges in five to ten meter heightened rapidly growing plant. The pale green, soft leaves of *M. oleifera* measure between 30 and 60 cm and have several tiny leaflets. The fragrant, bisexual flowers of *M. oleifera* have five uneven, milky, or white petals. After being planted, they flower within the first six months. Furthermore, the flowers typically develop into anthem, which is a structure that is between 12 and 30 centimeters in length, between April and June on the hairy, thin pedicels. In geographically chilly areas, flowering occurs once a year; in areas with more consistent seasonal temperatures and persistent rainfall, it blooms twice a year or even year-round. Fruit yields are typically modest in the initial years. A tree can produce as many as 1000 grains of pods after three years of planting (Liu et al., 2018).

Because practically every portion of the *M. oleifera* tree has some use, it is regarded as one of the most multipurpose plants on the planet. Because of its abundance in some macro and micronutrients that are crucial to human nutrition, this tree is known as a miracle. Different components of *M. oleifera* are prepared differently and used as vegetables or dietary supplements in many underdeveloped nations. Furthermore, practically every component of this tree has already been used to successfully treat a range of illnesses. Forage uses include leaves, tree trunks for gums, flower nectar in honey, and ground seeds used to purify water. A substitute food supply for malnutrition, particularly in young children and newborns, is *M. oleifera* leaf (Oyeyinka and Oyeyinka, 2018).

Fig. 1: Moringa 'drumstick' plant leaves

Table 1: Moringa species are widely cultivated in different countries(Boopathi and Abubakar, 2021)

Series:	Species of Moringaceae:	Most widely cultivated in:
01	*M. oleifera*	Pakistan, India
02	*M. peregrina*	Red Sea Area, Arabia
03	*M. concanensis*	Pakistan, Bangladesh, India
04	*M. drouhardii*	Madagasar
05	*M. stenopetala*	Ethiopia, Kenya
06	*M. hildebrandtii*	Madagasar
07	*M. ovalifolia*	Angolia, Namibia
08	*M. rivae*	Ethiopia, Kenya
09	*M. longituba*	Somalia, Kenya
10	*M. arborea*	Kenya
11	*M. pygmaea*	Somalia
12	*M. borziana*	Somalia, Kenyya
13	*M. ruspoliana*	Ethiopia, Kenya, Somalia

Bioactive Compounds Present in *M. oleifera*

The benefits of the moringa tree for the environment, water sanitation, health, and nutrition have led to its designation as a tree of life. Moringa is a tree of great diversity that is prized in many tropical regions and used in a wide range of traditional remedies. Because it contains a variety of bioactive chemicals, moringa is a useful traditional medicinal plant. It contains a variety of nutrients, including protein, vitamins, minerals, and phytonutrients like tannins, alkaloids, flavonoids, polyphenols, and carotenoids. In some locations where there are nutritional issues, this plant is utilized as a nutritional supplement for young children (Duranti et al., 2021). Moringa leaf’s nutritive and bioactive composition is affected by agroclimatic factors, plant age, genotype, and harvest timing (Managa et al., 2021; Rébufa et al., 2021).

Phytochemicals Present in Moringa

Phytochemicals are organic molecules that are physiologically active and present in plants that humans eat. Although they have not been linked to any particular human deficiency illness, they may have health benefits. Generally speaking, phytochemicals are plant-derived secondary metabolites i.e., materials produced by plant cells that support the survival of the entire plant. Numerous phytochemicals are thought to have the same properties as natural pesticides. Some phytochemicals provide color or aroma, while others serve as signaling molecules within the plant or in connection to other organisms. Even in Western countries, that cultivate and eat relatively few plant species as food, thousands of phytochemicals that are found in food are ingested in substantial amounts. Phytochemicals have been used by humans as medication to treat and prevent a variety of illnesses, especially cancer or illness related to old age (Johnson and extraction, 2013). Plant-based phytochemicals are classified into five types depending on their chemical structures: carotenoids, polyphenols, terpenoids, alkaloids, and compounds containing sulfur (Bøhn et al., 2012). Moringa trees have almost all these types of phytochemicals due to which Moringa has vast medicinal uses. The phytochemicals called alkaloids are produced when amino acids are broken down. The predominant alkaloid found in Moringa leaves is N, α-l-rhamnopyranosyl vincosamide (VR), which possesses a cardioprotective function (Panda et al., 2013).

The Moringa has polyphenols that include high concentrations of tannins, lignans, and phenolic acids. Comparatively speaking, the plant's leaves have a higher concentration of polyphenols than its flowers or seeds do. It has been discovered that they have antifungal, antibacterial, and antioxidant properties (Leone et al., 2015). Studies have shown that *M. peregrina* leaves have a roughly 22 percent greater total phenolic content than *M. oleifera* leaves (Al Juhaimi et al., 2017). Furthermore, the concentration of phenolic compounds is contingent upon many parameters, including the variety, time of year, and geographical position. For instance, compared to cultivars grown in India, America, and Africa, those grown in Pakistan had a higher phenolic content (Saini et al., 2016).

Flavonoids make up the majority of the polyphenols found in moringa. Since the human body is unable to synthesize flavonoids, this class of diphenyl propane molecules must be obtained through diet. Furthermore, because they are quickly digested, regular supplementation is required (Wang et al., 2017). Anthocyanidins, chalcones, flavanones, flavones, and flavanols are some of the substituents of flavonoids. The flavonoids quercetin, about 47 percent, and kaempferol, approximately 30 percent, are prominently found throughout the Moringa tree, except its roots and seeds. While kaempferol is linked to a decreased risk of cancer, including epithelial ovarian cancer, quercetin has strong antioxidant activity and possesses anti-diabetic, hypotensive, and hypolipidemic qualities. There are also other flavonoids present, such as luteolin, epicatechin, myricetin, and apigenin (Rodríguez-Pérez et al., 2015).

Chlorogenic Acid is another important phenolic acid found in moringa. It is a dihydro cinnamic acid ester that is involved in glucose control. It is discovered to exhibit anti-dyslipidemic action by lowering the level of triglycerides and total cholesterol in plasma (Amaglo et al., 2010). These are the pigments that give fruits and vegetables their color and are typically found in them. One of the best sources of α-tocopherol and other carotenoids is the leaves of *Moringa oleifera*. There are six main types of carotenoids found in *M. oleifera's* vegetative components, including its leaves, flowers, and fruits. All-E-zeaxanthin, all-E-lutein, 13-Z-lutein, all-E-luteoxanthin, 15-Z-β-carotene, and all-E-β-carotene are some of these molecules. All-E-lutein makes up the majority of these, making up roughly 53%. Additionally, they suggested that the high concentration of carotenoids found in moringa will aid in avoiding or lessening vitamin A insufficiency (Saini et al., 2014).

Antioxidant in Moringa

The antioxidant activity of different parts of the moringa tree has been done by in vitro and in vivo analysis. Moringa Leaves have ascorbic acids, β-carotene, glucoside, quercetin, kaempferol, chlorogenic acid, phenolic acids, isothiocyanates, polyphenols and rutin (Tumer et al., 2015). Moringa Flowers have Phytosterols, palmitic acid, and 9-octadecenamide while Moringa seeds are rich in oil and contain oleic acid, mono palmitic acid, tri-oleic triglycerides, tocopherols, Myricetin, and lectins(Mahajan et al., 2007). Moringa Pods has glucosinolates, Procyanidins, flavonoids, isothiocyanates, and thiocarbamates. These all show high antioxidant activity (Singh and Navneet, 2018).

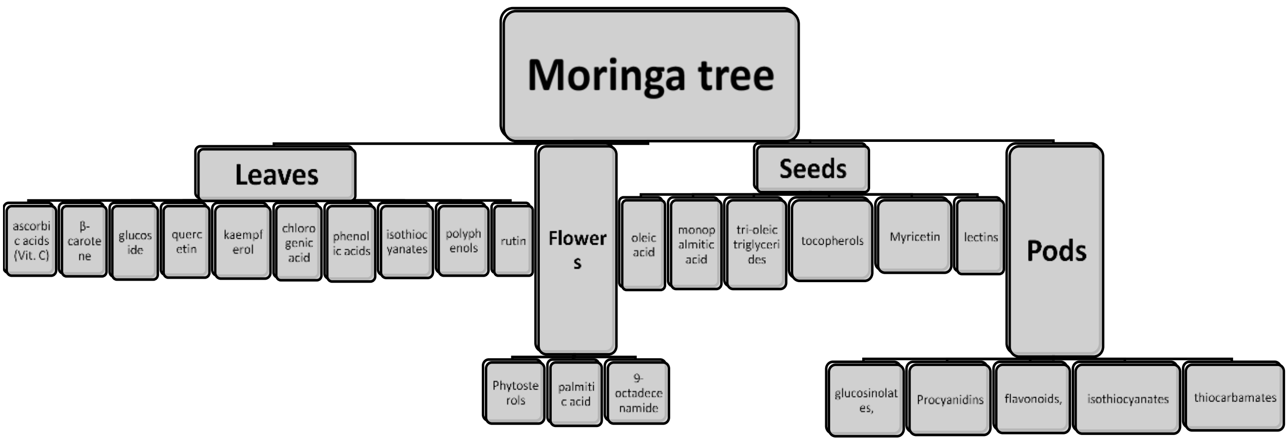

Fig. 2: Composition of different parts of Moringa tree.

Vitamins and Minerals present in Moringa

By consuming moringa, vitamin deficiency can be cured (Olson and Fahey, 2011). The dried powdered leaves of Moringa contain a high vitamin E and βeta-carotene content. Betacarotene, ascorbic acid, niacin, riboflavin pyridoxine, thiamine, cholecalciferol, biotin, tocopherol, and vit. K have all been found to be abundant in moringa powder. These vitamins are necessary for normal body functioning as Vit. A is necessary for vision, and Vit D is compulsory for bone development, without Vit. K blood clotting is impossible, Vit C is required for skin as well as maintains iron levels in the blood, etc.(Isitua et al., 2015). The leaves are a valuable source of minerals and vitamins. Indeed, compared to citrus fruits, carrots, yogurt, dairy products, spinach and bananas, and, moringa is believed to provide seven times more vitamin C, ten times more vitamin A, seventeen times more calcium, nine times more protein, fifteen times more potassium, and twenty-five times more iron (Rockwood et al., 2013).

As compared to bananas and green leafy vegetables like spinach, moringa has more iron and potassium (Gómez et al., 2014). The fact that dried moringa leaves have a significant mineral element deposit is also really intriguing. It was found that the amount of calcium was greater than in other plant sources. Calcium is necessary for bones and teeth, preventing osteoporosis, and required for blood clotting, nervous system, immunity, and muscle movement. Thus, moringa is a rich source of this valuable mineral (Nkafamiya et al., 2010). The leaves of this plant were discovered to be highly abundant in iron, a mineral that is frequently lacking in diets based on plants. Iron plays a vital part in energy metabolism by facilitating the transmission of electrons in the electron transport chain, which is important for the synthesis of ATP. Iron is a component of myoglobin and hemoglobin for oxygen transport (Kozat, 2007).

Cu, thought to have profound impacts on the immune system, was present in the dried leaves of the moringa plant. Zn and copper work together to support superoxide dismutase function and the elimination of oxygen-free radicals. As a result, it plays a crucial role in the cellular membranes' defense mechanism against the damage caused by superoxide free radicals. Furthermore, it has been demonstrated that the copper-containing enzyme ceruloplasmin has anti-inflammatory action, which may be helpful in mastitis situations (Kozat, 2007). Studies revealed that dried Moringa leaves are said to contain higher amounts of zinc. Zinc is necessary for the creation of insulin, RNA, DNA, and many enzymes' structures and/or functions. Additionally, zinc is necessary for the growth and reproduction of cells, particularly sperm cells. Furthermore, zinc has been linked to anti-viral, antimicrobial, anti-fungal properties, and anti-cancer effects. The sulfur found in moringa is essential for the rumen microbes' efficient growth and function. Thus, the mineral makeup of moringa is important for its therapeutic, pharmacological, and nutritional benefits (Busani et al., 2011).

Protein Content

Since amino acids are chemical substances that combine to produce proteins, they have an impact on both the amount and type of protein. The classification of amino acids into essential and non-essential categories varies depending on the type of animal and how it is produced. Essential Amino acids are that are not produced by the body. It must be necessary to take them by food while non-essential amino acids are not necessary in the diet (Swanepoel et al., 2010). The protein content level is especially important nutritionally because it may help animals meet their needs for protein and energy while also strengthening their immune systems against illness. According to reports, moringa contains high-quality, readily digested protein that is influenced by the quality of its amines. Nineteen amino acids were present in the dried Moringa leaves. Out of the typical 20 amino acids, only glutamine was not found; however, glutamine may be produced from glutamic acid. Of the 19 amino acids found, 10 were identified as essential amino acids as includes, phenylalanine, threonine, lysine, methionine, leucine, tyrosine, valine, isoleucine, tryptophan and histidine (Sánchez-Machado et al., 2010).

The Healthy Fat Present in Moringa

The dried leaves of Moringa were found to contain 17 different fatty acids, 11 of which were classed as saturated fatty acids despite having lower values. The compounds with the greatest and lowest values were henicosanoic, palmitic, and capric. There were three types of polyunsaturated fatty acids found: α-linolenic, linoleic, and g-linolenic. Of these, α-linolenic had the highest value. The value of α-linolenic acid is higher, at 56.87 percent. α-linolenic acid, an n-3 fatty acid that falls under the category of essential fatty acids, caught our attention (Sánchez-Machado et al., 2010).

Dietary polyunsaturated fatty acids are present in greater amounts in moringa than saturated fatty acids. Because Polyunsaturated FA has a higher content and a lower level of Saturated FA, it is recommended to include more of it in the diet as it helps to avoid diseases and promote overall health. Increased intake of α-linolenic acid is advised as it supports the body's natural production of long-chain omega-3 fatty acids. Total omega 3 fatty acids are almost 45 percent more in moringa leaves as compared to omega 6 fatty acids which are mostly present in our diet. But generally, our diet is deficient in omega-3 fatty acids so by incorporating moringa leaves in our diet we can get healthy fats (Wood et al., 2008).

Therapeutic Effects of Moringa

Many researchers have used the leaves, seeds, and pods of Moringa to report on a variety of pharmacological qualities. It addresses undernourishment, acts as an antidiabetic, reduces inflammation, and treats a variety of conditions affecting the bones, muscles, liver, etc. (Paikra et al., 2017).

Antidiabetic Effects

Diabetes is a degenerative blood glucose system disease that is characterized by insufficient or absent pancreatic beta cell production of insulin, leading to chronic hyperglycemia. This condition is linked to long-term microvascular complications such as retinopathy, nephropathy, and neuropathy, as well as macrovascular complications such as cardiovascular problems. Additionally, oxidative stress brought on by hyperglycemia is a serious side effect of diabetes (Forbes and Cooper, 2013). Previous research found that MO can prevent the development and adverse effects of diabetic-induced damage to the kidney by way of its beneficial impact on oxidative damage and cytokines associated with inflammation in the kidneys of diabetic rats. *M. oleifera* has a high antioxidant amount and broad medicinal properties. Abilities (Fahey, 2005). Strong phytochemical components found in MO protect against inflammation, reactive oxygen species (ROS), and renal damage caused by diabetes. As a result, MO may help prevent diabetic complications, especially in developing nations like Africa where most people cannot afford orthodox medicine (Fahey, 2005). The decrease in insulin resistance, enhanced insulin secretion, and suppression of intestinal glucose were found to be the mechanisms underlying Moringa's ability to lower blood sugar (Muhammad et al., 2016).

Anti-anemic Effects

Anemia is characterized by a drop in the blood's erythrocyte mass or hemoglobin concentration, which lowers the blood's capacity to carry oxygen. Anemia affects both physical and mental health when hemoglobin levels in the blood fall under the normal range, which is below twelve g/dL for female and less than 13 g/dL for male(Dary et al., 2006). Moringa leaves have anti-anemic effects as a study was conducted on rats. After inducing hydrolysis, treatment of moringa's dried leaves powder was given and parameters to check anemia were then improved, including RBC count, MCV, Hb, HCV etc. The normal spleen showed typical white and red pulps with few megakaryocytes and little hemosiderin pigment deposition; the anemic group showed hyperplasia of megakaryocytes with significant hemosiderin deposition; the best results were observed in the groups treated with *Moringa oleifera* flower extract; the other treated groups indicated ranging degrees of improvement as indicated by a decrease in the number of megakaryocytes and accumulation of hemosiderin pigments. The effect of *M. oleifera* flower extract might be attributed to the presence of vitamins and iron content in them(MANJEGOWDA et al.).

Antibacterial Activity of Moringa

Moringa oleifera has been shown to have antibacterial activity against several bacteria, including *Bacillus subtilus, Escherichia coli, Staphylococcus aureus, Proteus vulgaris, Pseudomonas aeroginosa,* and *Streptococcus mutans* greatest action against *Streptococcus* mutant was demonstrated by the ethanol leaf extract, whereas greatest activity against *P.vulgarisas* was demonstrated by the aqueous extract(Patel et al., 2014). In another study, bacteria's ability to proliferate is inhibited by the plant leaves' aqueous, ethanol, and methanol extracts. Escherichia coli was substantially more susceptible to the inhibitory effects of water, ethanol, and methanol extracts compared to *Staphylococcus aureus* and *Pseudomonas aeruginosa*, respectively. Furthermore, at a greater dose of 120 mg/ml, the inhibitory impact of both ethanol and methanol extract was significantly larger. Thus, the gram-positive bacteria *Staphy aureus* and the gram negative bacteria *E. coli* and *Pseudomonas aeruginosa* that were examined were susceptible to the powder made from the leaves of the moringa plant(Singh and Tafida, 2014).

In another study, Methanol leaf extract inhibited *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* same as *P. aeruginosa* and it is more effective than water leaf extract(van den Berg and Kuipers, 2022).

Anti-inflammatory Activity

The Ethanol extract from boiling *M. oleifera* pods on the expression of inflammatory mediators released by the macrophage cell line stimulated by lipopolysaccharide (LPS). The extract from the pod demonstrates a strong anti-inflammatory effect by inhibiting LPS-induced NO generation, iNOS, COX-2 protein expression, and TNF-α and IL-6 secretion in a dose-dependent manner. Additionally, this food extract dramatically lowers levels of its mRNA cognates, which could have an impact on their transcription process or mRNA stability, according to the RT-PCR study. The findings also showed that by preventing the activation of all three MAPKs and reducing IκB-α phosphorylation, this dietary extract reduced the production of these proinflammatory mediators. As a result, the extract inhibited the production of pro-inflammatory genes, which are MAPKs and NF-κB's downstream targets, by acting on the upstream signaling pathway(Muangnoi et al., 2012). In LPS-stimulated murine macrophages, isothiocyanates derived from Moringa seed extract demonstrated anti-inflammatory efficacy by reducing NO generation and inflammatory gene expression as iNOS, cytokines such as IL-1 and IL-6. Moringa basically targets inflammatory cytokines such as IL-1, IL-6, etc. (Jaja-Chimedza et al., 2017)

Anti-cancer Activity

Many research studies showed that moringa has anticancer effects on human cancer cells. Glucosinolates may be able to decrease the development of carcinogenesis through some molecular targets as part of *M. oleifera's* chemoprevention strategy. It also involves anti-inflammatory, anti-tumor expansion of cells, induction of the death of cells, prevention of tumor angiogenesis, and inhibition of carcinogen activation and detoxification. Because glucosinolate is present in *M. oleifera* and has been shown in anticancer trials to trigger apoptosis, its chemopreventive benefits are expected.

Additionally, investigations using *M. oleifera* leaf extract to stop the expansion of human cancer cell lines have shown the plant's chemopreventive efficacy(Karim et al., 2016). In human malignant lung cells (A549), an aqueous extract of moringa leaves suppresses cancer proliferation and development by triggering apoptosis, DNA breakage, and increased oxidative stress. The level of p53 increased significantly(Tiloke et al., 2013). In another investigation, human peripheral blood mononuclear cells were exposed to an aqueous extract of moringa seeds, which had cytotoxic effects on them but had no influence on the hemolytic activity of erythrocytes (Araújo et al., 2013).

Hepatoprotective Effects

Eating a high-fat diet causes nonalcoholic fatty liver disease and can have several negative health effects. It has been documented that moringa leaf extract helps mice with liver damage in a high-fat diet. The liver homogenate was used to quantify liver histology, serum activity of hepatic enzyme markers such as reduced glutathione, ferric reducing antioxidant power, aspartate aminotransferase, and alanine aminotransferase, as well as lipid peroxidation. It's interesting to note that moringa also reduced the early symptoms of fatty liver brought on by HFD. Additionally, all Moringa-treated groups' livers showed a significant decrease in lipid peroxidation and a rise in endogenous antioxidant characteristics. The study's findings showed that moringa has hepatoprotective effects that are both preventative and curative(Das et al., 2012). The rats that were given antitubercular medications (isoniazid, rifampicin, and pyrazinamide) also demonstrated hepatoprotective action against liver damage caused by the ethanolic extract of Moringa leaves. This was achieved by preventing hepatic LPO and lowering serum levels of ALT, ALT, ALP, and bilirubin (Pari and Kumar, 2002).

Effect on Skin

Glutathione, the pigment melanin, and enzymatic antioxidants are examples of endogenous antioxidants found in skin (Weschawalit et al., 2017). The skin can become exposed to chemicals, air pollution, ultraviolet radiation, psychological stress, alcohol consumption, smoking, free radicals, and reactive oxygen species. However, to minimize oxidative stress and improve DNA repair, the overproduction of free radicals necessitates the topical use of exogenous antioxidants (Pham-Huy et al., 2008). Antioxidants lessen photodamage, which stops the production of skin pigment. Antioxidants have also been demonstrated to improve skin moisture, which helps to revive the skin. Unsaturated fatty acid-containing natural oils are frequently utilized as natural moisturizers and antioxidants to stop dry, aging skin (Montenegro et al., 2017).

The seed oil of *Moringa oleifera* is pale yellow and has a subtle nutty scent. Studies have indicated that *M. oleifera* seed oil has a protective impact on the skin. Because *M. oleifera* seed oil has a slight sun protection effect, it was recommended to preserve the natural skin pigmentation. There have been reports of *M. oleifera* seed oil's anti-fungal properties (Chuang et al., 2007). When compared to those utilizing the cream base, the skin moisture level of those applying moringa seed oil cream was much higher. By preventing dehydration and forming a hydrophobic barrier on the skin, moringa seed oil improves skin hydration. The presence of oleic acid in moringa seed oil caused the skin barrier to be disturbed, increased the oil's molecular interactions with lipids in the stratum corneum, and improved the oil's penetration effectiveness into the epidermis (Lin et al., 2017).

Role in Weight Loss

One of the main epidemic issues endangering people's health globally is obesity. An active endocrine organ, visceral adipose tissue secretes adipokines such as resistin, adiponectin, and leptin which are critical for metabolism, inflammation, endothelial function, insulin secretion and insulin sensitiveness, energy expenditure, and food intake. Insulin resistance and anomalies in the cardiovascular system resulted from this (Catalano et al., 2010). In a different study, compared to untreated obese control rats, *M. oleifera* extract increased the expression of the adiponectin gene and down-regulated the mRNA expression of resistin and leptin in obese rats. In comparison to the obese control group that did not get treatment, this improvement in gene expression was accompanied by a decrease in body weight, improvements in the atherogenic indices and coronary artery index, as well as improvements in glucose levels and insulin resistance values (Metwally et al., 2017).

Decrease Muscle Pain

It has been confirmed that consuming Moringa reduces joint, muscle, and stiff shoulder or neck discomfort effectively. Those with relatively high levels of oxidative stress showed substantial impacts based on the indicators of oxidative stress. Among female individuals with MSE intake, there was also a larger reduction in physical discomfort, decreased weariness, and improved quality of sleep. Consuming moringa has demonstrated promise in reducing fatigue-related physical discomfort, enhancing general quality of life, and enhancing sleep (Abe et al., 2023). Through improving energy consumption in adult skeletal muscle and upregulating the expression of important metabolic markers, such as those related to glycolysis, ATP synthesis, mitochondrial biogenesis, and angiogenesis, *M. oleifera* has the potential to be an ergogenic aid (Eze, 2020).

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Chapter 26

Benefits of Veterinary Phytotherapy in Animal Health and Welfare

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ABSTRACT

Worldwide, the use of medicinal plants has a long historical history. Currently, to the ancestral empirical knowledge about the healing properties of plants, we add those generated from scientific methodologies, which expand the understanding of the forms of use, the spectrum of action and the active substances present in different plants, such as foundation of Medicinal Herbalism or Phytotherapy. The basis of its application is in the metabolic compounds produced by plants; among others, phenols, flavonoids, phytosteroids, tannins and polyphenols represent active ingredients that give plants their therapeutic action. The options available in each region depend on the diversity of endemic and exotic plants available, and the variants in the active ingredients, determined by the geographical, climatic and soil conditions that influence the metabolism of the plants. Phytotherapy is not limited to livestock species; it also includes farm animals (fish and crustaceans) and companion animals. The benefits that veterinary phytotherapy brings to animal health and well-being are extended to the environment, by using medicines made from non-polluting natural materials.

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INTRODUCTION

Throughout history, the use of natural treatments based on medicinal plants appears as a common denominator in all times, regions and cultures. Ancestral empirical knowledge about the healing properties of plants increases with that generated under different scientific methodologies, as the foundation of current Medicinal Herbalism or Phytotherapy. Thus, from the administration of infusions, juices, plasters, poultices, among others, made with whole plants, we have moved on to the use of dosages of extracts obtained from specific parts of the plants, due to the knowledge about the active compounds they present and the benefits they provide for well-being and health (Altemimi et al., 2017; Martínez and Jiménez, 2017).

The botanical diversity existing on the planet offers countless therapeutic options, both for humans and animals. In humans, since the 90's, the World Health Organization (WHO) has identified medicinal plants as an invaluable treasure for health. They associate this assessment with the abundance and therapeutic active ingredients of plants, their low costs, accessibility, as well as the wide use estimated in about 80% of the world population (Akerele, 1993).

Although there is no explicit recognition by the World Organization for Animal Health (WHO), the truth is that for decades veterinary phytotherapy has been part of the alternative medicine used in animals, based on the forms of use and spectrum. of action of its active substances, with the purpose of preventing, controlling or curing diseases in favor of animal well-being (García, 2008).

Bioactive Compounds of Plants and Therapeutic Properties

Plant metabolism involves two different processes. Primary metabolism, which is responsible for generating the metabolites that are, involved in the growth, development and reproduction processes of plants. Secondary metabolism, on the other hand, produces metabolites that allow plants to develop defense mechanisms against environmental stress and their predators. Unlike the rest of living beings that only have primary metabolism; as an adaptation mechanism, plants develop a second metabolism in which they use a significant amount of the carbon they assimilate, in the production of metabolites for their defense: secondary metabolites (Ávalos and Pérez-Urria, 2009).

The basis of phytotherapy is the use of these metabolites, «natural products» or «bioactive compounds». Unlike veterinary homeopathy, which uses plant resources (in addition to those of animal and mineral origin), to activate the immune response of the sick animal; Veterinary Phytotherapy makes use of these compounds to directly combat infectious agents and parasites that cause diseases, organic disorders and other conditions in animals (García, 2008).

The type and amount of active compounds vary in their proportion and concentration, between a plant, between one portion and another (root, stem, bark, leaves, flowers, fruit) and even in the same species of plant that grows in different places. Climatic and geographical conditions and particularly the nutrient contents in the soil are determining factors in these differences. Likewise, the type of extractions carried out usually introduces variations in performance, regarding the amount of metabolites obtained and the effectiveness of the extract. (Degaïchia et al. 2022), carried out the extraction on leaves of two *Cupressus* species originating from Algeria (*C. siempervirens* and *C. arizonica*) using solvents of different polarities, chloroform (low), petroleum ether (intermediate) and aqueous methanol (high). They found that with the hydroalcoholic methanol solution, a greater number of secondary metabolites were extracted in both species (9/11), gallic tannins and saponosides were not extracted. In ether extraction, there were differences between species. For *C. arizonica* 2/11 (saponosides and triterpenes) and for *C. siempervirens* (4/11) in addition to those obtained in the other species, leucoanthocyanins (flavonoid) and steroids. While with chloroform 2/11 and 3/11, respectively. However, the yield of phenolic extracts was higher in chloroform extractions with 52,27% for *C. arizonica* and 61,23% for *C. siempervirens*. The yields for methanol were very close for both species (33,55 and 33,22%) and for ether; they turned out to be minimal, 1,29 and 0,39%, respectively. In the comparison of effects against *Pseudomonas aeruginosa*, they determined that methanolic extractions induced a strong sensitivity, while, with ether and chloroform extracts, the sensitivity was weak.

The number of bioactive compounds identified in different plant species is usually variable. Table 1, integrates some of these compounds identified in plants for veterinary use. The information shows that no two plants are similar in their bioactive compounds. Some, such as phenolic acid, whitanoids, phlobatanins and anthraquinones, occur exclusively in some plant species with different geographical origins (Eguale and Giday, 2009; Moya and Escudero, 2015; Nair et al., 2016; Mumed et al., 2022).

Table 1: Bioactive compounds present in plants for veterinary use

PLANT	Chlorogenic	Phenolicacid	Paracoumeric acid	Alkaloids	Anthraquinonones	Carbohydrates	Coumarin	Phytosteroids	Flavonoids	Phlobatannins	Glycosides	Lignins	Monoterpenes	Polyphenoles	Saponins	Tannins	Terpenoids	Triterpenes	Whitanoids	REFERENCE
Allium sativum (Garlic)									*						*					(Moya and Escudero, 2015)
Aloe vera (Sabil)												*			*					(Rojas et al., 2017)
Alocasia indica (Gianttaro)				*				*	*					*	*	*		*		(Islam et al., 2015)
Ananas sativus (Pineapple)				*		*		*	*					*	*	*		*		(Islam et al., 2015)
Artemisia absinthium (Wormwood)	*	*	*						*				*			*				(Moya and Escudero, 2015)
Chenopodium ambrosioides (Epazote)											*		*	*	*					(Ketzis et al., 2002; Eguale and Giday, 2009)
Croton macrostachyus (Croton)							*		*		*	*				*				(Mumed et al., 2022)
Curcuma longa (Turmeric)														*						(Mesa et al., 2000; Al-Khafaf et al., 2023)
Dennetia tripetala (Pepper fruit)				*		*			*		*			*	*					(Solomon et al., 2013)
Echeveria elegans (Alabaster rose)				*	*			*	*		*				*	*		*		(Nair et al., 2016)
Erythrina variegate (Coral tree)				*				*	*					*	*	*		*		(Islam et al., 2015)
Jatropha curcas (Tempate pine nut)														*						(Eguale and Giday, 2009)
Lawsonia inermis (Henna)								*	*		*			*					*	(Eguale and Giday, 2009)
Lippia graveolans (Oregan)	*		*						*								*			(Barahona, 2016)
Nicotiana tabacum (Tobacco)				*			*		*			*				*				(Mumed et al., 2022)
Silybum marianum (Marian thistle)									*											(Moya and Escudero, 2015)
Zingiber officinale (Ginger)				*				*	*	*					*	*	*			(Mumed et al., 2022)

Source: Own elaboration with case in the cited references.

The most common are flavonoids, saponins, polyphenols and tannins. Its form of action is different, such as tannins that participate in the capture of free radicals or saponins that reduce cholesterol levels. Despite this differentiation, both flavonoids, lignin and tannins are phenolic compounds, which prevent oxidative damage. For some plants, it has been possible to make a more specific characterization of these bioactive compounds, as well as their properties. Such is the case of curcumin (polyphenol) in turmeric or the flavonoids of oregano (apigenin and luteolin), garlic (apigenin and myricetin) or wormwood (artemisetin and artemetin). These compounds confer different therapeutic properties to plants (Solomon et al., 2013; Islam et al., 2015; Barahona, 2016; Rojas et al., 2017). Table 2 shows some therapeutic properties of plants, listing some of the associated species.

Table 2: Therapeutic properties of plants used in veterinary phytotherapy

Therapeutic property	Plants	Reference(s)
Anti-stress	*Ambrosia cumanensis*	(Villalobos, 2006)
Anthelmintic	*Allium sativum*, *Artemisia ansinthium*, *Aspidosperma quebracho-blanco*, *Azadirachta indica*, *Baccharis coridifolia*, *Chenopodium ambrosioides*, *Cydista aequinoctialis*, *Croton macrostachyus*, *Drimys winteri*, *Flaveria bidentis*, *Foeniculum vulgare*, *Heliotropium indicum*, *Juglans regia*, *Kalanchoe daigremontiana*, *Lupinus albus*, *Momordica charantia*, *Nicotiana tabacum*, *Otholobium glandulosum*, *Peumus boldus*, *Punica granatum*, *Ruta chalepensis*, *Tecoma stans*, *Thymus vulgaris*, *Vallesia glabra*, *Zanthoxylum coco*	(Avello et al., 2006; García, 2008; Mayer et al., 2014; Moya and Escudero, 2015; Espinosa-Moreno et al., 2016; Martínez and Jiménez, 2017; Rivero-Pérez et al., 2022)
Anti-inflamatory	*Aloe vera*, *Salpichroa origanifolia*, *Croton menthodorum*, *Curcuma longa*, *Echeveria elegans*, *Ficus racemosa*, *Manguifera indica*, *Opuntia fícus indica*, *Piper lenticellosum*	(Mandal et al., 2000; Boerisa and Toso, 2009; Souza et al., 2017; Soleimani et al., 2018)
Antihyperlipidemic	*Artemisia absinthium*,*Curcuma longa*	(Moya and Escudero, 2015; Soleimani et al., 2018)
Antimicrobial	*Anethum graveolens*, *Curcuma longa*, *Hibiscus sabdariffa*, *Kalanchoe daigremontiana*, *Lippia graveolens*, *Silybum marianum*, *Thymus vulgaris*	(Olaleye, 2007; García, 2008; Barahona, 2016; Soleimani et al., 2018; Ponsati and de Freitas, 2020; Rivero-Pérez et al., 2022)
Antioxidant	*Artemisia absinthium*, *Curcuma longa*, *Echeveria elegans*	(Castro et al., 2023)
Antipyretic	*Croton macrostachyus*, *Lawsonia inermis*	(Eguale and Giday, 2009; Mumed et al., 2022)
Antiseptic	*Eucaliptus cinerea*, *Pimpinella anisum*, *Rosmarinus officinalis*, *Thymus vulgaris*	(García, 2008)
Antiviral	*Artemisia absinthium*	(Moya and Escudero, 2015)
Healing	*Aloe vera*, *Daptura ferox*, *Mycenastrum corium*	(Martínez and Jiménez, 2017; Carrasco and Mariño, 2022)
Gastrointestinal disorders	*Achillea millefolium*, *Aloysia polystachya*, *anadenanthera colubrina*, *Artemisia absinthium*, *Cocos nucifera*, *Chamaemelum nobile*, *Lavandula angustifolia*, *Linum usitatissimum* (semillas), *Mentha spicata*, *Opuntia ficus-indica*, *Origanum vulgare*, *Sambucus nigra*, *Schinus fasciculatus*, *Sphaeralcea bonariensis*	(García, 2008; Mayer et al., 2014; Martínez and Jiménez, 2017)
Hepatoprotective	*Angelica sinensis*, *Artemisia absinthium*, *Astragalus membranaceus*, *Bidens odorata*, *Capparis spinosa*, *Cichorium intybus*, *Cuscuta chinensis*, *Cynara scolymus*, *Equisetum hyemale*, *Ginkgo biloba*, *Glycyrrhiza glabra*, *Linum usitatissimum Litsea coreana*, *Lycium barbarum*, *Peumus boldus*, *Phyllanthus amarus*, *Rosmarinus officinalis*, *Salvia miltiorrhiza*, *Sapindus mukorossi*, *Schisandra chinensis*, *Silybum marianum*, *Solanum nigrum*, *Tecoma stans*, *Vitex trifolia*, *Woodfordia fruticosa*	(García, 2008; Rosales et al., 2017; Alí et al., 2018; Ponsati and de Freitas, 2020)
Hypoglycemic	*Artemisia absinthium*, *Cicer arietinum*, *Citrullus colocynthis*, *Echeveria elegans*	(Afsheen et al., 2013; Moya and Escudero, 2015)
Hypotensive	*Echeveria elegans*	
Inmunoestimulant	*Aloe vera*, *Lupinus albus*	(Mayer et al., 2014; Souza et al., 2017)
Painkiller	*Aloe vera*, *Salpichroa origanifolia*	(Boerisa and Toso, 2009; Souza et al., 2017)
Nutraceutical	*Artemisia absinthium*	(Moya and Escudero, 2015)

Source: Own elaboration with case in the cited references.

Phytotherapy: Different Options for the Same Objective

Research carried out with plants to test their therapeutic effects tends to focus on diseases that cause significant effects on the health and well-being of animals. The approximations that are generated account not only for the effectiveness of the treatments, but also for the range of options used in each region, based on the native plants available. Taking as a reference to show these differences, Hemonchosis caused by *Haemonchus contortus*, the most important parasitosis in sheep worldwide, due to its wide distribution, prevalence and incidence. Considered the most pathogenic gastrointestinal nematode, since it usually affects all stages of the life of sheep, although the most susceptible are lambs and pregnant females. Its hematophagous habits and its location in the abomasum significantly affect the digestive processes and nutrient absorption. Consequently, animals develop anemia, weight loss, diarrhea, and in the most serious cases of infestation, it causes emaciation and sudden death, with consequent economic losses for producers (Hamad et al., 2013; Ojeda et al., 2022).

The impact of this parasitosis is associated with the great capacity for adaptation of *H. contortus* to different climates and multiple resistance to commercial anthelmintics such as Levamisole, Ivermectin, Closantel and Fenbendazole (Muchiut et al., 2013). In addition to this, the serious damage caused to the environment by waste disposal, the costs of treatments, their low availability and access in some regions, have encouraged the search for alternative treatments for this parasitosis (Mumed et al., 2022).

As part of the search for new alternatives, various investigations analyze the anthelmintic effectiveness of different plants against this nematode. In a study carried out in Addis Ababa, capital of Ethiopia, we sought to test *in vitro* the effectiveness of aqueous and hydroalcoholic extracts of henna leaves (*Lawsonia inermis*) and epazote (*Chenopodium ambrosioides*), as well as tempate pine nut seeds (*Jatropha curcas*), collected in their natural environment, against *H. contortus*. Seven concentrations of the extracts were used (0.03, 0.06, 0.125, 0.25, 0.5, 1 and 2 mg/mL). The greatest efficiency in inhibiting egg hatching was for *C. ambriosioides*, followed by *J. curcas*, for both types of extracts, although it was higher in the first, with 100% in concentrations 0.5-2 mg/ mL and *J. curcas* only for 2 mg/mL. For *L. inermis*, little significant efficacy is reported, the highest percentages of inhibition 25-30% were achieved at the highest doses. As for adults, only the aqueous extracts of *C. ambriosioides* reduced motility and increased mortality of larva 3 (L3) (Eguale and Giday, 2009).

In another study also with plants from Ethiopia, but in Haramaya, eastern area of Haraghe, Mumed et al. (2022), carried out an *in vitro* evaluation of the anthelmintic efficacy of crude methanolic extracts of leaves of two plants (*Croton macrostachyus* and *Nicotiana tabacum*) and the rhizome of *Zingiber officinale* against adults of *H. contortus*. For each extract, they used concentrations of 62.5, 125, 250 and 500 mg/mL, distilled water as a negative control and Albendazole as a positive control at a concentration of 1.25 mg/mL. At 2 hours post-treatment, in all cases, the highest mortality was associated with the highest concentration (500 mg/mL). With greater effectiveness for *N. tabacum* (9,33±0,667/10) and Albendazole with the same effectiveness as *Z. officiniale* (4,67/10). At 6 hours all concentrations with 100% mortality, except for *N. tabacum* with 8,33 (62.5 mg/mL) and *Z. officiniale* with 6.33% (dose 62.5 mg/mL), 9,00% (125 mg/mL); 8,33% (250 mg/mL) and 9,33% (500 mg/mL). Albendazole achieved a mortality of 6.00 (4 hrs), 8.00 (6 hrs) and 10.00 (8 hrs). A high nematicidal efficacy of the extracts was determined, except for *Z. officiniale*, comparable to the commercial anthelmintic, but without the risks entailed by its use.

On the other hand, in a study carried out in Mexico with plants of traditional use collected in Macuspana, Tabasco, Espinosa-Moreno et al. (2016), evaluated *in vitro* the anthelmintic activity against L3 larvae of *H. contortus*. They used aqueous extracts of *Cydista aequinoctialis* and *Heliotropium indicum* leaves and from leaves and fruit of *Momordica charantia* at a concentration of 20 mg/mL. As a negative control, distilled water and positive Fenbendazole (1 mg/mL). They recorded the mortality of L3 from the beginning of the confrontation (0), and at 24, 48 and 72 hours. At 24 hours, they obtained the highest percentage of mortality with the extracts of the fruit of *M. charantia*, (23%) and the lowest with the leaves of *C. aequinoctialis* (9.67%), with Fenbendazole with 99,1%. At 48 hours, the highest percentage was recorded in the *M. charantia* leaf extract (46,87%), followed by the fruit extract of this plant (43,37%), Fenbendazole with 100%. In the last measurement (72h) the highest percentage of mortality corresponded to the test with fruit extract (68,13%) followed by the leaf extracts of *M. charantia* (53.83%), *C. aequinoctialis* (39,57%) and *H. indicum* (19.75%).

Finally, Islam et al. (2015) carried out an *in vitro* evaluation of the anthelmintic effect of three plants from Bangladesh against adults of the trematode *Paramphistomum cervi* and the nematode *H. contortus*. They used aqueous extracts of *Ananas sativus* leaves, *Erythrina variegata* bark, and *Alocasia indica* rhizomes at concentrations of 25, 50 and 100 mg/mL, distilled water as a negative control and Albendazole as a positive control (15 mg/mL). They quantified the anthelmintic effect based on the times of paralysis and death of the adult parasites. In the different concentrations of the extracts used, the quantified times were shorter for *P. cervi* than for *H. contortus*, likewise, lower at the concentration of 100 mg/mL. For *P. cervi*, Albendazole had a paralysis time (minutes) of 14.62 and death time of 22.10, while for *H. contortus* of 26,56 and 37,24 min, respectively. From the results, it was determined that the *E. variegata* bark and *A. sativus* rhizome extracts had a significantly lower anthelmintic effect than the *A. sativus* leaves, which showed greater efficacy, especially with the hydroalcoholic extracts. Likewise, the effects are greater in *P. cervi* than in *H. contortus*.

The set of these studies and their results serve to highlight several aspects that are important in phytotherapy. In principle, the way to approach the generation of knowledge about the therapeutic applications of plants presents various approach options. Thus, although we seek to address the same objective, as in this case, the anthelmintic efficacy of different plant structures against *H. contortus*, the methodological approach is different. In the aforementioned studies, they used different local plants, as well as components (leaves, bark, rhizome or fruit). There are variations in the types of extraction, the concentrations used, the exposure times, as well as the phase of the life cycle affected (egg, larva or adult). These differences highlight other relevant aspects in phytotherapy, among others:

1. Distribution and availability: Plant diversity is variable in each region of the world. The ecological, geographical and climatic characteristics are determining factors in its distribution. Although many may be native, endemic, and therefore available only in some places, others can expand their distribution by being artificially introduced as exotic species, which also increases their availability (Galán et al., 2019).
2. Characteristics of plants: The bioclimatic distribution, time of year, as well as the environmental and soil characteristics in which plants grow, are determinants of the types and quantity of secondary metabolites that may be present in them. Variations in soil nutrients have a direct effect on the secondary metabolism of plants and, therefore, on the phytochemicals they produce (Ávalos and Pérez-Urria, 2009; Solomon et al., 2013).
3. Plant components: Plant components can serve different purposes, which depends on the secondary metabolites that are present in each portion. For example, in a phytochemical screening carried out on *Dennettia tripleta*, it was determined that flavonoids and saponins were present in the stem bark extracts, but were absent in the roots of this plant (Solomon et al., 2013).
4. Characteristics of the extractions and identification of active compounds: The protocols followed in the extractions determine the characteristics of the phytotherapeutics. The plant/solvent proportions, the types of solvents and the procedures to determine the presence of active compounds (secondary metabolites) are decisive for the confrontation of their effects. Between solvents, there are differences in extraction efficiency. Dimethylformamide and acetone are highly effective in the extraction of antioxidants. Ethanol extracts greater amounts of phenolic compounds than water, acetone and methanol. However, given the high polarity of methanol, it has greater precision in the extraction of different bioactive compounds. In general, the higher the polarity of the solvent, the better the precision of the extraction (Altemimi et al., 2017; Mumed et al., 2022).
5. Differentiated extraction: Depending on the solvents used for the extraction of bioactive compounds, the results are different. In the phytochemical analysis of *Dennettia tripleta*, using as solvents: water, 70% ethanol, acetone, methanol and hexane. Hexane extracted the sterols from the plant, while the Terpenoids, from the extracts with water and methanol. In the analysis of *Echeveria elegans* leaves, using benzene, acetone, hexane, chloroform and ethanol as solvents, it was only possible to extract anthraquinones with benzene, steroids with all solvents except benzene, while triterpenoids, only with hexane and chloroform. From this, success in determining the active components will depend on the type of solvents used and their presence in the selected part of the plant (Solomon et al., 2013; Kumar et al., 2016).
6. Concentration of doses and exposure time: All studies carried out *in vitro* show that the concentrations used of the extracts, as well as the exposure times, vary in their results. Furthermore, there are variations between the parasite species in question (Mumed et al., 2022).

Use of Phytotherapy in the Health and Well-being of Animals

Veterinary phytotherapy is an alternative for animal care, whether for prophylactic purposes, to treat diseases in their early stages, recurrent infections or chronic diseases. Likewise, it is used in feeding supplementation, to promote the growth and development of animals, as well as to increase the production and quality of milk, improve the quality of colostrum and the composition of milk, which means benefits for offspring and for human consumption (Davidović et al., 2012; Al-Khafaf et al., 2023).

In pets (dogs and cats) it is usually used with high frequency to control stress, improve blood circulation, treat dermatitis and wounds, promote good gastrointestinal, liver and kidney functioning, diabetes, hepatitis and mainly for the control of parasites such as ticks, fleas and *Toxocara* spp., among other conditions (Villalobos, 2006; Ponsati and de Freitas, 2020; de Almeida et al., 2023).

However, its use is usually broader in domestic species, particularly livestock. The great diversity of plants used for veterinary therapeutic purposes in the world is incalculable, since until now there is a lack of inventories in this regard. Some countries already have the identification of medicinal plants useful for Ecological and Organic livestock: 92 plant species in Spain, 31 in Panama (García, 2008) and 590 in Europe (Mayer et al., 2014).

Veterinary phytotherapy uses plants with therapeutic properties to treat different conditions of animals, with the purpose of restoring their health and contributing to their well-being. In general, they include care for respiratory and digestive conditions, hepatic colic, cystitis, skin infections, wounds; as well as its use as antibacterial, antidysenteric, antiamebiotic, fungicidal, spasmolytic, appetite stimulant, antifungal, diuretic, purgative, antihemorrhagic, healing, antidiarrheal, tranquilizer, among many others. Those most frequently used are dewormers, mainly for endoparasites of cattle and sheep (García, 2008).

In the latter, there is evidence that shows that depending on the plant and the type of preparation carried out, the results obtained are different. For example, in a study in goats in which the effectiveness of epazote (*Chenopodiumambrosioides)* on *H. contortus* was tested, they observed that the essential oil is highly effective in inhibiting the larval activity of these nematodes. In the form of extracts, aqueous extracts inhibit egg hatching and larval activity, while hydroalcoholic extracts act on the activity of adults (Ketzis et al., 2002).

Likewise, the dose administered may vary depending on the type of extraction used to prepare the preparation, the parasite in question and the severity of the parasitosis. In the case of *Allium sativum* (garlic), to inhibit the activity of gastrointestinal nematodes, doses of 100 mg/mL are required in aqueous extracts and in ethanolic extracts, the dose varies between 25-50 mg/mL. In the case of fennel (*Foeniculum vulgare*), different concentrations (25, 50, 100, 200 mg/mL) of aqueous and ethanolic extracts of fruits with high anthelmintic efficacy are used. However, for the total inhibition of infecting larvae (L3) of *H. contortus*, the concentrations have the same numerical scale (25, 50, 100, 200) but in microliters (µL) (Moya and Escudero, 2015). Table 3 integrates some diseases and the components of the plants used for their treatment, in different domestic species.

Table 3: Phytotherapy in domestic species

Species	Disease	Plant	Portion	Reference(S)
Dogs	Ectoparasites (fleas and ticks)	*Gloricidia sepium, Azadirahta indica*	Leaves	(Villalobos, 2006)
	Diabetes and hepatitis	*Silybum marianum*	Seeds	(Ponsati and de Freitas, 2020)
Rabbits	Hyperglycemia	*Cicer arietinum*, *Citrullus colocynthis*	Fruit	(Afsheen et al., 2013)
Poultry	Ectoparasites and scabies	*Anadenanthera colubrine*, *Larrea divaricata*, *Tecoma stans*	Leaves Cortex	(Villalobos, 2006; Martínez and Jiménez, 2017)
	Infectious coryza (distemper)	*Bixa orellana*, *Clematis montevidensis*	Leaves	(Villalobos, 2006)
	Newcastle	*Pedilanthus tithmaloides*	Stem	(Villalobos, 2006)
	Colibacillosis	*Lippia graveolens/Psidium guajaba*	Leaves / Fruit	(Barahona, 2016)
Pigs	Inflammation due to fracture, blows	*Manguifera indica*	Leaves	(Villalobos, 2006)
	Orchiectomy wound healing	*Daptura ferox*, *Mycenastrum corium*	Spores	(Martínez and Jiménez, 2017)
Sheep	Low milk production	*Curcuma longa*	Rhizome	(Jaguezeski et al., 2018)
	Hemonchosis	*Guazuma ulmifolia/Nicotiana tabacum*	Cortex/ Leaves	(Hamad et al., 2013)
	Wounds and injuries	*Anadenanthera colubrina*	Cortex	(Martínez and Jiménez, 2017)
Cows	Tick infestation	*Cymbopogon citratus*	Fruit	(Heimerdinger et al., 2006)
	Inflammation of the udder, bruises	*Manguifera indica*	Leaves	(Villalobos, 2006)
	Malnutrition	*Curcuma longa*	Rhizome	(Mesa et al., 2000)
	Retained placenta	*Cucurbita moschata/ Hylocerus undatus/ Jodina rhombifolia*	Seeds / Stem / Leaves	(Martínez and Jiménez, 2017)
	Tympany	*Guazuma ulmifolia*	Cortex	(Mesa et al., 2000)
	Spider bite	*Bursera simaruba*	Cortex	(Villalobos, 2006)
	Wounds and injuries	*Allium sativum*, *Agave americana*, *Anadenanthera colubrina*	Bulb	(Martínez and Jiménez, 2017)
Horses	Heat stress	*Ambrosia cumanensis*	Leaves	(Villalobos, 2006)
	Spider bite	*Crescentia alata*, *Enterolobium cyclocarpum*	Fruit	
	Muscle regeneration	*Aloe vera*	Pulp	(Rojas et al., 2017)

Source: Own elaboration based on the references that are registered

Conclusion

Within alternative medicine, veterinary phytotherapy offers the possibility of using local and accessible resources available based on the diversity of both endemic and exotic plants to apply treatments that have shown their effectiveness. More than a displacement of the use of drugs, the use of secondary metabolites obtained from plant extracts is presented as a more accessible and effective alternative to address animal diseases from their initial manifestations, as well as to propose new strategies for their prevention and complementary treatment. Advances in the identification of active compounds such as tannins, polyphenols, flavoniods and phytosterols, among others, as well as their therapeutic characteristics expand the possibilities of their application. This, in addition to contributing to animal health and well-being, has a positive impact on the development of sustainable and safe production, by not generating waste in livestock products, essential to meet the growing demand for protein of animal origin.

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Chapter 27

Phytochemicals as Promising Defense against Infectious Bursal Disease

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ABSTRACT

Infectious Bursal Disease (IBD), is a highly contagious disease caused by the infectious bursal disease virus (IBDV) that affects young chicks and causes large financial losses for the poultry industry. The illness suppresses the immune system and makes birds more vulnerable to secondary infections by attacking the bursa of Fabricius, an organ that is essential for the formation of B cells. The advent of new virus strains and vaccine failures present problems with the use of vaccination and other traditional control methods. Phytochemicals present a viable path for IBD management. Phytochemicals are naturally occurring bioactive substances that have a variety of biological roles in plants, such as immune-stimulating and antiviral qualities. Many phytochemicals have shown antiviral action against IBD in both in vitro and in vivo investigations, including curcumin, resveratrol, epigallocatechin gallate (EGCG), quercetin, and silymarin. These substances work by reducing oxidative stress and inflammation, inhibiting the growth of viruses, and altering immunological responses, among other methods. The incorporation of phytochemicals into disease management methods has the potential to improve the well-being and efficiency of chicken farms while decreasing dependence on artificial pesticides and antibiotics.

KEYWORDS Phytochemicals, Infectious bursal disease, Antiviral, Poultry, Immunity,	Received: 17-May-2024 Revised: 12-Jul-2024 Accepted: 12-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Gumboro disease, also known as Infectious bursal disease (IBD), is caused by a highly contagious virus infectious bursal disease virus (IBDV) that mainly affects young chicks, especially those between the ages of 3 and 6 weeks (Wagari, 2021). The bursa of Fabricius, an important organ in the immune system in handling B cell development, is the target of the IBDV, which causes the disease. IBDV is spread by water, contaminated feed, and microbes in addition to direct interaction with infected birds (Yuan et al., 2020) In addition, contaminated equipment, insects, and wild birds can transfer the virus, accelerating its spread among chicken flocks. IBD's rapid propagation and negative impacts on chick health and productivity make it a danger to the chicken farming industry. The virus strain (vvIBDV), the birds' age, and their immunological status all affect the clinical symptoms of IBD (Eladl et al., 2020). Dehydration, diarrhea, depression, ruffled feathers, and an inability to eat or drink are typical signs. Birds that are severely impacted may display immunosuppression, bursal atrophy, heightened vulnerability to subsequent infections, and higher mortality rates.

IBD pandemics have a significant financial impact on the chicken economy. Reduced egg production, slower development rates, higher treatment expenses, and bird death are all consequences of the condition. IBD outbreaks can also cause trade and export disruptions, which can cost chicken farmers and the larger agriculture industry financially (Yadav et al., 2020). For veterinary professionals and poultry farmers, containing and controlling IBD epidemics presents several difficulties. IBD outbreaks remain because of vaccine failures, and the introduction of novel virus strains. Viral antigenic diversity, incorrect storage, and mishandled administration can all reduce the effectiveness of vaccinations. Novel techniques, such as the consumption of phytochemicals and other natural substances, are being investigated as possible additions to or substitutes for traditional techniques (Jha and Sit, 2022). Preserving the health and viability of poultry farms requires a thorough understanding of how IBD affects poultry farming and the investigation of innovative solutions. Phytochemicals are naturally occurring bioactive molecules found in plants that have a variety of positive effects on human health but are not necessary for the growth or development of the plant. Plants produce these substances as a component of their defensive mechanisms against infections, UV rays, and herbivores, among other environmental stresses. Phytochemicals provide foods made from plants with their distinctive tastes, colors, and fragrances (Onuh and Pathak, 2024). They are frequently found in grains, fruits, legumes, vegetables, nuts, and seeds. A wide range of chemical groups, each with distinct characteristics and biological functions, make up phytochemicals. Among the most well-known categories of phytochemicals are the following: Flavonoids are comprised of isoflavones, anthocyanins, flavonols, flavones, flavanones, and flavan-3-ols (catechins) (Ullah et al., 2020). Phenolic Acids are comprised of ferulic acid, ellagic acid, and caffeic acid among others (Valanciene et al., 2020). Beta-carotene, lutein zeaxanthin, and lycopene are examples of carotenoids (Huang et al., 2021). Alkaloids are comprised of morphine, nicotine, and caffeine (Manna et al., 2020). Terpenoids are comprised of diterpenes, triterpenes, monoterpenes, and sesquiterpenes. Sulfides and Thiols are comprised of Garlic and onions contain allyl sulfides. Polyphenols are comprised of lignans and stilbenes (like resveratrol) (Hazafa et al., 2022). Various biological actions are displayed by these substances, such as immunomodulatory, antiviral, antibacterial, antioxidant, and anti-inflammatory properties (Sobhani et al., 2021). Research has been done on the antimicrobial qualities of phytochemicals, and many of the substances have been shown to have inhibitory effects on fungi, viruses, bacteria, and parasites. These substances can target invasion, adhesion, and replication of the production of virulence factors, among other stages of the microbial life cycle. Phytochemicals can modulate immunity, which can strengthen the host's defenses against infectious pathogens (Behl et al., 2021). Phytochemicals can strengthen the body's resistance against invasive pathogens by inducing both adaptive and innate immune processes. This can lower the risk of infection and assist in the healing process. This chapter will examine the potential of phytochemicals in the fight against infectious diseases, emphasizing their modes of action, effectiveness against certain pathogens, and uses in the prevention and management of disease.

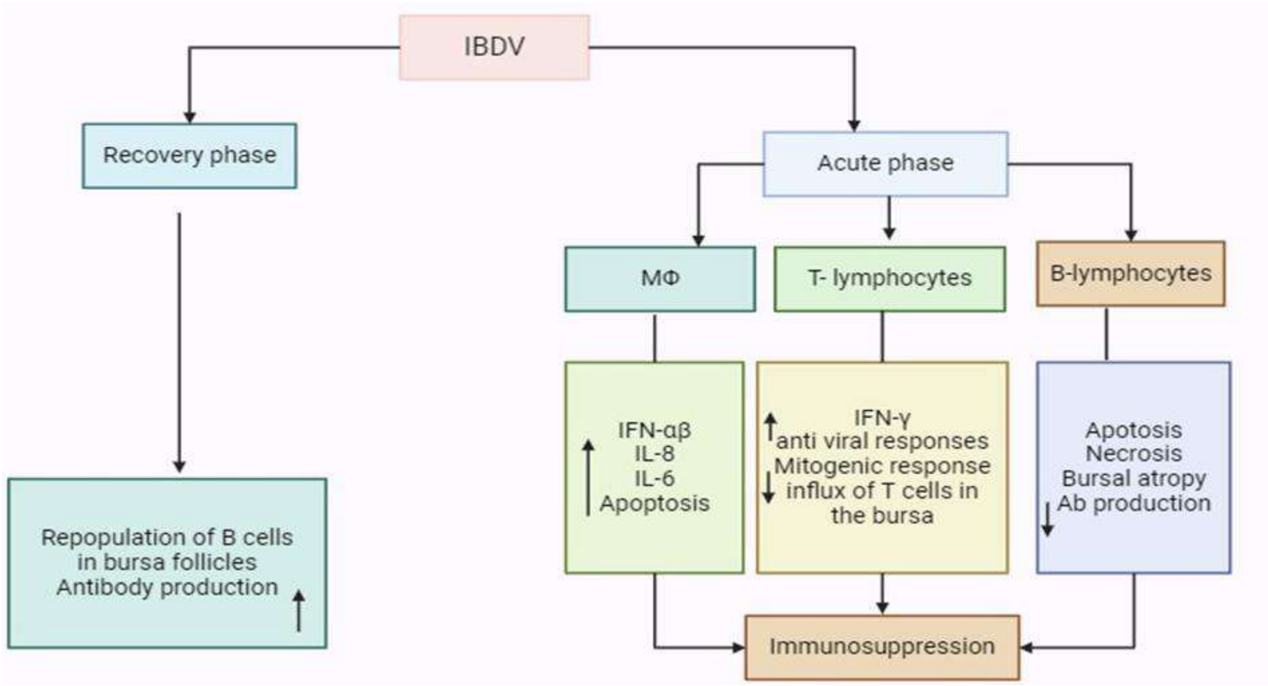

Fig. 1: Immunosuppressive and pathogenic aspects of IBDV (Retrieved from Biorender).

Phytochemicals with Potential Anti-IBD Activity

A variety of phytochemicals have been thoroughly investigated for their possible ability to improve immunity and prevent viruses.

Quercetin

A flavonoid called quercetin can be found in a variety of grains, fruits, and vegetables (Batiha et al., 2020). It shows strong antiviral properties against a variety of viruses, including coronaviruses and influenza, which are respiratory viruses. Quercetin works by preventing the growth of viruses, altering the signaling pathways of host cells, and boosting immune responses by encouraging the synthesis of chemokines and cytokines (Shorobi et al., 2023).

Over the past 20 years, flavonoids and their potential chemo-preventive bioactivities have gained a lot of attention, especially because of their antiviral properties in viral infectious illnesses (Sharma et al., 2021). Flavonoids are now being researched against a range of viruses with DNA and RNA. They show a range of physiological effects in humans, such as antibacterial, antioxidant, antiviral, cytotoxic, anti-inflammatory, and anti-allergic properties (Al-Kahtani et al., 2022). Flavonoids are substances that strengthen the humoral immune system of broilers by promoting the synthesis of IgM and IgG antibodies. By stimulating macrophages, flavonoids promote the manufacture of cytokines, including interferon. They inhibit infectious IBDV in broilers especially well by reducing bursal lesions and viral protein expression. These characteristics of flavonoids have led numerous researchers to propose their potential application in the management of IBDV (Shehata et al., 2022).

Epigallocatechin Gallate (EGCG)

A catechin called EGCG can be found in green tea along with various types of tea. It has antiviral qualities against many viruses, such as the herpes simplex virus (HSV), HIV, and influenza. By inducing immune cell activation and boosting cytokine production, EGCG suppresses viral attachment and penetration into host cells, interferes with viral replication, and boosts immunological responses (Zhao et al., 2021). Research shows that EGCG has the ability to prevent the IBDV from replicating in vitro. By inhibiting the virus's capacity to enter and multiply within host cells, it lowers the viral load and stops the infection from spreading infections (Yasmin et al., 2020).

Curcumin

Turmeric, a spice that is frequently used in Asian cooking, is the source of the polyphenol curcumin. It shows antiviral action against several viruses, such as HIV, hepatitis viruses, and influenza. Curcumin has immunomodulatory effects by controlling the production of cytokines and the activity of immune cells. It also inhibits the replication of viruses and modifies host cell signaling pathways associated with viral infection (Makuch et al., 2021). Curcumin's anti-inflammatory properties help in lowering inflammation caused by IBDV. It also possesses antioxidant qualities which help in reducing oxidative stress and absorbing free radicals, both of which may increase viral damage (Hartady et al., 2021).

Resveratrol

A stilbenoid called resveratrol can be found in berries, red wine, and grapes. It has antiviral qualities against a range of viruses, such as herpesviruses and respiratory viruses. By interfering with the production of viral proteins and modifying the host cell's response to viral infection, resveratrol prevents the spread of viruses. Resveratrol also has immunomodulatory effects by lowering inflammation and improving immune cell function (Alesci et al., 2022). The anti-inflammatory properties of resveratrol help in reducing inflammation caused by IBDV. Because of its antioxidant properties, host cells are protected from viral pathogen-induced damage and oxidative stress (Shehata et al., 2022).

Silymarin

A flavonolignan called silymarin is extracted from milk thistle seed. It shows antiviral action against influenza, HIV, and hepatitis viruses. By preventing viral entry into host cells, interacting with the development of viral proteins, and boosting host immune responses to viral infection, silymarin prevents the spread of viruses (Palit et al., 2021). There have been few research specifically examining silymarin's benefits against IBDV, its broad-spectrum antiviral characteristics and immunomodulatory actions point to possible uses in chicken farming to reduce IBDV infection.

Mechanism of Action

Many modes of action displayed by phytochemicals may contribute to their potential effectiveness in treating IBD. Some phytochemicals prevent viruses from replicating by focusing on important proteins and viral enzymes involved in the virus life cycle. Flavonoids such as EGCG and quercetin reduce the activity of the viral RNA polymerase, which in effect suppresses the reproduction of the IBDV virus (Wu et al., 2023). Phytochemicals can stop viruses from attaching to surfaces and entering host cells by inhibiting viral binding sites or interacting with viral entry pathways by inhibiting viral binding sites or interacting with viral entry pathways. Curcumin has been shown to prevent IBDV from attaching itself to cell surface receptors, preventing the virus from entering host cells. Phytochemicals may induce innate immune responses by stimulating immune cells including dendritic, natural killer (NK), and macrophage cells (Gasmi et al., 2023). These immune cells are essential for recognizing and getting rid of viral infections. Certain compounds, such as resveratrol and curcumin, increase the cytotoxic activity of NK cells and both the phagocytic function of macrophages targeting infected cells. Phytochemicals can modify the synthesis of pro- and anti-inflammatory cytokines to control immunological responses to viral infection (Baranwal et al., 2021). Quercetin inhibits the synthesis of pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) but stimulates the synthesis of anti-inflammatory cytokines like interleukin-10 (IL-10). Some phytochemicals influence T helper cell (Th) actions, facilitating a balanced Th1/Th2 immunological response (Gandhi et al., 2020). Sufficient Th1/Th2 balance is necessary for antiviral immunity to be effective. EGCG causes a Th1/Th2 imbalance to be shifted in favor of a Th1-dominated action, which may strengthen the immune system against IBDV. Viral infection-induced oxidative stress can be reduced by phytochemicals having antioxidant qualities. These substances defend host cells from oxidative damage brought on by viral replication by absorbing reactive oxygen species (ROS) and preventing lipid peroxidation. Quercetin and EGCG are flavonoids with strong antioxidant activity that may help reduce oxidative stress brought on by IBDV infection (Hartady et al., 2021). By lowering excessive inflammatory responses brought on by a viral infection, phytochemicals may reduce tissue damage and diseases linked to inflammation. Curcumin and resveratrol are examples of compounds that have anti-inflammatory properties because they prevent the synthesis of mediators that promote inflammation, such as leukotrienes and prostaglandins. Phytochemicals possess the ability to fight against IBDV infection and reduce its harmful consequences by focusing on multiple stages of the viral life cycle and adjusting the immunological responses of the host (Faisal et al., 2023).

Efficacy of Phytochemicals against IBD

Several research have been carried out both in vitro and in vivo to assess the phytochemicals' effectiveness against the IBDV. Several phytochemicals have been shown to have antiviral action against IBDV in vitro investigations utilizing cell culture models (Jumaa et al., 2021). Usually, these investigations involve the infection of vulnerable cell lines (such as DF-1 cells or chicken embryo fibroblasts) with IBDV and the evaluation of cytopathic effects and viral replication in the light of phytochemical treatments (Rekha et al., 2014). To assess the inhibitory impact of phytochemicals on IBDV replication, antiviral techniques like quantitative PCR tests, virus yield reduction assays, and plaque reduction assays are frequently employed. Viral RNA levels, viral titer, viral protein expression, and infected cells injected with phytochemicals are only a few of the characteristics that these investigations examine. Phytochemicals like curcumin, quercetin, EGCG, and resveratrol have been shown in vitro to reduce IBDV proliferation and lower viral infectivity in cell culture models (Mehrotra, 2020).

Studies on animals, specifically chickens, have been carried out in vivo to assess the effectiveness of phytochemicals in combating IBDV infection. These trials usually entail giving oral, intramuscular, or dietary phytochemical therapies to chickens that have been infected with IBDV. Several clinical criteria are evaluated by in vivo efficacy trials, such as death rates, bursal weight-to-body weight ratios, histological alterations in the bursa of Fabricius, bursal lesion evaluations, and serum antibody titers (Ray et al., 2021). These metrics shed light on how phytochemicals affect host immune responses and IBDV development. In vivo, research might investigate the immunomodulatory influence of phytochemicals on the human immune system in addition to their antiviral action. These studies evaluate the reaction of immune cell populations, lymphocyte proliferation, and cytokine production to phytochemical treatments. Phytochemical therapies can lessen bursal lesions, boost immunological responses, and lessen IBDV-induced mortality in infected hens, according to in vivo investigations (Guo et al., 2022). Inhibiting viral attachment, entrance, protein synthesis, and replication as well as modifying host immunological responses to viral infection are some of the ways phytochemicals can carry out their antiviral actions. Overall, the results of research conducted in vivo and in vitro provide validity to the possible use of phytochemicals as all-natural remedies for the management and prevention of IBD.

Challenges and Limitations

Although phytochemicals appear to have potential as therapies or preventatives for IBD, several limitations and restrictions must be considered. A large number of phytochemicals are poorly absorbed and used by the body due to their low bioavailability (Shahidi and Pan, 2022). The efficiency of phytochemicals in vivo can be decreased by factors that impact their bioavailability, such as limited tissue distribution, fast metabolism, and low solubility. It can be difficult to determine the best phytochemical dosage and delivery system (Ahmad et al., 2021). Dosing regimens can become complex due to factors including individual variability in absorption rates, variations in the phytochemical content of plant sources, and the requirement for sustained release formulations. Although different phytochemical combinations can have synergistic benefits, it can be difficult to determine the best ratios and combinations of different components. The particular phytochemicals involved, their quantities, the target pathogen, and the host immune response can all affect synergistic interactions. Chronic use of phytochemical therapies carries a danger of developing virus resistance. The effectiveness of treatment may be diminished if viruses become resistant to the antiviral effects of phytochemicals due to changes that they have developed in response to their presence. Phytochemicals can interact or cause negative effects with other drugs or food ingredients (Pham et al., 2020). To assess the safety properties of phytochemicals at dosages for therapy and identify any possible side effects, toxicity studies are required. Obtaining regulatory approval to use phytochemicals as therapies or preventatives for IBD might be difficult. Phytochemicals are frequently categorized as herbal treatments or dietary supplements, which may need different regulation processes than traditional pharmaceutical pharmaceuticals. Accessibility to phytochemical-based goods may be restricted by the cost of obtaining and manufacturing them, especially in environments with limited resources (Díaz-Puertas et al., 2023). Furthermore, there may be differences in the accessibility of standardized phytochemical formulations that are consistently high-quality and effective. The absence of defined techniques for phytochemical characterization, extraction, and quality control can lead to variations in the efficacy and content of products derived from phytochemicals (Fonmboh et al., 2020). To assess the safety, effectiveness, and best usage of phytochemicals for the prevention and treatment of IBD, extensive preclinical and clinical research are required.

Future Perspective

The development of standardized phytochemical formulations with constant quality, potency, and purity should be the main goal of future studies. Standardization guarantees the consistency and dependability of goods derived from phytochemicals, allowing for easier comparisons between research and enhancing the safety and effectiveness profiles of these products (Gupta et al., 2021).

Systematic dose-response studies are required to determine the best phytochemical dosage schedules. This involves assuming out the lowest effective dose needed to maintain antiviral effectiveness while reducing toxicity or unfavorable effects. To help with dosage optimization, pharmacokinetic studies can shed light on the distribution, metabolism, excretion, and absorption of phytochemicals. It is essential to research the synergistic effects of mixing various plants or phytochemicals with traditional antiviral medicines. Combination medicines have the potential to overcome viral resistance, improve antiviral activity, and lower the risk of side effects related to high dosages of individual drugs (Shyr et al., 2021). Assays for synergy screening and in vivo, research can assist in identifying combinations that show promise for additional assessment. It is necessary to further clarify how phytochemicals work against IBDV. Mechanistic research can shed light on the molecular targets and pathways that explain the immunomodulatory and antiviral properties of phytochemicals, which can help develop more specialized treatments and practical approaches to drug manufacturing. Testing the results from preclinical investigations and field trials requires clinical studies in populations of chickens (Van de Wall et al., 2023). These investigations can evaluate how well phytochemicals work to stop IBD outbreaks, lessen viral shedding, and enhance clinical results in birds with the disease. Studies of long-term surveillance can also assess the long-term viability of phytochemical-based therapies and the possibility of the development of viral resistance. To assess the financial viability of using phytochemical-based therapies in chicken farming techniques, a cost-effectiveness analysis ought to be carried out (Manickam et al., 2021). This involves estimating the expenses related to the manufacture, formulation, and distribution of phytochemicals as well as the possible financial benefits from lower rates of illness, death, and antibiotic use. It is necessary to establish or modify regulatory frameworks for the licensing and registration of medicines based on phytochemicals for use in veterinary medicine. In addition to addressing regulatory issues with product classification, registration procedures, and global harmonization, this entails developing guidelines for quality control, labeling, product safety, and marketing authorization. The possible role of phytochemicals as useful instruments for IBD treatment and prevention can be realized by solving these research priorities, which will enhance the welfare and health of chickens as well as promote sustainable agricultural methods.

Conclusion

In conclusion, investigation into phytochemicals as all-natural treatments for IBD offers a bright future for the chicken industry. Phytochemicals have been shown to have immunomodulatory and antiviral properties, making them an effective means for managing illness. The potential advantages of phytochemicals as affordable and environmentally friendly substitutes for antibiotics exceed these drawbacks. Phytochemical-based therapies can change disease control procedures in the chicken sector by enhancing animal welfare and decreasing dependency on synthetic pesticides. However, more research and cooperation are required to solve issues like bioavailability, dosage optimization, and regulatory approval. There is potential for improving the productivity, sustainability, and health of chicken production systems through the incorporation of phytochemicals into controlling disease measurements.

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Chapter 28

Homeopathy in Health and Nutrition Management: A Comprehensive Approach

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ABSTRACT

Homeopathy is a holistic form of complementary and alternative medicine that relies on treating a whole body rather than dealing with just physical symptoms. The basic work principle of this approach is that a person's mental and emotional status are linked, so physical symptoms cannot be treated alone without them in view. A German doctor Samuel Christian Hahnemann is considered the father of homeopathy. He proposed that homeopathy is based on two principles 'like cure like' and 'law of potentization'. He wrote an extensive book 'Materia Medica Pura' on homeopathic remedies. In his book, he mentioned all the observations and key findings, so that it is considered a key book for any homeopath. The remedies are mostly extracted from plants, animals, and minerals sources. Once they are extracted and purified, they are potentized before usage. Homeopathy plays an extensive role in health management and nutrition management. Its holistic approach and minimal side effects make it more suitable for disease treatment. This chapter covers the history, types, and sources of homeopathic remedies and some important remedies used for health and nutrition management.

KEYWORDS		
Homeopathy, Complementary medicine, Health, Nutrition, Allopathy	Received: 10-May-2024 Revised: 12-Jul-2024 Accepted: 18-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Homeopathy was established by the German physician Samuel Christian Friedrich Hahnemann (1755-1843) in 1796. It is a combination of the Greek words 'homoios' meaning same/similar, and 'pathos' meaning suffering. It is predicated on two absurd theories: One is based on "Latin: "similia similibus curentur" or "Like cures like" which refers to the theory that a drug that causes identical symptoms in healthy individuals can also treat a sickness. Second: The "law of minimum dose" states that a medication's effectiveness increases with a decreasing dose. A lot of homeopathic remedies are diluted to where the original substance's molecules are gone (Hahnemann, 2003).

The word 'homeopathy' was not used by Hahnemann until 1807. He employed the word "homeopathic," and the term "homeopathy" in the first edition of his most famous work, "The Organon of Medicine", which was released in 1810. Eventually, The Organon was published in six versions, the latest of which was released in 1921, over eighty years after his death. This book is the foundation of homeopathic principles and practices and it is used by homeopathy practitioners and students (Hahnemann, 1992).

Fortunately, Edward Jenner in 1796, administered the first smallpox vaccination. This incidence aligned with the era of 'Heroic Medicine', which endorsed treatments like bleeding and purging in high doses, sometimes leading to patient death. The notion of Heroic Medicine traces back to John Brown's (1735-1788) work and earned support from influential figures such as Benjamin Rush (1745-1813), a participant of the American Declaration of Independence. The shift away from Heroic Medicine could have influenced homeopaths to encompass the use of diluted doses (Fisher, 2012).

Hahnemann's Contribution for Homeopathy

Early in his career, Hahnemann became so dissatisfied with the practice of medicine that he stopped it, instead earning his living as a translator. It was while translating, in 1790 'A Treatise of Materia Medica', by Brown's mentor, William Cullen, that he made his first, crucial observation. In a footnote, he recorded his disagreement with the claim that Peruvian bark's (the bark of *Cinchona officinalis*, also known as China bark) effectiveness in treating malaria stemmed from its bitterness (now known to contain quinine), a concept Hahnemann found illogical because of his knowledge of other bitter substances with no impact on malaria (Lockie et al., 2006). Regardless of this, he decided to personally ingest Peruvian bark instead of merely explaining Cullen's text. To his surprise, he experienced fever alternating with chills, mirroring the symptoms it alleviated in malarial patients. Rather than dismissing this as a coincidence, Hahnemann pondered whether the bark's curative properties were linked to its similarity to the disease (Bailey, 2002; Lockie et al., 2006).

Driven by a rigorous scientific approach, he embarked on a series of experiments to validate his hypothesis. Administering various test substances (primarily plant extracts or basic minerals) to himself, his family, and friends, he meticulously documented all observed symptoms, both physical and mental. Symptoms reported by three or more subjects after a specific substance intake were included in the substance's "symptom picture." This method enabled him to compile detailed symptom profiles for numerous plant and mineral substances. When encountering a patient exhibiting symptoms corresponding to these profiles, he administered the relevant substance, often resulting in improvement. Through this process, Hahnemann not only affirmed the principles of homeopathy but also established a systematic understanding of the medicinal properties of numerous basic substances, some of which were already utilized therapeutically, while others were not recognized. Hahnemann's pioneering approach over two centuries ago, which emphasized the inclusion of psychological symptoms alongside physical ones in his provings, demonstrated his insightful recognition of the significance of psychological manifestations. Eventually, he accorded even greater importance to psychological symptoms than physical ones in determining the most suitable remedy for each individual. This was the empirical 'Newton's Apple' of homeopathy (Bailey, 2002; Fisher, 2012).

Hahnemann described 'homeopathy' and 'allopathy' as the two main modalities of medical treatment. Hahnemann described two main methods of treating medical conditions: homeopathy and allopathy, sometimes known as the enantiopathic technique (from the Latin "contraria contrariis," which means "opposites oppose"). It was Hahnemann who first used the words allopathy and homeopathy. Sometimes, though incorrectly, the latter phrase is used to refer to all forms of traditional medicine (Fisher, 2012).

In his work "Essay on a new curative principle for ascertaining the curative power of drugs with a few glances at those hitherto employed," he elucidates three fundamental strategies for treating ailments. The first, aiming 'to eliminate or eradicate the root cause, is deemed 'the most superior'. The second approach, involving 'the alleviation of symptoms through medications inducing an opposing state', was strongly opposed by him, urging his peers to refrain from this method (contraria contrariis) in chronic illnesses. Consequently, he concluded that 'the only option left is to test the medicines we intend to study on the human body itself'.

References to both these treatment modalities can be traced back to the Hippocratic corpus, as illustrated by the following: 'Illnesses are healed by opposites; for every illness, there exists a suitable remedy; thus, for a naturally warm ailment affected by cold, there exists a warming agent, and so forth. Another approach is through the administration of similar substances; a disease originates through similar means, and health is regained by administering similar substances; for instance, a substance causing strangury not present before, when introduced, will alleviate it. Similarly, coughing, like strangury, arises and is alleviated by the same substances. Homeopathic principles were also predicted by Theophrastus von Hohenheim (1493–1541), a physician from Switzerland, who said that "all substances are toxic, none are devoid of toxicity, it is the dosage that distinguishes a poison from a remedy."(Fisher, 2012).

Hahnemann wrote his first book, Materia Media Pura, in 1811. He published a total of six volumes. His book is considered a basic book for any homeopathic practitioner. In his book, he has given details about diseases with their symptoms, along with their prescribed remedies and observations.

Concept of Low Dose or Potentization

Homeopathic preparations undergo dilution processes that result in a significant reduction of the initial ingredient, leading to minimal presence of the original substance. The medical community frequently expresses skepticism due to this circumstance. But if we think of the medication as expressing a frequency of energy in the solution, it makes more sense that this energy can persist even after the base molecules are gone. Just as irradiating water with gamma rays imparts new energy without adding new molecules. The diluted homeopathic remedy carries the medicinal energy derived from the molecules it no longer contains.

The process of potentization, discovered by Hahnemann, involved diluting medicines initially due to their toxicity. He was astounded to see that the drug concentrations had increased in potency while maintaining their efficiency. As to Hahnemann, the patient's physical and mental health may be more significantly impacted by the subtler life force of the diluted drug. Multiple dilutions combined with vigorous shaking may boost the therapeutic efficacy of some treatments. Stronger cures, such as 10c (1:100 dilution) potency that required ten dilutions (1 in 100) and a minute-long shaking in between, might be achieved with this procedure (Loudon, 2006).

Sources of Homeopathic Medicines

There are three main sources of homeopathic medicines: plants, animals, and minerals. Plant sources are made up of various plant components that are utilized to make homeopathic mother tinctures, which serve as a stock solution for potencies. Herbs, flowers, stalks, leaves, bark, weeds, roots, seeds, and occasionally the entire plant may be included. Animal parts or their fluids are the origins of various medications found in animal sources. These consist of various insects, flies, lizards, crabs, toads, snakes, and worms. The majority of components and compounds used in the manufacture of medicines come from mineral sources, including salts, metals, nonmetals, alkalis, and acids (Rehman & Ahmad, 2017).

Sarcodes, Nosodes, and Imponderabilia are the other three sources of homeopathic remedies. Sarcodes encompass the typical products and secretions of the endocrine glands as a whole. Additionally, they are made using animal products. Examples include the pituitary (the posterior part of the pituitary gland in sheep), pancreatinum (the pancreas of beef), insulin (pancreatic hormones), and pepsinum (the digestive enzyme pepsin) (Tenka, 2021).

Nosodes are produced by bacteria or viruses that cause disease, or they might be caused by sick human, animal, or plant tissue. Toxins that are inside cells are eliminated from the body via a nosode. Since they are not antibiotics, they have no bacteriostatic or bactericidal properties. Medicorrhinum (from gonorrhea virus), carcinosin (from carcinogenic tissues), Baccilinum (from tuberculous sputum), pyrogenium (infected pus), and psorinum (psoric viral preparation) are a few examples of these (Rehman and Ahmad, 2017; Preena Jane et al., 2023).

Imponderabilia are medicines derived from energy, either synthetic or natural. "Even many imponderable (immaterial) substances can produce the most violent medicinal effects on human beings," according to Hahnemann. (Aphorisms 280 in Organon). The following medications are sourced from this source: radium, magnetis artificialis, electricitus, X-ray, sol (sun rays), magnetis poli ambo (magnet), magnetis polus Australia (South Pole of the magnet), and magnetis polus Arcticus (North Pole of the magnet) (Somaru, 2008).

Homeopathy in Health Management

Global health systems are currently experiencing an increase in chronic diseases and escalating healthcare costs. To highlight this issue, healthcare services should be strengthened, emphasizing personalized and patient-centered care, as encouraged by patients and healthcare professionals. Homoeopathy has a rich history of being utilized in the management of chronic ailments, as well as in the prevention and treatment of diseases (Tripathy et al., 2023).

Homeopathy stands out as the most commonly utilized form of complementary and alternative medicine (TCAM). The practice of homeopathy has gained official recognition in various regions, including Central and South America (Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, Mexico); Asia (India, Pakistan, Sri Lanka); and Europe (Belgium, Bulgaria, Hungary, Lithuania, Portugal, Romania, Russia, United Kingdom), where governments have acknowledged it as a distinct medical system or specialty. Several of these countries have integrated homeopathy into their national healthcare systems, such as the UK, India, Pakistan, Sri Lanka, and Brazil. In countries like India, Sri Lanka, and Pakistan, homeopathy holds the same legal status as traditional Western (allopathic) medicine; numerous practitioners are dually certified in both homeopathy and allopathic medicine, serving as primary care physicians for many patients (Manchanda, 2016).

Various factors, including cultural norms, historical importance, and legal frameworks, influence the adoption of Traditional, Complementary, and Alternative Medicine (TCAM) at both domestic and international levels. Many nations have policies mandating the integration of specific traditional healing practices into their healthcare systems, typically limited to the indigenous medical traditions of that particular country. In these nations, it is imperative that homeopathy be classified under the TCAM. The World Health Organization (WHO) is in favor of strengthening primary health care (PHC) services and integrating all TCAM modalities into national healthcare systems (Bodeker & Ong, 2005).

Disease Management by Homeopathic Remedies

Several homeopathic remedies are used for the treatment of various chronic and acute diseases. As discussed previously, they can be from minerals, plants, and animal sources. Some of the commonly used remedies are discussed below. The data is extracted from the book (Lockie et al., 2006)

a) Sulfur

Sulfur is a mineral-originated remedy. It is produced by volcanic activity and this volcanic rock can be found around hot springs and craters in the Italian peninsula, Sicily, and the US, and. Sulfur is recommended to cure a comprehensive range of illnesses than any other remedy in the homeopathic repertory. Homeopathy uses sulfur to treat acute fevers, inflammations, skin problems, and respiratory concerns. It is recommended for symptoms such as burning sensations, skin irritations, persistent coughs, digestive disorders, vomiting, diarrhea, and urinary problems.

- Key uses: Skin conditions, respiratory illnesses, men and women health, and digestive disorders (Lockie et al., 2006).

b) Nux Vomica

It is sourced from the poison-nut tree *Strychnos nux-vomica* . Strychnine is a toxic alkaloid that is rich in its seeds and was well known as a poison before the 17th century. The health practitioners of earlier times discovered its stimulating effect on the digestive and nervous systems. Small doses can stimulate the appetite, diuretic, and aid digestion, but excessive amounts can be fatal. In 1805, Nux vomica was proved by Hahnemann.

- Key uses: colds and influenza digestive disorders, asthma, headaches, cystitis, menstrual and pregnancy problems, irritability, and insomnia (Bodeker and Ong, 2005; Lockie et al., 2006; Tripathy et al., 2023).

c) Apis

Apis is an animal-based homeopathic remedy derived from native European *Apis mellifica* (honeybee) and now it can be found throughout Europe, the US, Canada and many other countries. This remedy was proved by Dr. Frederick Humphries in 1852 and it is commonly used to treat insect bites and stings. It is prepared mainly by crushing the whole bee in alcohol and then diluted and potentized. Individuals who would benefit from Apis tend to be fussy, restless, and irritable, with oversensitivity, melancholy, and a need for company. The symptoms treated include itchy, red, and swollen skin, frequent urination along with stinging pain in the urethra and urine passing, and swelled body tissues or parts like mouth, lips, and throat.

- Key uses: Edema, bites and stings, urticaria, fever, cystitis, inflammation of mouth or throat, lips, and eyes (Lockie et al., 2006; Tripathy et al., 2023).

d) Aconite

Aconitum napellus is a poisonous plant from which aconite is obtained. The juice extracts from this plant were used in ancient times for arrow poison hence named aconite (Greek acon = dart). The roots of this plant are rich in poisonous alkaloids. Special care is taken during its preparation. Initially, it was only used as an external medicine until Hahnemann proved a homeopathic remedy in 1805. It is used to treat problems caused by shock, fright, exposure to cold, dry winds, acute infections, anxiety states, and post-partum for mothers and babies Aconite is given for those who have a significant loss of strength, are prone to severe phobias, panic attacks, or are afraid of dying.

- Key uses: acute respiratory infection, fear, shock and anxiety, eye and ear infections, and problems in labor (Lockie et al., 2006).

e) **Belladonna**

It is sourced from the plant named deadly nightshade (*Atropa belladonna*). The genus name is given after the Greek Fate Atropos, who held the authority of life and death over people. The species name also had a story. In the 16th century, Italian women utilized the poisonous nightshade plant to enhance the gleam of their eyes which turned out “bella dona” a nickname meaning “beautiful woman”. Hahnemann developed Belladonna in 1799 as a homeopathic treatment for scarlet fever, after observing the similarities in symptoms between nightshade poisoning and scarlet fever. Belladonna is a popular treatment for acute diseases with a quick, violent start, and is frequently administered to active people who have sudden rage and a high temperature. It treats symptoms such as high temperature, dilated pupils, flushing, dry skin, and throbbing pain, mainly in the head. Belladonna can treat acute pain, inflammation, or infection in the upper respiratory system, menstruation discomfort, sunstroke, febrile convulsions, cystitis, nephritis, teething pain, and mastitis while nursing.

- Key uses: acute fever and pain, menstrual pain, headaches and migraines, sore throat, and dry cough (Lockie et al., 2006).

f) Arnica

An aromatic perennial plant *Arnica montana* is the source of homeopathic remedy arnica. Arnica reduces inflammation and improves tissue healing. It has been utilized in European traditional medicine as an ointment for over 400 years due to its therapeutic powers. Due to its potentially toxic nature, its use is limited to external applications only. So it cannot be applied to broken/injured skin. Arnica is frequently used as a first-aid treatment following accidents, operations, births, and dental procedures, as well as for joint discomfort, fever, and skin disorders. It treats symptoms such as hard, dry, swollen skin, painful boils, and red skin eruptions.

- Key uses: skin conditions, fever, tooth and gum pain, joint and muscle pain, shock, post-childbirth pain, injury, and postoperative care (Lockie et al., 2006).

g) Spongia

Euspongia officinalis also known as ‘Spongia’ is a commonly used sponge mostly obtained from the Mediterranean Sea, close to Syria and Greece. In the 13th century, the alchemist Arnold von Villanova used this sponge for the first time for goiter treatment. It is prepared by washing and then toasting in a metal container after which it is triturated. It is given to those patients with a fear of heart diseases and death due to suffocation. The focus of this remedy lies on heart-related symptoms such as palpitations and uneasiness in the heart area, accompanied by congestion and a sensation of blood rushing into the chest and face. Spongia is also recommended for treating upper respiratory tract infections that affect the larynx, manifesting as a dry, hollow, barking cough.

- Key uses: heart complaints involving exhaustion and palpitations, upper respiratory tract infections, and croup (Lockie et al., 2006).

h) Chamomilla

The homeopathy remedy chamomilla is extracted from a plant named *Matricaria chamomilla* also known as ‘German chamomille’ or ‘Corn feverfew’. It is indigenous to central Europe, North America, and Australia. The scent of its flower seems like an apple scent and because of this, the name chamomilla is given, which originated from the Greek word 'chamaimelon'. Initially, it was advocated mainly for uterus strengthening, especially after an arduous labor. It was also used for skin conditions like burns or eczema. Chamomile tea is familiar as a calming drink that aids sleep and its usage for treating digestion disorders has been common since the 1st century CE. It is specifically recommended for individuals exhibiting a notably low tolerance for pain, accompanied by heightened irritability, anger, and hostility, particularly observed in children.

- Key uses: diarrhea, colic issues, fever, menstrual and labor pains, irritability, earaches, toothache, and teething (Lockie et al., 2006).

i) Crotalus

Crotalus is an animal-sourced remedy, derived from the venom of rattlesnake *Crotalus horridus horridus*. The venom of the live snake is taken out by 'milking' and dropped onto lactose sugar, which is then triturated. In ancient times, this venom was used for neutralizing the poison from a snakebite, which triggers antibody production and helps to heal. In 1837, the US homeopath Dr. Constantine Hering proved this remedy for an assortment of serious ailments, including strokes, angina, hemorrhaging, and infection.

- Key uses: cancer, bleeding, delirium, throat infections, heart disorders, and strokes (Lockie et al., 2006).

j) LAC CAN.

Lac caninum is a female dog from which Lac Can. is derived. Fresh milk from a lactating bitch is extracted and diluted in a mixture of water and alcohol for the preparation of tincture. Ancient Romans used remedies derived from bitch's milk for uterine and cervical problems and for ovarian pains. Lac Can. is used for individuals with self-contempt, irrational fears, and bouts of depression. It is administered in those patients having excessive dryness in the throat, and burning pain, which makes swallowing difficult. It is also given to the females having swollen or sore breasts during menstruation and breastfeeding, and unusual bleeding between menstrual periods. Those people having mental hypersensitivity due to an overactive imagination are also treated with this remedy.

- Key uses: Hypersensitivity, breast problems, phobias, vaginal bleeding, and discharge and throat infections (Lockie et al., 2006).

k) Carcinosin

Carcinosin (*Carcinosinum*) is a nosode homeopathic remedy made from cancerous breast tissue. Breast cancer is the second most prevalent cancer. The specimen tissue is washed thoroughly and mixed and succeeded. The honor of this derivative remedy goes to two British homeopaths, Dr. Clarke and Dr. Compton Burnett, who foremost attested the tonic in the late 19th century. Later on, its uses extended significantly following work by Royal London Homeopathic Hospital Doctor D. M. Foubister. In 1989, Dr. J. Shore published research on it. This remedy is considered for noncancerous conditions in people who have a strong family history of cancer. Cancer, diabetes, tuberculosis, emotional stress, chronic fatigue syndrome, and mononucleosis are main targets of this disease.

- Key uses: insomnia, respiratory illnesses, abdominal pain, skin growths and blemishes, and chronic fatigue syndrome (Lockie et al., 2006).

l) **ARSEN. ALB.**

Acidum arsenicosm syn. Arsenicum album is sourced from arsenopyrite (mineral rock), mostly found in Germany, Norway, England, Sweden, and Canada. It is said to be too poisonous, so it is diluted much before use. Hahnemann approved this remedy in his book Materia Medica Pura for the treatment of respiratory and digestive tracts of mucous membranes. This remedy is used mostly for indigestion and colitis, asthma or severe breathlessness, headaches, and food poisoning, mostly aggravated by stress or anxiety. In some cases, it is also used for eczema treatment.

- Key uses: food poisoning, digestive disorders, headaches, eye inflammation , respiratory illnesses, Raynaud's syndrome (Lockie et al., 2006).

Homeopathic remedies can also be in formulations for disease treatment. Many manufacturers sold these formulations. Table 1 shows a few examples.

Table 1: Homeopathic formulations for disease management (Lockie et al., 2006; Boger, 2007)

Ailments	Remedies in formulations
Piles	Aesculus hippocastanum, Hamamelis, Peonia, Nux.vomica, collinsonia, sulpher, graphite
Kidney stones	Berb.Vula, Sarsaparilla, Lycopodium, Hydrengia, Thlaspi, Nux.vomica
Abdominal bloating	Nuxvomica, Lycopodium, Argent. Mit, Arsenic Alb., Carbo veg., Asafetida, Dioscorea.

Homeopathy in Nutrition Management

According to a study by Fernandaz and Lubeck, made in 2019 by the United Nations, it is estimated that the global population will rise up to 9.7 billion by 2050. So, with the increasing population, the demand for nutritional items also increases, which are nutritious and sustainable for human consumption. The source of these nutritional items can be animals and plants (Santamaría-Fernandez and Lubeck, 2020). As we know, homeopathic remedies are extracted from these food sources, so besides the healing effect, they also help in nutrition management, which we will discuss later about the remedies used for nutrition management.

According to the philosophy of homeopathy, an integral part of health maintenance is nutrition management. Every health practitioner believes that if one maintains his/her health, the illness will not affect much compared to a nutrient-deprived person, as proper nutrition plays a vital role in people's natural healing and restoring abilities. Homeopaths believe that every person has his nutritional requirements and sensitivities, like digestive issues, allergies, etc. which must be kept under consideration while prescribing any dietary supplements or plans (Janbow, 2022).

Below are some significant aspects that are followed by homeo-health practitioners for nutrition management:

i. Some food items may be banned during treatment because of their healing hindrance property, like some herbs or spices, may work as antagonists against prescribed remedies, which may create adverse effects and vice versa.
ii. Diet/nutrition plans are tailored according to a person's history, symptoms, and overall health objectives rather than recommending a one-size-fits-all method.
iii. Homeopathic remedies may be used to cure underlying digestive issues like food sensitivities, poor absorption, and poor gut flora, which affect overall health.
iv. Homeopaths also consider emotional well-being during treatment.
v. Homeopaths typically favor eating whole instead of processed foods having artificial additives or preservatives. Whole food consumption helps in more nutrient absorption (Janbow, 2022).

Homeopathic Remedies used in Nutrition Management

In this section, we will discuss some nutritional remedies used by homeopaths:

a) Alfalfa

Alfalfa tonic is made from a herb *Medicago sativa* which is rich in vitamins (A, C, E, K) macro and micronutrients (Ca, K, P, Fe). It helps in resolving digestive issues like poor food absorption and constipation, muscle weakness, and skin dullness and helps in restoring body stamina (PoojaYadav and Shinde, 2022; Rawat et al., 2018).

b) Avena sativa

Avena sativa is a herb from which homeopathic remedies is prepared commonly known as oats. It is rich in fibers. Lower body cholesterol levels, which strengthen heart muscles. Besides its major health benefits, It is mainly given for neurological weakness, insomnia, and opium addiction (Singh et al., 2013).

c) Calcarea carbonica

Calcium carbonate, also known as *Calcium carbonicum Hahnemanni* is mineral remedy made from the oyster shell which is rich in calcium carbonate. Calcium is one of the major constituents of bones. Thus, this remedy helps in improving bone health and development, reducing dental ailments and joint pains, and is also used for children with delayed milestones (Lockie et al., 2006).

d) Ferrum Phos.

Ferrum phosphoricum is made from iron phosphate, it is usually given to improve overall energy. Mostly given to anemic patients and in treating the first stage of inflammation (Bhalla and Arora, 2023; Lockie et al., 2006).

e) Kali Phos.

Kali phosphoricum is made from potassium phosphate. According to Dr. Schussler, a deficiency of potassium phosphate leads to despondency and anxiety. This remedy is mainly given to support nervous health, and improving stress conditions and mental fatigue (Lockie et al., 2006).

f) Silica

Silica (*Silicea terra syn. Acidum silicicum*) is a nonmetallic material found in the Earth's crust. It plays an important role in plant structures. In the human body, it fortifies hair, teeth, and nails, as well as connective tissue (Lockie et al., 2006).

g) Zincum metallicum (Zinc)

Zinc remedy is usually used for strengthening the immune system and reproductive system, in improving cognitive skills and memory issues, etc (Ramya Gade, 2023).

Conclusion

Homeopathy is one of the holistic approaches to health management and nutrition management. A person’s whole physical and emotional health is kept under consideration along with disease symptoms for remedy prescription. Besides its beneficial aspects including low side effects, individualized and holistic approach, etc., some critics talk about its disadvantages too, which include long healing time, potentization reduces the molecule number to null which may be just non other than a placebo, some also say that there is no enough data repository for considering its beneficial effects and there is also lack of regulation by health authorities. To eradicate these issues, our homeohealth practitioners should publish their data just like allopath practitioners. This may eventually increase the data repository and will eventually help in the regulation of this approach and its remedies.

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Chapter 29

Use of *Moringa* and Barley for the Control of Hyperlipidemia

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ABSTRACT

Cardiovascular diseases affect the heart and blood vessels. Increased level or deposition of circulating lipids that is hyperlipidemia is among the most significant hazards for coronary heart disease. Coronary heart diseases caused 17.5 million deaths worldwide. Due to chronic heart diseases, 20.28% deaths occur in Pakistan. In recent years, the popularity of natural products has grown. Phytosterol is effective in treating hyperlipidemia. Beta sitosterol, that is a phytosterol, is present in *Moringa Oleifera* leaves which lowers the cholesterol by inhibiting the reabsorption of cholesterol. Soluble fiber Beta glucan present in Barley binds bile acid and prevents the body's ability to breakdown and eliminate cholesterol. There were significant increases in HDL. The data shows a significant reduction in low-density lipoproteins, serum triglyceride level, total cholesterol and increase in high-density lipoproteins. It is concluded from the present study that *moringa* and barley have great ability to manage the above-described hyperlipidemia biomarkers.

KEYWORDS
Moringa, Barley, Control of Hyperlipidemia

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INTRODUCTION

Hyperlipidemia, a chronic ailment connected to cardiovascular disease, has a significant impact on community health as the world's leading cause of death (WHO, 2015).

The risks associated with people's bad lifestyles, such as consuming alcohol, smoking, eating poorly, and not exercising, are linked to hyperlipidemia. According to WHO statistics, 15 million people between the ages of 39 and 69 die each year from noncommunicable diseases (NCDs), with more than 80% of these deaths occurring in developing countries. Because of the rise in their prevalence and the relationship between them and hyperlipidemias that have reached epidemic statistical proportions, it is more vital than ever to keep an eye on how NCDs effect premature mortality, particularly in the population of young people. The total prevalence of hyperlipidemia was 33.8%, with risk values for triglycerides, hypercholesterolemia, cholesterol on high density lipoproteins and cholesterol on low density lipoproteins of 12.8, 15.0, 16.1, and 6.1%, respectively (Ramírez et al., 2020).

Moringa oleifera is a multipurpose herb that is used in human diets around the world. Many detractors argue that a plant with numerous medical benefits includes healing and therapeutic harmonizing circumstances. The *Moringa* plant possesses a high concentration of carotenoids in its leaves and other sections that have nutraceutical qualities. The leaves and stems have grown to an unusually healthy appearance. One of the most important aspects is the therapeutic application of *Moringa oleifera*. It contains all the necessary antioxidants, anti-infection agents, nutrients, and minerals (Abdull Razis et al., 2014).

Hyperlipidemia is the medical term for high lipid levels in the blood or lipid accumulation. The biggest issue with the cardiovascular system is atherosclerosis, which is caused by elevated cholesterol levels. It is characterized by hypercholesterolemia and inflammation. It can also lead to many other health problems, such as failure of heart and stroke, which raise mortality and morbidity (Verma, 2017).

Various studies show that grains rich in soluble fibre, like barley and oats, are useful in decreasing cholesterol as compared to cereals with mostly insoluble fibre, such as wheat or rice. β-glucan is a non-starch polysaccharide soluble fibre found in barley and oats that has the ability to lower LDL by increasing intestinal viscosity, which may reduce cholesterol absorption (El Rabey et al., 2013). An active component of barley β-glucan has the ability to reduce cholesterol.

β-glucan binding bile acid and preventing the body's ability to breakdown and eliminate cholesterol (Andersson et al., 2010). Table 1 shows the lipid profile reference range.

Hyperlipidemia Reference Ranges:

The lipid profile parameters along with their ranges are as follow:

Table 1: Lipid profile reference range

Lipid Profile	Desirable	Moderately High	High
Cholesterol	< 200mg/dl	200-239mg/dl	240mg/dl
Triglycerides	< 150mg/dl	150-199mg/dl	200-499mg/dl
HDL	60mg/dl	35-45mg/dl	<35mg/dl
LDL	69-130mg/dl	130-159mg/dl	160-189mg/dl

Classification of Lipids

A naturally occurring diverse set of biomolecules is referred to as lipids, which dissolve in organic solvents that are non-polar. Small compounds that are either hydrophobic or amphiphilic can be used to characterize them. These include fatty substances, oils, waxes, and fats. Fat-soluble vitamins, phospholipids, monoglycerides, diglycerides, and triglycerides, as well as sterols and steroids. Lipids are necessary for many bodily biological activities because they make up a large part of the cell membrane, which acts as a mechanical barrier between the cell and its external environment.

They give 9Kcal/g of fat intake and are also a dense source of energy. They are crucial to signaling as well. Mammals who live in cold climates use their subcutaneous fat to slow down the loss of body heat. Lipoproteins are made up of proteins and lipids. They play a crucial role in the transit of lipids and are a component of the cell membrane. In addition to being lipid-based, fat-soluble vitamins provide a source of vital fatty acids (Kumar et al., 2019).

Composition-based Classification

The lipids are divided into three categories based on the makeup of their molecules: simple, complex, and derived lipids.

Simple Lipids

Simple lipids are fatty acid esters with different alcohol contents. They are also categorized as waxes and fats. Triglycerides make up the majority of fats and are present in adipose tissue. These different fat sources include fish, lard, butter, and oils derived from plants like corn or olives. Three fatty acids and a glycerol molecule are joined in triglycerides. The fatty acids could differ or be the same. Esters of fatty acids, waxes are composed of monohydric alcohol with a molecular weight greater than glycerol. Wax has been discovered in a variety of sources, including lanolin, carnauba oil, sperm whale oil, and bee wax.

Lipid Compounds Lipids

Esters of fatty acids that have an extra group added to them in addition to an alcohol and a fatty acid are known as compound lipids. The many kinds of lipid compounds are as follows:

Phospholipids

Phospholipids, sometimes referred to as phosphatides, are mostly present in the tissues of animals. They are made up of two fatty acids, one alcohol-modified 9-phosphate group, and one glycerol molecule. Both hydrophilic (phosphate group) and hydrophobic (uncharged fatty acid) characteristics are present in phospholipids.

Glycolipids

Glycolipids, sometimes known as glycosphingolipids, are molecules made up of carbohydrates, sphingosine, and fatty acids.

Lecithin

A phosphatide connected to choline is present in lecithin. Another name for it is phosphatidyl either serine or choline. It is mostly present in the brain, egg yolk, and organ meats. It facilitates the movement and metabolism of fats. In the food business, it is also employed as an emulsifier.

Cephalin

It is attached to serine or ethanolamine via a phosphatide bond. This primarily affects nerve tissue and aids in blood clotting.

Plasmalogen

Plasmalogen is a key component of structural membranes, particularly when it comes to the stability of cholesterol-rich membranes used in cellular signaling. They are classified as glycerophospholipids and have ester and vinyl-ether bonds at positions sn-1 and sn-2. It is present in the heart, brain, and muscles.

Lipositol

When phosphatide is joined to inositol, it is also referred to as phosphatidyl inositol. In the brain, it is generated and broken down quickly. Lipositol is mostly found in the kidneys, heart, brain, and tissues of plants. It is involved in the mechanisms of cell transport.

Sphingomyelin

It is a phosphatide that contains sphingosine that produces choline, fatty acids, and phosphoric acid, and upon hydrolysis, sphingosine. But no glycerol is generated on the hydrolysis. The brain, nerve tissue, and red blood cells are the main suppliers. It serves as a source as well of the body's phosphoric acid.

Cerebrosides

Ceramide, which is a sphingosine and fatty acid, along with a mono sugar attached to the C1 of esfingol via a β-glycosidic link, makes up cerebrosides. In these, galactose is the most frequently occurring carbohydrate, and the fatty acids are either 24 carbon lignoceric, cerebonic, or hydroxylignoceric acid. Cerebrosides containing lignoceric acid are named kerasin, whilst those containing cerebronic acid are referred to as phrenosin. Cerebrosides originate from the white matter of the brain and the myelin sheaths surrounding nerves. Other tissues' cell membranes also contain trace amounts of it.

Ganglioside

A glycosphingolipid makes up ganglioside. It has an oligosaccharide or ceramide that is connected to fatty acids, sphingosine, n-acetylneuraminic acid, and hexose sugar. The spleen, brain, and nerve tissue all contain this.

Sulfolipid

This glycolipid has sulfur in it, and the sulfur is linked to galactose through an ester bond. This can be found in the chloroplasts of plants, testicles, liver, and brain. lipids in proteins.

Proteolipids

These consist of proteins that are covalently attached to lipid molecules such as cholesterol, fatty acids, isoprenoids, and glycosylphosphatidylinositols. They exist in the nerve and brain.

Precursors and derivatives Lipids

By hydrolyzing simple or conjugated lipids, these lipids are produced. Fatty acids, glycerol, fatty aldehydes, ketone bodies, steroids, hydrocarbons, lipid-soluble vitamins, and hormones are all members of this class.

Steroids, Terpenes, and Terpenoids

Terpenes are basic hydrocarbons made up of five carbon isoprene units connected in various ways to one another. These make up the greatest class of secondary metabolites and are present in rubber, resin acids, essential oils, and colors derived from plants, such as lycopene and carotenoids. Terpenoids are modified terpenes that have distinct functional groups. Terpenoids can be categorized as monoterpenes, diterpenes, triterpenes, sesterpenes, and sesquiterpenes based on the units of carbon.

Classification on the basis of Chain Length and Unsaturation

Lipids are made up of tiny units called fatty acids. These are even carbon atoms in a linear hydrocarbon chain. The carboxyl group (-COOH) is at one end of this chain and the hydrogen atom (H) is at the other. FAs often assemble in a group and are not seen in nature in their free form. trio used with alcohol to create triglycerides. The length of the chain, the degree of unsaturation, and the quantity of essential acids present can all be used to categorize fatty acids. Cerebrosides are found in the brain and nerve myelin sheaths of fatty acids with less than eight carbon atoms in their chain, eight to twelve carbon atoms in their chain for medium chain fatty acids, and fourteen carbon atoms or more for long-chain fatty acids. Other tissues' cell membranes also contain trace amounts of it.

Ganglioside

A glycosphingolipid makes up ganglioside. It has an oligosaccharide or ceramide that is connected to fatty acids, sphingosine, n-acetylneuraminic acid, and hexose sugar. This is found in the brain, nerve tissue, and spleen.

Sulfolipid

This glycolipid has sulfur in it, and the sulfur is linked to galactose through an ester bond. This can be found in the chloroplasts of plants, testicles, liver, and brain.

Proteolipids

These consist of proteins that are covalently attached to lipid molecules such as cholesterol, fatty acids, isoprenoids, and glycosylphosphatidylinositols. Both the brain and the nerve tissue contain them.

Precursor

By hydrolyzing simple or conjugated lipids, these lipids are produced. Fatty acids, glycerol, fatty aldehydes, ketone bodies, steroids, hydrocarbons, lipid-soluble vitamins, and hormones are all members of this class.

Terpenes, Terpenoids and Steroids

Terpenes are basic hydrocarbons made up of five carbon isoprene units connected in various ways to one another. These make up the greatest class of secondary metabolites and are present in rubber, resin acids, essential oils, and colors derived from plants, such as lycopene and carotenoids. Terpenoids are modified terpenes that have distinct functional groups.

Classification on the basis of Chain Length and Unsaturation

Lipids are made up of microscopic units called fatty acids (FAs). These are even carbon atoms in a linear hydrocarbon chain. The carboxyl group (-COOH) is at one end of this chain and the hydrogen atom (H) is at the other. In nature, FAs are not found in their free form. Instead, they usually combine with alcohol in groups of three to produce triglycerides. The length of the chain, the degree of unsaturation, and the quantity of essential acids present can all be used to categorize fatty acids. A fatty acid is classified as a short chain if it has less than eight carbon atoms, medium chain if it has eight to twelve carbon atoms, and long chain if it has fourteen or more carbon atoms.

Mechanism of Action of *moringa* in our Body

The *Moringaceae* family, which contains the plant species *Moringa*, can be found across the tropics and subtropics (Boonchum et al., 2011). Leaves of these trees have been shown to be useful in treating a variety of chronic conditions, including hypercholesterolemia (Vergara-Jimenez et al., 2017). *Moringa* leaves, for example, are high in vitamin C, vitamin A, calcium, iron, and potassium (Aborhyem et al., 2016). *Moringa* has been around since 150 B.C. Old kings and queens drank *Moringa* leaves and fruit to maintain mental alertness and healthy skin, according to historical records (Zaku et al., 2015). *Moringa's* bioactive component, Beta-sitosterol lowers cholesterol. The impact of lowering cholesterol is caused by a decrease in endogenous cholesterol reabsorption (Mehta et al., 2003).

It is considered one of the old and useful trees; it is famous for curing a lot of diseases like asthma, bronchitis, liver fibrosis, cholera, renal disorders, chest congestion, as well as several other kinds of illnesses (Khawaja et al., 2010; Hamza, 2010). Different parts of the *Moringa* plant have cholesterol lowering properties. Because many phenolic compounds exist like zeatin, quercetin and sterol like beta sterol (Anwar et al., 2007).

Leaves of *moringa* are riches are enriched with beta sitosterol, a plant sterol that is same as cholesterol but varies in structure due to the presence of ethyl group in the side chain at C24 which exist in cholesterol. It lowers the cholesterol of serum cholesterol in the body by stopping the absorption of cholesterol in the intestine. Moreover, it also promotes its excretion and acts as natural steroids. This mechanism directly contributes to the hypolipidemic activity of MO (Jain et al., 2010).

Classification of Beta-Sitosterol

Synthesis of Beta-Sitosterol

Even though β-sitosterol hasn't been entirely synthesized yet, there are two methods that can be used to create it from pure stigmasterol. The first route involves selectively hydrogenating the side chain Δ22–23 alkene to yield β-sitosterol, as well as varying amounts of stigmasterol and fully saturated stigmastanol. The second approach aims to achieve the same selective hydrogenation while shielding the Δ5–6 alkene from cyclopropylcarbinyl ether. After this procedure, the Δ22–23 double bond should be hydrogenated, and the cyclopropane should be solvolyzed to create the C3–alcohol and Δ5–6 alkene once more. The latter approach appears to be highly beneficial, since it produces high-purity β-sitosterol. In actuality, semi-synthesis of β-sitosterol remains a challenge due to the production of methyl ether byproducts, which are difficult to remove.

β-Sitosterol Biosynthesis

Membrane biogenesis involves the regulation of phytosterol biosynthesis. Research has indicated that the synthesis of β-sitosterol occurs naturally through the routes of both deoxyxylulose and mevalonate. The mechanism of β-sitosterol production has been examined using the 13C-labeling technique. Cycloarteol has been identified as an initial substrate, however, the exact identification depends on the organism utilized. Farnesyldiphosphate (FPP) is actually created when two molecules of dimethylallyldiphosphate (DMAPP) combine with one molecule of isopentenyl-diphosphate (IPP). After that, two of the latter molecules (FPP) are joined tail to tail to generate squalene, a triterpene, and ultimately cycloartenol (Saeidnia et al., 2014).

Distribution of β-Sitosterol in Plants and Algae

β-sitosterol is an ancient plant-based molecule. From single-celled organisms to vascular plants, simple sterols have developed into more complex forms. β-sitosterol has been extracted and purified from a variety of plant families using various chromatographic techniques, according to a literature study. The plants included here are only a few of the well-known sources of the compound's distribution and its derivative components, which span many different plant families.

Mechanism of Action of Barley in Our Body

Barley with reduced glycemic index and rich soluble fiber such as β-glucan and high level of magnesium and chromium are beneficent grains to prevent and treat diabetes and changes in blood fat composition. The usage of barley, as well as the consumption of β -glucan supplements made from barley, resulted in a reduction of lipids in healthy persons (Babitha and Priyamvada, 2016). β-glucan binding bile acid and preventing the body's ability to breakdown and eliminate cholesterol (Andersson et al., 2010).

Recommended Dosage of *Moringa* and Barley

The recommended dosage of *moringa* leaves powder is 10-15g per day per person to cure hyperlipidemia. And 30g barley daily is effective to overcome hyperlipidemia. This dosage is proved effective after so many clinical research trials.

Product Develpoment with *Moringa* Leaf powder and Barley

Procurement of Raw Material

Moringa leaves and barley were purchased from the local market. All standards or chemicals were obtained from the local market.

Preparation of Procured Material

Sorting of *Moringa* leaves

Green, fresh and undamaged *moringa* leaves were selected whereas damaged, willed, bruised and discolored leaves were discarded. The reason is that damaged and decayed leaves give bad flavor as well as it also leads to loss of essential nutrients.

Washing of *Moringa* leaves

Selected *moringa* leaves were washed under the running water and the leaves were soaked in the solution of 1% saline for five minutes in order to remove all microbes. Leaves were washed with distilled water. This step is considered crucial in order to get rid of all types of microbes present on the surface of *moringa* leaves.

Preparation of Barley Flour

Barley was purchased from the local market then sun dried and milled into fine flour.

Preparation of Product

- Weighed the barley flour and *moringa* powder
- Mixing of all the ingredients
- Bake at 180°C for 10-15 minutes

Total Phenolic component

Total phenolic component of *moringa* and barley-based cake was determined by Folin- ciocalteu method. This method is described by Kulkarni et al., (2006). The method states, the sample solution was prepared by 5g *moringa* and barley-based cake powder and extracted it with 20ml of n-hexane. The solution was kept for 1 hour. After that, the resultant solution was centrifuged. The centrifugation process took only two minutes at exactly 6000 rpm then filters the solution. Supernatant was saved and was also extracted with 25ml 80% methanol solution for 3 hours. Then filter the solution again the filtrate then evaporates in rotatory evaporator until 3-5ml solution remained left. However, the total phenolic content of *moringa* and barley-based cake was evaluated by using gallic acid as the standard.

Take 125µl sample in the test tube and add 500µl distilled water and 125µl of Folin-Ciocalteu reagent in it. The whole mixture was mixed well after that, the mixture was incubated for about 8 minutes at room temperature. In the mixture 1.25ml of 7% sodium carbonate solution was also added to make the final volume 3ml with distilled water and give stay time of 90 minutes. The absorbance was taken 760nm with the help of UV light spectrophotometer.

In the whole process, Gallic acid was used as a calibration standard. All the readings were recorded with gallic acid equivalents. TPC of extract in gallic acid was calculated with the help of the following formula:

$$C = c \times V/m$$

C= Total phenolic content (mg/g plant extract, in GAE)
c = Concentration of gallic acid (mg/mL)
V= volume of extract (mL)
m= Weight of *moringa*-based cake extract (g)

Total Flavonoids Content

In a test tube, combine 0.25ml phytochemical extracts as needed for TPC with 1.25ml distilled water. After mixing, pour 75µl of sodium nitrite (5% solution) into the test tubes and leave for 6 minutes at 25°C. After 6 minutes, add 150µl

aluminum chloride (10%) and distil water to make a volume of 2.5ml and thoroughly mix. The absorbance of the sample was immediately measured at 510nm against a blank using a UV-Vi spectrophotometer. Catechin was used as the standard, with methand concentrations of 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, and 0.9mg/ml.
TFC is calculated against a standard curve of catechin [µg/g catechin equivalent (CE)] as below.
TFC=C x (V/m)
Where,
C= concentration of catechin in mg/ml
V = volume of plant extract in ml
m= weight of *moringa* based cake extract in g

Free Phytosterol Determination by UV-Vis Spectrometry using method of Extraction

The samples were macerated for three days in between 100 and 150mL of ethanol for the ethanolic extraction. The obtained ethanolic extract was filtered to remove solid residues, and the filtrate was concentrated at 50°C on a rotary evaporator under reduced pressure. The residue was resuspended in 30mL of ethanol and centrifuged at 8000g for 15 minutes to obtain a clear supernatant. This was transferred to a 50 mL volumetric flask and the volume was adjusted with ethanol. The absorbance was recorded in UV-Vis spectrophotometer equipment at 650nm, in a time range no longer than 10 min after the end of the incubation. Comparative graph of the phytosterols concentrations of each sample by extraction methods (Badilla et al., 2020).

Conclusion

This evaluation has explored the potential curative effects of *Moringa oleifera* and barley cake on hyperlipidemia. *Moringa* and Balrey plant renowned for its health benefits, whole grain known for its potential impact on heart health, are both theoretically capable of beneficial impacts on lipid profiles. This evaluation has explored the potential curative effects of *Moringa oleifera* and barley cake on hyperlipidemia. *Moringa* and Balrey plant renowned for its health benefits, whole grain known for its potential impact on heart health, are both theoretically capable of beneficial impacts on lipid profiles.

It is also the substituted way against the higher prices of pharmacological and traditional food products day by day. So, high prevalence of hyperlipidemia is the major health sickness throughout the world. The important factors in the initiation of hyperlipidemia is the lifestyle modification, high amount of energy intake, unhealthy eating patterns and decreased physical activity. Unhealthy dietary behavior usually causes uncontrolled fat intake and also responsible for the elevation of adiposity.

It is high nutritional value, especially the leaves of *moringa* contains beta sitosterol in highlighted amount, which acts as binding agent and allow the body to flush out all the unwanted substances from the body. It also protects from blood coagulation and increases energy production. Barley contains an active component beta-glucan binding bile acids and preventing the body's ability to breakdown and eliminate cholesterol.
Antioxidant potential of *moringa* based cake was checked by TPC and TFC present in the product.

Cake containing *moringa* powder had shown to possess the capability of lowering the Cholesterol of hyperlipidemic subjects. *Moringa* and Barley based cake are highly nutritious food and used any time during the day, so patients enjoy the food and overcome their higher lipid profile. This product also contains sufficient calories, minerals and antioxidants.

Recommendations

- Nutritional and health awareness programs must be developed, as well as educating people about the health benefits of *moringa* and barley-based cakes.
- Hyperlipidemic patients can use this as a snack at any time during the day to overcome CVD. This is also beneficial to treat obesity.

Therapeutic potential of *moringa* and barley utilized for reducing cholesterol.

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Chapter 30

Medicinal Benefits of Zingerbreaece Family, Ginger Root and Turmeric

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ABSTRACT

Turmeric and Ginger's roots are associated with the Zingerbreaece family. Turmeric has carminative, stimulating, and fragrant properties, making it a moderate digestive. Curcumin is the active component of turmeric. Turmeric (*Curcuma longa*) has been broadly studied for its various pharmacological properties, as well as its potential role as an anticancer agent, antioxidant, and radio protector. Turmeric is believed to possess numerous medicinal benefits, such as enhancing the body's overall energy, reducing gas, eliminating worms, enhancing digestion, controlling menstruation, breaking down gallstones, and alleviating arthritis. Most drugs used in conventional and contemporary medical systems worldwide are derived from plants. On the other hand, changes made to the molecular structures of these medications are reducing their toxicity and side effects while increasing their biological function, selectivity, and ability for metabolism, absorption, distribution, and excretion. When curcumin is used medicinally, it treats a wide range of diseases, including hysteria, diabetes, indigestion, vomiting, smallpox chicken pox, asthma, cough, fever, anemia, eye disease, and hysteria. Curcumin, which a compound called bis desmethoxycurcumin, triethyl Curcumin, tetrahydro Curcumin, circumoral, circumoral, zingiberene, eugenol, turmeric, turmerones, and turmerones are only a few of the many phytoconstituents found in turmeric. Curcumin, the compound that provides curcumin its yellow color and much of its medicinal properties, is the most active of them. Ginger is also said to be a potent aphrodisiac. Wear and tear of the cell. Rich in vitamins and minerals, ginger also includes essential oil, starch, and oleoresin, which is made up of chemicals called gingerol and shegrohaol that have anti-inflammatory and antiemetic properties and quicken intestinal transit.

KEYWORDS Medicinal, benefits, *Zingerbreaece* family, Ginger root, Turmeric, Curcumin, Gingerol, Shegrohaol, Diseases	Received: 21-May-2024 Revised: 16-Jul-2024 Accepted: 05-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Zingiber officinale roscoe commonly known as ginger, it is a popular spice that has exhibited a variety of pharmacological activity, as well as antioxidant, anticancer, and anti-inflammatory effects. Gingers are valuable natural resources that may be useful to make a wide range of items as well as food, spices, medications, colors, perfume, and more. The *Zingiberaceae* family is widely dispersed in tropical climates, especially in Southeast Asia, and is well renowned for its medicinal properties (Mao, 2019). Rhizomatous herbs, either annual or perennial, make up the Zingiberaceae family. The color of the rhizomes varies depending on the species; they can be any of these colors pink, mild yellow, deep yellow, greenish blue, or a combination of them. In terms of structure, form, size, texture, and venation, the leaves differ morphologically. They are also distichous (Karpuz Ağören, 2024).

Ginger root (ground) contains the following minerals: manganese (33.3 mg/100 g), magnesium (114 mg/100 g), iron (19.8 mg/100 g), potash (1320 mg/100 g), sodium (27 mg/100 g), phosphorus (168 mg/100 g), and zinc (3.64 mg/100 g). Raw ginger root contains the following minerals: 16 mg/100 g of calcium, 0.6 mg/100 g of iron, 43 mg/100 g of magnesium, 34 mg/100 g of phosphorus, 415 mg/100 g of potassium, 13 mg/100 g of sodium, and 0.34 mg/100 g of zinc, corresponding to the USA (2013). Ginger was found to have trace minerals, coloring matter, essential oil (1.5–3%), fixed oil (2–12%), and 40–70% starch as well, 6-20% proteins, 3-8% fiber, 8% ash, 9–12% water, and other fragrant ingredients (Shahrajabian et al., 2019a).

Inflammation is the immune system's response to an injury or illness. These are the five classic indicators of inflammation: heat, redness, swelling, discomfort, and loss of function, which were identified by the ancients based on visual observation. Long-term inflammation can have detrimental effects on health, such as cancer. Therefore, redness must be neutralized. Herbs and spices are examples of medicinal plants that are essential in treating pathologies linked to inflammatory responses. Due to their anti-inflammatory properties, spices have long been used as an effective treatment for inflammatory illnesses like fevers, migraines, and arthritis. Since inflammation is thought to be the cause of many diseases in the modern world, spices like ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*) can help treat inflammatory conditions (Azeez et al., 2021).

The tuberculous or non-tuberous rhizomes of the *Zingiberaceae* family of plants are highly aromatic and therapeutic. It is widely acknowledged as ginger and is primarily found in South and Southeast Asia. It is found worldwide in roughly 50 taxa and 1,300 species. In several Asian nations, powdered ginger from *Zingiberaceae* plants is used as a food additive. Medicinal uses in the treatment of illnesses like Traditional treatments also often mention rheumatism, diarrhea, coryza, and dermatosis problems. Numerous essential oils, such as terpenes, alcohols, ketones, flavonoids, carotenoids, and phytoestrogens, are found in Zingiberaceae plants. For example, 6-gingerol is present in Zingiber officinale water extract and is mostly found in the rhizome at 130–7,138 parts per million. Curcumin, the primary functional component of Curcuma turmeric, can be found in certain species at quantities of up to 38,000 parts per million (Chen et al., 2008).

The Zingiberaceae family includes approximately 1300 types of aromatics, flowering perennial herbs with properties with sneaking horizontally or tuberous rhizomes. The Americas, Africa, and Asia are the three continents where they are most widely dispersed. The most well-known members of this family are the following: galangal, often known as Thai ginger (*Alpinia galanga (L.) Willd.*), Javanese ginger (*Curcuma zanthorrhiza* Roxb.), turmeric (*Curcuma longa L.*), ginger (*Zingiber officinale Roscoe*), and turmeric. This family has a diverse range of bioactive chemicals identified, isolated, and studied (Table 1). Given the belief that "you are what you eat," researchers have worked hard to identify naturally occurring sources of antioxidants in food. The main function of these exogenic antioxidants is to eliminate excess free radicals in addition to enhancing the body's natural antioxidant defense system. Notable products considered good sources of exogenous antioxidants include green, other spices, and herbs. Usually phenolic or thiolic chemicals, the Zingiberaceae family is a major source of these dietary antioxidants (also recognized as the ginger family (Alolgla et al., 2022).

Table 1: The medicinal value of ginger root and turmeric.

Parameter Name	Tumeric	Ginger Root	References of Tumeric	References of Ginger root
Scientific Name	(*Curcuma Longa* Linn.) *Curcuma Aromatica*	(*Zingiber Officinale.* Linn)	(Meena et al., 2015)	(Saribaeva et al.,2024)
Origin	India	Southeast Asia	(Kaur, 2019)	(Pázmándi et al.,2024)
Daily Dose	500g per day of dry root	170mg to 1 g 3 to 4 time of fresh root	(Eke-Okoro et al., 2018)	(Apalowo et al.,2024)
Treat Diseases	Boost Immunity, improve liver, and help to Maintain Diabetes	Vomiting from motion, Sickness, Pregnancy, Cancer and Chemotherapy	(Hayet al., 2019)	(Sharma et al.,2024)
Principle Compound	Curcumin(diferuloylmethane) causes the yellow color in Tumeric and Desmethoxycurcumin	Gingerols, long time heating, and storage convert into Shogaols, Paradol	(Sony et al., 2014)	(Xiong et al.,2024)
Vitamins	vitamin C, vitamin B6,	Vitamin C Carbohydrate (50-70) %, Lipid (3-8) %	(Yestemirova et al., 2024)	(Matin et al., 2024)

Antibacterial Activities in Ginger

Spices are used for more than just flavoring food; they are also commonly prescribed in traditional medicine, employed as food maintenance and antifreeze, and extend food life span to avoid food deterioration and food-borne illnesses (Zaman et al.,2017). Antibiotics, which were incredibly successful in treating bacterial transmittable at the start of the 20th century, are now losing some of their effectiveness because bacterial cells have been gradually developing resistance to common antibiotics for decades, and the human host is unaware that this is happening. Consequently, medicinal plants may be a new and intriguing substitute for these inactive antibiotics. By examining the available published research, this minute review seeks to determine the effectiveness of ginger root Salk (*Zingiber officinale Rosc.*) as an antibacterial factor (Abdalla and Abdallah 2018).

The ginger possesses direct anti-microbial activity, making it a useful tool for treating bacterial illnesses. In Chinese Traditional Medicine, it is utilized as a stimulant and in conjunction with collagen to treat dyspepsia (Tan and Vanitha, 2004). As a Yang herb, ginger is said to lower Yin and sustain the body. Ginger is described as spicy and fiery in traditional Chinese medicine, and it is said to heat the body and medicate cold extremities, refine pale and sluggish pulses, direction pale complexions, and vigor the body after blood loss. Herbal therapy is used in traditional Chinese medicine to manage a variety of cardiovascular conditions (Shahrajabian et al., 2019b).

Research has revealed that, as a result, new antibiotics must be developed to treat these illnesses and infections caused by Propionibacterium. This discovery has made it necessary to look for novel plant-based medicinal compounds with antibacterial properties that can combat harmful microbes. Research has only been done on garlic, ginger, cinnamon, and turmeric, according to (Aqeel et al., 2024). So, the antibacterial activity of turmeric (*Curcuma louga*) and ginger (*Zingiber officinale roscoe*) against Propionibacterium spp. proves crucial to treating the diseases that are caused by bacteria (Flores et al., 2021).

Antibacterial Activities in Turmeric

Turmeric is a mild digestive due to its stimulating, carminative, and aromatic qualities. Turmeric is one of the universe's energetic remedies. Turmeric's biologically active is called Curcumin. Turmeric has been consumed more than 2500 times in India, in which it was probably first utilized as a color. The medicative healthful properties of these condiments have progressively become apparent over time. More recent research has revealed that turmeric is an amazing ingredient that can assist in treating extensive conditions, including cancers and Alzheimer's disease, even though it has long been renowned for its anti-inflammatory properties. An antibiotic ointment made with the spice is used in India. (Debjit Bhowmik et al., 2009).

It has been proved experimentally that Curcumin works effectively against Staphylococcus aureus (infections that cause pus) diseases including anemia, cancer, diabetes, staph infections, wounds, gallstones, indigestion, IBS, parasites, and poor circulation. Since turmeric reduces Kapha, it is used to treat watery discharges such as leucorrhea, pus in the eyes, ears, or wounds, and throat mucus. Turmeric is a mild digestive due to its stimulating, carminative, and aromatic qualities. Turmeric is one of the universe's most powerful remedies. Turmeric's active ingredient is called curcumin. Turmeric has been consumed for more than 2500 years in India, in which it was probably first utilized as a color. The medicinal properties of this spice have progressively become apparent over time. More recent research has revealed that turmeric is an amazing ingredient that can assist in treating a wide range of conditions, including cancers and Alzheimer's disease, even though it has long been renowned for its anti-inflammatory properties. An antibiotic ointment made with the spice is used in India (Bhowmik et al., 2009).

Polyphenolics Content in Ginger Root

The maximum concentration of total polyphenols (840 and 830 mg/g) was found in the aqueous separate at nearly identical levels at different temperatures. In acetonic, there were the fewest polyphenols excerpts. Plant extracts' antioxidant properties were typically associated with their phenolic content. The hampering of the lipid's capacity to scavenge free radicals and produce oxygen species, including singlet oxygen, superoxide free radicals, and hydroxyl radicals, is due to the hydrogen-donating properties of phenolic compounds (Hinneburg et al., 2006).

It is widely acknowledged that non-phenolic antioxidants may also play a role in the plant extract's antioxidant activity. Researchers calculated the total polyphenol content in an 80% methanolic evoke of 35 distinct herbs and medicinal herbs. According to Keservani et al. (2025), the polyphenol content ranged from 0.8 to 42.1 mg of trioxyhydrobenzoic acid galop identical per g of dry weight (DW). Aqueous ginger extract was come across to have a total phenolic content of 23.5 mg gallic acid/g. The total phenolic content of the ginger 60% ethanolic extract was calculated by Rababah et al. (2004) to be 39.9 mg of chlorogenic acid equivalent/g DW (Prakash, 2010).

Biological Role of Tumeric

An overview of turmeric's chemical makeup is given in this review, with a focus on the plant's primary bioactive ingredients, curcuminoids, and volatile oils. The most prevalent curcuminoids in turmeric, curcumin, has been the subject of considerable study caused of its wide range of biological activities, which include anti-inflammatory, antioxidant, and anti-cancer properties. Curcumin can affect several signaling pathways implicated in carcinogenesis, as shown by several in vitro and in vivo studies. This can result in the hampering of cancer cell growth, the activation of apoptosis, and the subduing of metastasis (Prasad and Aggarwal, 2011).

Curcumin has demonstrated encouraging promise as a radioprotective drug by reducing DNA damage and oxidative stress brought on by radiation. Furthermore, studies have shown that curcuminoids, which are found in turmeric extracts, have strong antioxidant properties that scavenge free radicals and shield cells from harm caused by oxidative stress. Turmeric's diverse pharmacological characteristics make it a good option for the creation of innovative therapeutic approaches for managing the effects of oxidative stress-related illnesses as well as the prevention and dealing with cancer (Cozmin et al., 2024).

The synthetic drug-based treatment now in use is costly and alters metabolism and genetics. To limit the development and course of the condition, however, a sound and safe treatment plan is required. Medicinal plants and their components contribute significantly to managing diseases by modifying biological processes. The rhizome of Zingiber officinale, or ginger, has long been used therapeutically to manage health issues and is thought to have chemopreventive properties. Much research using animal models and clinical trials has demonstrated the important function ginger and its ingredients play in disease prevention by altering genetic and metabolic activity (Rahmani et al., 2014).

Biological Role of Ginger Root

For millennia, people have used herbs in traditional healthcare and cooking (Gupta et al., 2024). The hot water extract from ginger peels shows great promise as an antioxidant, antibacterial, antiradical, and anticancer agent. Since ancient times, ginger has been used extensively in Chinese, Ayurvedic, and Unani medications and home remedies to cure various illnesses, including inflammation, pain, and gastrointestinal issues. Because of its anti-inflammatory properties, it is also well-known as a common alternative therapy treatment for vomiting and nausea during pregnancy. Biologically active chemicals have been identified through phytochemical investigation (Grabsi et al., 2024).

Phytochemical Composition

More than 60 different chemicals make up the complex molecule known as ginger. Oleoresin, a combination of essential oil and resin, is found in the rhizome of ginger. The essential oil's makeup varies depending on where it comes from, but its main ingredients are 6 the distinctive scent is caused by sesquiterpene hydrocarbons, which are identified by (Bhat et al., 2013). The primary phenolic compound is gingerole, which breaks down to produce zingerone, paradol, and shogaols (Toor et al., 2023). Small levels of gingerone and shogaols can be found in raw ginger, whereas greater amounts can be found in dried or separated products (Srivastava et al., 2000).

During this process, gingerols are also converted into the less pungent molecule gingerone, which has a spicy-sweet scent (Kumar et al., 2013). Other sesquiterpenoids that have been found in smaller proportions include alpha-pinene, limonene, zingerone, batabeasabolene, alpha paradol, farnesene, and the monoterpenoid fraction (β-phellandrene, cineol, and citral). Gingerenone is one of a unique class of chemicals found in ginger known as diasyleheptanoids. Ginger also has a very small quantity of curcumin. (Kumar et al., 2013)

Furthermore, it has trace levels of cardinolides, alkaloids, tannins, carotenoids, saponins, flavonoids, and steroids (Ajith et al., 2007). Fresh ginger oil has a higher concentration of oxygenated chemicals in its composition than dried ginger oil, which gives it greater potency. Dry ginger oil has a higher concentration of hydrocarbon components than fresh ginger oil. Sesquiterpene molecules lack the activity of monoterpene compounds. Sesquiterpene hydrocarbons, which are found in greater concentration in dry ginger oil, are also said to be less active than those found in oxygenated compounds (Srivastava et al., 2006). Sesquiterpene hydrocarbons, such as β-sesquiphellandrene (27.16%), caryophyllene (15.29%), zingiberene (13.97%), α-farnesene (10.52%), and others, are highly present in ginger oil (GEO). Ginger oil (GEO) has been characterized to have a high content of sesquiterpene hydrocarbons, including β-sesquiphellandrene (27.16%), caryophyllene (15.29%), zingiberene (13.97%), α-farnesene (10.52%) and curcumin (6.62%) (El Baroty et al., 2010).

A warm, humid atmosphere is best for growing ginger. Another use for ginger is as an ornamental plant (Retana-Cordero et al., 2022). The ginger plant is an intriguing and notable decorative plant with its patterned foliage, sweetly fragrance blossoms in a rainbow of hues, and startling seed pods. Grown for ornamental and therapeutic purposes only, rather than as spices, are Cautleya, Globba, Roscoea, Kaempferia, and Siphonochilus (Branney, 2005). The crop is ready for harvesting when the leaves begin to progressively wither and turn yellow (Toor et al., 2024). The plants utilized for this might have been gathered even later because the proportion of essential oils of rhizomes rises with age. Harvesting is carried out either by machine diggers or by hand using a digging fork or spade. However, South India, Australia, and Jamaica produce the priciest and best varieties (Ali and Gilani, 2007).

There are at least forty antioxidant chemicals found in ginger. Following thirty studies, it was listed as one of the fourteen types of vegetables with the greatest antioxidants, along with broccoli, Brussels sprouts, mint, coriander, and turmeric.

Conclusion

Our results show that several spices have significant and variable action against a range of species, suggesting the presence of antimicrobial capabilities in natural items such as turmeric and ginger. The greatest inhibitory activity against a variety of isolates was demonstrated by ginger. Because of its many phytotherapeutic benefits, ginger is a vow herb that is used all across the world. The ginger extract under analysis contained bioactive chemicals with significant biological applications. The term "Mahaushdi" in Ayurveda refers to the herb's ability to enhance bodily processes and aid in the elimination of toxins from the body. I noted that ginger has a wide range of medicinal benefits, which include as direct anti-inflammatory effects, the capacity to avoid the synthesis of inflammatory chemicals, and antibiotic, antibacterial, and antioxidant activities. In addition, ginger helps lower cholesterol, promotes blood circulation, regulates blood pressure and hypertension, and is associated with the prevention of several malignancies and cardiac muscle issues. Plant medication development employs a multidisciplinary approach that combines botanical, ethnobotanical, phytochemical, and biological methods. As stated by the World Health Organization, more than 75% of people worldwide use traditional medicine. They have been used for health reasons throughout the world for a very long time as folk and traditional medicines. As a result, because of their safety, efficacy, absence of adverse effects, and cultural acceptability, herbal remedies have been used for millennia.

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Chapter 31

Homeopathic First Aid: Natural Remedies for Common Ailments

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ABSTRACT

Homoeopathy is an alternative medicine system that was established in the late 18th century by Samuel Hahnemann, a German physician. The foundation of this concept rests upon two fundamental principles: the "Law of Similars" and the "Law of Infinitesimals. It gained popularity in the 19th century due to its efficacy in treating epidemics, but experienced a fall over the majority of the 20th century. This popularity had a significant surge during the late 20th and beginning of the 21st centuries across many regions worldwide. Homoeopathy, an individualised and holistic medical approach, plays a key part in modern healthcare by providing natural and non-invasive treatment choices. The significance of this approach rests in its capacity to target the underlying causes of illnesses, taking into account the patient's physical, emotional, and psychological conditions. Homoeopathic medicines, which are generated from natural components and undergo extensive dilution to minimise adverse reactions, are especially attractive due to their mild methodology, rendering them suited for a diverse array of patients, including youngsters and the elderly. The individualised approach of homoeopathic therapy improves patient contentment and compliance and cultivate a more profound doctor-patient connection.

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INTRODUCTION

Complementary and alternative medicine (CAM) refers to any diagnosis, treatment, or prevention method that supplements conventional care. The utilization CAM has had a significant surge in recent years, gaining substantial prominence in the fields of medicine, economics, and sociology (Bartlett et al., 2013). Homeopathy, a component of CAM, is a medical profession aimed at restoring health to the sick and achieving a rapid, gentle, and lasting remedy. At first, a homeopathic practitioner, also referred as a homeopath, conducts a comprehensive assessment of all the symptoms, including both typical and atypical, associated with a condition. Subsequently, the homeopath administers an individualized remedy or a blend of various remedies, selected for their efficacy in alleviating the particular ailment or illness (Ge et al., 2017; Huang et al., 2020).

As global renaissance has been taking place in homoeopathy, which was an important part of healthcare in the 1800s. This alternative way of treating disease is based on the Principle of Similars and the use of very small amounts (Shaikh et al., 2009).

When a patient present with symptoms, clinical indicators, or a sick state, a homoeopath will utilize a combination of medications that mimics those effects in a healthy person. These homeopathic medications are made by repeatedly diluting and shaking them, and are often administered in potentized versions (Hashempur et al., 2018). Currently, the practical use of homeopathic research in the field of high-altitude (HA) medicine is still in its early stages (Zhang et al., 2018). With increasing attention on alternative therapeutic approaches, several clinical investigations have been carried out in the field of homeopathy (Kass et al., 2020). This chapter provides a concise overview of scientific discoveries and identifies areas that need additional investigation to develop homeopathic treatments for HA-related medical disorders, specifically acute mountain sickness (AMS). The text examines essential homeopathic treatments, such as homeopathic coca, Aloe vera extract, and other possible contenders for addressing HA ailments (Singh et al., 2015).

The Origin and Principals of Homeopathy

A common belief is that the German physician Samuel Christian Hahnemann (1755–1843) was the first to practice homoeopathy. Scottish physician William Cullen (1710–1799) indicated that the bitter taste of Cinchona bark (China officinalis) was an efficient treatment for malaria in herbal document that he came across in 1790. But Hahnemann still wasn't convinced and decided to run some trials anyhow (Kass et al., 2020). He started giving them higher and higher amounts of Cinchona bark powder to see what the long-term effects would be. The effects that were seen were very much like the signs that are usually linked to malaria. He came to the conclusion that Cinchona bark worked because it might give healthy people symptoms similar to periodic fever (Bartlett et al., 2013). He conducted experiments with various other medications in a like fashion, employing him, family members, and acquaintances as test subjects. It was a common occurrence, he noticed, for a treatment to have the opposite effect on healthy people as it did on sick ones (Iqbal et al., 2011). An old term for this procedure was a "proving"; modern homoeopathy uses the term "human pathogenic trial." The "like cures like" notion, or similia similibus curantur, was the cornerstone of homeopathy, according to Hahnemann's exhaustive and painstaking investigation of this phenomenon (Bannuru et al., 2018).

In his alternative theory, Hahnemann postulated that very small doses of drugs, obtained by thorough dilution or trituration, are more effective when given. Thirdly, he postulated that most chronic diseases are actually manifestations of psora or suppressed itching.

In the 1820s, Hahnemann made an unexpected discovery. He found that his remedies were actually made more potent when he combined serial dilution with succussion, which is shaking drugs. He proposed a method of dilution and shaking that he named potentization or dynamization for making medicinally active substances that are normally inactive (Wu et al., 2019). Initially, Hahnemann mainly used these methods to lessen the negative effects of the numerous toxic ingredients he employed in his medications (Brown et al., 2006). On the other hand, he later claimed that the potentization process was responsible for releasing the drugs' vital or "spirit-like" qualities. It was in Hahnemann's latter years that the limit of molecular dilution, Avogadro's number, was found. Back then, homeopaths all over the globe were recording that dilutions lower than Avogadro's number—extremely high potencies—were still producing noticeable therapeutic effects. Some people have decided to treat any evidence of homeopathy's effectiveness as a result of human mistake or a mistaken belief because such claims are highly implausible (Atif et al., 2018).

Therefore, it is just as important for a homeopath to choose the right potency as it is to choose the best treatment for a patient's ailment. The number of diluted solutions and succussions that a drug experiences during its processing determines its effectiveness (Cameron and Chrubasik, 2014). The physical manifestations of an illness, particularly in the body's structures or functions, are the primary targets of low potencies (Sweileh et al., 2009). On the other hand, larger potencies address more profound pathological conditions that impact the emotional and mental aspects of a medical condition, and their effects are more enduring. Low potencies are typically administered in combination with other substances and used to treat long-lasting diseases that primarily affect the physical body (Dubey et al., 2024).

Worldwide Prevalence and Further Scope of Homeopathy

If you're experiencing the acute symptoms of a physical, mental, or other kind of sickness, homoeopathy may be the way to go. A wide variety of substances, including living organisms, minerals, chemicals, and even some plants, are used to make homeopathic treatments (Kumar et al., 2020). The medicinal substances are subjected to a quick shaking process in between each dilution stage and a succession of dilutions to decrease toxicity. Some researchers have found that homeopathic medications are not very likely to have serious side effects. Several researchers argue that the concepts underlying homeopathy are scientifically dubious. However, many governments throughout the world still recognize the validity of homeopathic treatment and medicine, and they even include it in publicly financed healthcare systems (Koley et al., 2015). Consider India: their Ministry of Health incorporates homeopathy, and there are an estimated 300,000 homeopathic practitioners in the country. Nearly half of France's doctors and nurses use homeopathic remedies, sometimes in combination with allopathic prescriptions. The United Kingdom's National Health Service has provided homeopathy since its inception in 1948 (Bowker et al., 2006; Monami et al., 2009).

Even though it was originally practiced in Germany, homeopathy is widely used in India. Homoeopathy is one of the medical modalities that have received formal recognition in India. Several placebo-controlled, randomized trials and laboratory studies have documented unforeseen effects of homeopathic remedies (Harding et al., 2001). Nevertheless, the available information regarding the efficacy of homeopathy for particular clinical problems is scarce and of lower quality compared to studies conducted on allopathic treatment. Additional and enhanced research, devoid of any bias towards or against the system, is necessary (Clegg et al., 2006). Until there is a more comprehensive understanding of homeopathy, physicians should acknowledge the potential of homeopathy and continue to engage in dialogue with patients who choose to utilize it (Jeffcoate et al., 2004).

Homeopathic Remedies for High-altitude Ailments

AMS, High-Altitude Pulmonary Edoema (HAPE), and High-Altitude Cerebral Edoema (HACE) are more serious conditions that can affect climbers who reach elevations above 2500 m, as discussed above. AMS, acute precipitation effect (HAPE), and hemorrhagic shock event (HACE) are mostly caused by an individual's susceptibility as well as high altitude exposure duration and severity (Harding et al., 2000). Various therapeutic systems, such as homeopathy, play a role in preventing and treating medical disorders associated with exposure to harmful substances. A wide range of homeopathic remedies, primarily derived from plants, are being utilized to address diseases related to headaches (Heydari et al., 2010).

Aloe Vera

Succulent aloe vera Linn. Is a member of the Liliaceae family of plants (Fig.1). The plant exhibits a diverse array of biological actions, including as anti-inflammatory, hepatoprotective, immunomodulatory, anti-cancer, anti-allergic, antibacterial, antioxidant, and anti-ulcer properties. The polysaccharides acemamman and glucomannan are what induce these effects. People who live at high altitudes are particularly vulnerable to frostbite, the most severe form of cold injury (Chakrabarti et al., 2002). Frostbite is a serious cold ailment that can damage tissues and even cause amputation of digits. After being exposed to cold, the patient was given aloe vera tincture topically (Q) and orally (200 strength) for seven days (Fuggle et al., 2020). Afterwards, supplementary and supplementary therapy were gradually given. According to the findings, tissue damage was avoided by reestablishing microcirculation, which stopped necrosis in the injured areas. It was also shown that other detrimental effects of being outside in the cold, like losing your appetite and weight, were lessened. As a result, this formulation facilitated tissue regeneration (Driest et al., 2017).

Fig. 1: The succulent herb, Aloe vera.

Applying DIP-1 directly to the skin has been shown to improve the symptoms of UV-induced erythema, blistering and hyperplasia edema that occur after high-altitude exposure (Widatalla et al., 2009). The bioactive molecule prostaglandin E2, which is responsible for the redness and inflammation of skin in both humans and animals exposed to UV radiation, is what gives DIP-1 its protective action (Choi et al., 2012). It also controls the activity of vascular endothelial growth factor (VEGF), a potent substance that increases blood vessel permeability. Research has shown that DIP-1 increases NO signaling in human endothelial cells, which in turn promotes the regrowth of dermal fibroblasts and epidermal keratinocytes (Farzaei et al., 2014). Several human investigations have confirmed that DIP-1 promotes thermogenesis in areas damaged by frostbite and provides protection against skin damage caused by UV radiation at high elevations (Rhodes, 2000).

Arnica montana

Common injuries such as bruises, wounds, rheumatism, and swelling are among the 66 pathological disorders that have traditionally been treated with *Arnica montana* (*A. montana*) in homeopathic medicine. *A. montana* flowers has 0.04% sesquiterpene lactones, which is also known as dihydrohelenalin tiglate (Rutten, 2019).

The antioxidant capabilities of homeopathic *A. montana* (Fig 2) (Arnica 30cH) were demonstrated in a 2013 study by Camargo et al. (2013). Their research demonstrated that the administration of homeopathic *A. montana* resulted in enhanced mitochondrial oxidative stress as well as lipid peroxidation in the liver of rats (Eftekhar et al., 2013).

Calotropis gigantea

In the arid parts of Asia and Africa, one can find the poisonous *Calotropis gigantea* plant. Some common names for this plant include "shallow wort," "giant milkweed," and "crown flower." In India, the plant is referred as "aak," "akauwa," or "arka". The plant can be distinguished by its dense oblong foliage and scentless purplish blooms (Fig. 3). *C. gigantea* is commonly employed in Ayurveda, Chinese, and homeopathic remedies to alleviate symptoms of asthma, coughing, colds, fever, diarrhea, constipation, leprosy, leukoderma, and rheumatism. The homeopathic Materia Medica also lists its use in treating elephantiasis, vomiting, toothaches, and purging. Using an alcoholic extract of *C. gigantea*, DIPAS, an Indian company, makes DIP-2, a skin permeation enhancer (Niempoog et al., 2012).

Fig. 2: *Arnica montana*: a plant that produces yellow-colored flowers.

Fig. 3: *Calotropis gigantea* (© Keystone Foundation under Creative Commons Attribution 4.0 License [CC BY 4.0] https://indiabiodiversity.org/species/show/32452)

This formulation has DIP-1 as one of its active constituents. DIP-2 exhibits a variety of actions, including anti-inflammatory, antioxidant, antibacterial, vasodilatory, and wound healing properties (Al Sulaibi et al., 2020).

Carbo Vegetabilis

The homeopathic medicine carbo vegetabilis is prepared by burning vegetable charcoal with minimal oxygen. This mechanism replicates the energy metabolism observed in tissues with limited oxygen supply, where hydrocarbon molecules combine with oxygen to produce water and carbon dioxide. At high altitudes, when the body's metabolic processes in the tissues are deprived of oxygen, hypoxia occurs (Pourakbari et al., 2019). Homoeopathic treatment utilizing vegetable charcoal, specifically *Carbo vegetabilis* (Carbo veg), is thought to be in accordance with the primary concept of homoeopathy. Patients taken Carbo veg for altitude disease typically experience dyspnea and a strong desire for air circulation, either from natural wind or by using a fan. Frequently, individuals experience lightheadedness and may perceive a sensation of heaviness in the head, eyes, eyelids or other parts of the body. Abdominal bloating, accompanied by excessive gas, is a frequent occurrence (Rogoveanu et al., 2015).

Lycopodium clavatum

Lycopodium clavatum is an easily identifiable plant that is known by several names, including wolf's claw, ground pine, foxtail, clubfoot moss, Sulphur and club moss (Fig. 5). Many European countries, as well as tropical and subtropical regions, are home to this pteridophyte. This medicine is used in homeopathy to treat fevers, constipation, aneurysms, and bronchial and chronic lung disorders (Roos, 2005). It also helps control chronic kidney problems, reduces gastrointestinal inflammation, and facilitates digestion. *Lycopodium clavatum* has been shown in numerous studies to have anti-inflammatory, anti-free radical, anti-cancer, anti-microbe, nerve-protecting, immune-system-modulating, and liver-protecting properties. It can also help relieve chronic fatigue and lethargic moods. Indigenous Americans frequently use *Lycopodium clavatum* spores to alleviate nosebleeds and promote wound healing (Banerjee et al., 2014).

Fig. 5: *Lycopodium clavatum:* a petridophyte growing in the wild (© MikeN under Creative Commons Attribution-NonCommercial 4.0 International [CC BY-NC 4.0] https://www.inaturalist.org/photos/41653704).

Fig. 6: The herbomineral, Shilajit. (This picture is reproduced from Al-Salman et al., (2020) under a CC BY 4.0 - Creative Commons).

Shilajit (*Asphaltum punjabianum*)

The Ayurvedic medicine practiced in India places great emphasis on the use of shilajit, also known as mineral pitch or shilajatu. As a homoeopathic medicine, it is also used by people in Pakistan and India. The Ayurvedic medical tradition of India highly recommends the use of shilajit, mineral pitch, or shilajatu (Kumar et al., 2020). It is also a homeopathic treatment that people from India and Pakistan frequently use. The dehydrated secretion of the herb *Asphaltum punjabinum*, which grows on rocks, is collected to make shilajit (Lohmander et al., 2007). The substance that is characterized as the herbomineral medicine has a color that varies from pale-brown to blackish-brown. Shilajit is supposed to help with metabolism by increasing energy production, balancing anabolism and catabolism, and enhancing the body's capacity to absorb nutrients and flush out impurities (Miller and Clegg, 2011). It also supports the body's synthesis of red blood cells and improves the efficiency of the immune system. Shilajit (Fig 6) has a number of health benefits, including increasing physical strength, prolonging life, revitalizing the body, and having anti-aging qualities (Rothschild et al., 2012).

Others

Along with Aloe vera, the most common medicines suggested for chilblains are Pulsatilla 200 and Agaricus muscarius 200. Approximately 66 percent of patients reported positive outcomes from this therapy. Agaricus causes symptoms that are similar to frostbite and is quite harmful in cold weather (Milgrom, 2006). The symptoms of pulsatilla worsen in the evening and with heat exposure. Neuroendocrine symptoms such as anxiety and depression are frequently found among individuals at high elevations. Homeopathic remedies such as L72 for anxiety, Aconitum and *Argentum nitricum* (for adults) can be utilized to address anxiety and depression linked with HA. These medications are effective due to their broad, non-specific effects rather than targeting individual symptoms (Lotz, 2010).

Conclusions

A variety of treatments are available for many medical conditions and diseases through the alternative medical approach of homeopathy. The available information regarding the efficacy of homeopathy in treating certain clinical diseases, such as pathophysiology’s triggered by HA, is sparse. Hence, further investigation is necessary to have a deeper comprehension of the homeopathic idea and its potential in alleviating diverse health conditions, such as high-altitude illnesses.

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Chapter 32

Homeopathic Veterinary Medicine as an Alternative Treatment in Ruminants

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ABSTRACT

Within the complementary medicines used in the veterinary field, homeopathy is defining new horizons in both the prevention and treatment of diseases, contributing to animal health and well-being. Being a natural medical system that provides comprehensive care for the animal, it offers the possibility of non-invasive intervention for many diseases that affect ruminants. In addition to offering effective treatment, options with almost zero side effects, its low cost and range of options profile it as a fundamental element in sustainable livestock farming. Due to the natural origin of their compounds, they do not generate a negative impact on the environment. Conventional medications tend to accumulate in the body and contaminate products (meat and milk) and the environment, causing significant losses to producers and severe damage to ecosystems. In comparison, homeopathic treatments do not emit pollutants into the environment. This guarantees food production without organoleptic changes and free of medicine, which reduces the incidence of diseases, associated with toxicity due to the accumulation of medicine, contributing to the availability of safe foods.

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INTRODUCTION

Homeopathy, established as a therapeutic method in the 18th century, over the years has moved between two opposing positions. One, in which those who recommend its use and prescription are located due to its proven effectiveness and practically no side effects. Another, more orthodox, integrates those who consider it a pseudoscience of reduced scope. From this perspective, the infinitesimal dilutions used in the preparation of homeopathic medicines significantly reduce the active ingredient used, which is equivalent to providing placebos (Carreras et al., 2014; Aversa et al., 2016; Ochoa, 2018). However, double-blind research in both humans and animals shows the superiority of homeopathy over placebos (Linde et al., 1997; Cucherat et al., 2000; Mathie et al., 2014; Antunes et al., 2023). Regardless of this controversy, the truth is that homeopathy as alternative medicine shows progressive advances to be on par with conventional medicine (Harrer, 2013; Macías-Cortés et al., 2015; Waisse, 2017; Weiermayer et al., 2022).

As in human medicine, the foundations of Veterinary Homeopathy are a series of «Principles» and has the particularity of being a natural medical system, aimed at treating the causes of the disease, rather than the clinical manifestations. It starts from considering that each animal gets sick differently, depending on its physical condition, age and breeding conditions (Principle of individualization). Therefore, rather than having medications that address a particular disease, these are formulated based on specific needs (Principle of the single remedy). Likewise, it seeks comprehensive care, addressing both the therapeutic and semiological aspects (study of signs) of the patient, in order to provide the most suitable treatment. Medicines made from natural extracts of substances of natural origin, whether animal, vegetable or mineral; use harmless quantities in treatments (Principle of minimum-infinitesimal dose). The purpose of the administration of these substances is to stimulate the animal's immune system to boost its natural reaction and healing mechanisms, without generating side effects. This is achieved by potentiating the action of the extracts, by bringing them to the highest degree of division through multiple dilutions (Principle of similarity) (Obando, 2007; Avello et al., 2009; Lucca et al., 2019).

This Hippocratic principle of similarity *similia similibus curantur* "like is cured by like" is fundamental for homeopathy, maintaining that the symptoms caused by a toxic substance can be cured by a remedy prepared based on that same substance, but supplied in low quantities. Among many examples, such is the case of digitalis (present in the leaves of *Digitalis purpurea*). A glycoside-cardiotonic toxin that affects cardiac function by producing acceleration and irregularities in the heart rhythm. In homeopathy, it is used in tinctures of 1/1000 concentration (homeopathic dilution D3) to treat atrial fibrillations and cardiac arrhythmias, with good results (Briones, 2006; Esteva 2006).

The importance that homeopathy has achieved today is not only reflected in its proven effectiveness, but also in the increase in professional training options in different universities around the world, its incorporation into public health systems and the number of researchers who address this theme. In the field of veterinary medicine, the increase in demand for homeopathic medicines has led to regulating their registration, including, among other aspects: the name of homeopathic strains or mother tinctures, physical and chemical microbiological characteristics associated with the nature of the product, dynamization scale, target species and pharmaceutical form, mainly (BOE, 1995; SENASICA, 2012; ICA, 2020).

About Homeopathic Medicines

Homeopathic medicines are prepared from an original substance (strain, mother solution, mother tincture) in a 1:10 ratio, with which subsequent dilutions are prepared. This solution integrates an active component (isolated from fungi, plants, animals or minerals), diluted in distilled water, alcohol, glycerin, inert sucrose globules or a mixture of lactose and starch. From the original substance, the dilutions are prepared using three methods: the Hahnemanian (the most used), the Korsakovian and the fiftieth-simal (Lucca et al., 2019).

In the Hahnemanian method, decimal dilutions (expressed as 1D, 1DH, 1X or 1XH) are prepared by dynamization or vigorous stirring, from one part of the original substance and 9 of the solvent. The centesimals, 1:100 (1C or 1CH) with one part of the substance and 99 of the solvent. Thus, a 6DH medication is prepared by diluting it six times on a decimal scale (1:10) and a 6CH medication is prepared from six centesimal dilutions (1:100) and so on. An important aspect in the preparation is that after each dilution the material goes through a process of succussion or vigorous shaking, to potentiate (invigorate) its effects. In homeopathy, the more diluted and energized the original substance is, the greater its effects. However, it is important to consider that the potentiation of each medication will depend on the degree of development of the disease (acute or chronic) (Etchaberry, 2007; Aversa et al., 2016).

The most abundant medicines in homeopathy are of plant origin. They are prepared with the whole plant, some of its parts or from extractive products. Those of animal origin include the use of whole animals (bees, ants, scorpions, spiders); some of its parts (gastropod shells), organ extracts (liver, kidney) and secretions. Within these, «Nosodes» are prepared from the etiological agents that cause the disease. The base material is diseased tissues, metabolic products of the sick animal (saliva, urine, and blood), contaminated milk, and dust mites, among others. The administration of these preparations has the purpose of activating a specific immunity. While «Biotherapeutics» are prepared from proteins and other substances produced by the living organism. Finally, those of mineral origin are prepared from minerals obtained in their natural form, purified or from standardized processed chemical mixtures (Briones, 2006; Almeida and Coutinho, 2018; Goulart, 2019). Regardless of their origin, these medications generate a primary effect in the animal, with changes associated with the activation of the immune system. While the side effects reflect the process of recovery and improvement in the animal's health (Giordano, 2018).

Advantages of Veterinary Homeopathy in Livestock Production

Advances in veterinary homeopathy are defining new horizons in animal health, by providing alternatives for the prevention and treatment of diseases. In addition to treatments that follow the principle of individualization, in the field of livestock production, «population homeopathy» becomes very relevant. Given that the geographical, climatological and breeding conditions are common to herds or flocks, in this aspect, rather than treating individuals, the treatment is extensive for the entire population. This allows us to address the occurrence of diseases that, due to their very nature, forms of contagion and prevalence, manifest collectively. From these considerations, the administration of medications is widespread, including healthy animals, for whom it will serve as a preventive measure (da Costa et al., 2014; Lucca et al., 2019).

Likewise, the use of homeopathic therapy in livestock farming seeks to introduce natural, less aggressive treatments that benefit the health and well-being of animals. Indirectly it provides benefits to humans, both in the availability and safety of the products. This aspect is of great relevance today, joining efforts to develop sustainable livestock farms with less environmental impact, with the production of drug-free foods (Casali et al., 2011; Goulart, 2019). The advantages of using homeopathic medicines in livestock production include:

a) Economical: They are less expensive than allopathic medicines, with benefits for the producer (Corrêa et al., 2009; Giordano, 2018; Almeida and Coutinho, 2018).

b) Environmentally friendly: Due to their natural origin, they do not emit pollutants, avoiding damage to water and soil, as well as to biocenoses that provide services to the ecosystem (da Costa et al., 2014; Almeida and Coutinho, 2018; Lucca et al. al., 2019; Pinheiro et al., 2021).

c) Easy and non-invasive administration: The administration of oral homeopathic medicines, together with food, mineral salts or water, avoids trauma or restraint procedures associated with the use of injections. Likewise, in water or mineral salts, in outbreaks or cases in which the entire flock must receive prevention or control treatments. In the case of tablets or powders, they can be diluted in water, or sprinkled on the mucous membranes, or nose, so that the animal ingests it by licking it (Corrêa et al., 2009; Almeida and Coutinho, 2018; Lucca et al., 2019).

d) Stress reduction: The energetic power of homeopathic medicine contributes to reducing animal stress and promoting animal well-being. The decrease in stress during breeding increases quality production (da Costa et al., 2014; Lucca et al., 2019).

e) They do not cause adverse effects in the animal: The correct use of the homeopathic medicine avoids therapeutic shock due to intoxication and saturation of the organism, which prevents the development of resistance (Corrêa et al., 2009; da Costa et al., 2014; Asanza et al., 2017).

f) Animal products free of residues: Unlike drugs, homeopathic medicines do not accumulate in the body. This implies the production of food without organoleptic changes, free of medicines, reducing the incidence of diseases associated with toxicity due to the accumulation of medicines in meat and milk (Casali et al., 2011; Almeida and Coutinho, 2018; Lucca et al., 2019; Pinheiro et al., 2021).

Table 1: Homeopathic medicines used in the treatment of bovine mastitis

ORIGIN	MEDICATION	DILUTION
VEGETABLE	*Aconitum napellus*	6CH
	Arnica montana	30CH
	Asa foetida	6DH
	Atropa belladona	30DH, 12CH y 30CH
	Bryonia alba	30DH y 30CH
	Calendula officinalis	30DH
	Conium maculatum	30CH y 200 CH
	Ipecacuanha	30CH
	Phytolacca decandra	12DH, 30DH, 6CH, 12CH, 30CH y 200CH
	Pulsatilla nigricans	6DH, 30DH, 6CH y 30CH
ANIMAL	*Urtica urens*	30DH e 30CH
	Apis melifica	30CH
	Calcarea carbonica	6DH y 6CH
	Carbo animalis	12CH
	Lachesis muta	6DH y 12DH
	Sepia succus	6DH
MINERAL	*Calcarea fluorica*	200CH
	Calcium phosphoricum	6DH
	Hepar sulphur	200DH, 12CH y 30CH
	Kalium muriatium	6DH
	Lac vaccinum	12CH
	Magnesium fluoricum	200DH y 12CH
	Mercurius solubilis	6DH, 6CH y 30CH
	Phosphorus albus	12CH, 30CH y 200CH
	Silicea terra	6DH, 30DH, 6CH, 12CH y 30CH
	Sulphur	6DH, 30DH y 12CH

Source: Own elaboration based on the information reported by Almeida and Coutinho (2018).

Health Problems in Ruminants

At a global level, animal production faces the challenge of preventing, containing and eliminating animal diseases, due to the impacts they generate. In addition to the effects on production, productivity, profitability and food security, the implications that these diseases have for human health stand out (FAO, 2009). According to the World Organization for Animal Health, 60% of the pathogens that affect human health originate in domestic and wild animals. 75% of emerging diseases that affect human health have their origin in animals (WOAH, 2018).

The problem is complex, especially if one considers that at the human-animal-environment interface, the number of diseases tends to increase. In addition to the increase in zoonoses and the impact on food security due to the loss of sick animals, the scale and intensity of diseases is varying (FAO, 2024). In livestock, diseases associated with stress are increasingly common, mainly in intensive systems. The increase in the prevalence and distribution of originally endemic diseases and the growing resistance to antimicrobials represent a serious threat (WOAH, 2018; Weiermayer et al., 2022).

In ruminants integrated into livestock production, various diseases are generating negative effects. In cattle, the most notable are bovine brucellosis, foot-and-mouth disease, tuberculosis, contagious nodular dermatitis, bovine viral diarrhea, vesicular stomatitis, Rift Valley fever, enzootic bovine leukosis, contagious bovine pleuropneumonia, bovine trichomoniasis, bovine papillomatosis and infectious bovine rhinotracheitis. In small ruminants (sheep and goats), foot and mouth disease, scrapie, «peste des petits ruminants», vesicular stomatitis, Rift Valley fever, brucellosis, smallpox and contagious agalactia, mainly. Added to these diseases are reproductive disorders and parasitosis, caused by the action of endo- and ectoparasites (Aversa et al., 2016; MAPA, 2021; Ojeda et al., 2022).

Efficacy of Homeopathic Therapy in Ruminants

Given the global health challenges faced by livestock production, various studies carried out demonstrate the effectiveness of homeopathic therapy in the prevention and care of diseases in ruminants of livestock importance. The work carried out by Doehring and Sundrum (Doehring and Sundrum, 2016) exemplifies this diversity. From the review of works published from 1981-2014, they identified 4,448 scientific articles and 50 doctoral theses. They include individual trials, and mostly population trials. Methodologies vary with unblinded, single-blind, double-blind and mostly randomized controlled trials (RCTs), 34% used single medications, 56% combined homeopathic therapies and the remaining 10%, it was not possible to integrate them into this differentiation. The origin of the ingredients is variable (animal, vegetable, mineral, nosodes). In individual therapies (8%), the route of administration included oral, subcutaneous or topical (aerosols and cream). In the population, the route was always oral, 85% of the studies were carried out with dairy cows, with preventive and care treatments. Among the preventives, postpartum disorder and mastitis stand out. In care, acute or subclinical mastitis, reproductive disorders (retained placenta and endometriosis), mainly.

Table 2: Efficacy of homeopathic therapies in cattle

Animal Diagnosis Country	Treatment	Results	References
Holstein cows with cystic ovariopathy/50 days postpartum (Brazil)	Comparative Homeopathic (H): *Thuya occidentalis* 6CH, *Apis mellifera* 6CH and *Oophorinum* 6CH Allopathic (A): Ovsynch® Control (C): No treatment	Return to estrus rate C=100%; H=93.5%; A=11.11%; Pregnancy rate after the 1st Artificial Insemination (AI) C=0%; H=62.6%; A=22.22% Pregnancy rate after the 2nd AI C=31.82%; H=87.5%; A=55.56% Cystic persistence rate C=68.18%; H=12.5%; A=44.44% Number of services per conception C=3.36; H=1.40; A=2.14	(Rangel et al., 2003)
Crossbred cows with true anestrus (India)	Homeopathic treatment *Calcarea phosphorica* 30C *Alestris farinosa* 30C *Pulsatilla* 30C *Aurum muriaticum natronatum* 30C *Sepia* 30C *Phosphorus* 30C	100% of cows in anestrus presented estrus with an interval of 27.5±5.3 days All animals conceived with a rate of 54.5% with 1.83 services per conception Increase in serum estradiol concentration (20.88 pg/mL) compared to pretreatment (11.71) and control (10.43).	(Rajkumar et al., 2006)
Holstein, Jersey and Brown Swiss calves Diarrhea prevention (Honduras)	Homeopathic (H): Milk replacer added with homeopathic medicine Factor Infecciones® Control (C): No treatment	Prevalence of minor diarrhea in H calves (38.89%) compared to C (61.11%)	(Asanza et al., 2017)
Holstein cows. Early breast inflammation (France)	Homeopathic medicine Dolisovet® (*Belladona* 1DH, *Calendula* MT, *Equinacea* 1DH, *Dulcamara* 1CH)	Decrease in electrical conductivity, measured in the automated milking system Improvements in milk quality Disappearance of inflammation	(Aubry et al., 2013)
Cow with recurrent mastitis (Brazil)	Individual treatment Start: *Hepar Sulphur* 18CH y *Belladona* 18 CH Change 1: Milk nosode and *Pulsatilla* 18 CH Change 2: *Pulsatilla* y *Arnica* 18 CH	Total recovery from recurrent mastitis Increase in daily milk production	(Kriguer et al., 2015)
Swiss cows drying Mastitis prevention (Swiss)	Comparative Homeopathic (H): Biotherapeutic 10CH Allopathic (A): Orbeseal ® Control (C): No treatment	Incidence of H<A<C mastitis Normal milk secretion in H	(Klocke et al., 2010)
Lactating dairy cows Mild and moderate mastitis (Kazakhstan)	Homeopathic (H): Homeopathic preparation (Kazakhstan Agrotechnical University) Control (C): No treatment	Faster recovery from mastitis in H Higher concentration of γ-globulins in H (5.16%) *vs* 3.27% in C Increased calcium and phosphorus in blood serum H (12.2%) *vs* C (9.4%)	(Kukeyeva et al., 2023)
Holstein cows. Antibiotic-resistant mastitis (Brazil)	Comparative Homeopathic (H): Homeopathic complex 20g/d/60d Placebo (P): $CaCO_3$ 20g/d/60d	Better results in H than in C, in: Somatic cell count (cell/mL) Milk production (kg/d) Milk components (% protein, fat, lactose and total solids) Serum levels of lactic acid, glucose, ammonium and cortisol	(Antunes et al., 2023)

Crossbred cattle with massive flat and pedunculated papillomatosis (Brazil)	Homeopathic (H): *Thuya occidentalis* 30CH Phytotherapeutic (Ph): Mother tincture of *Thuya occidentalis* Control (C): No treatment	Higher percentage of animals recovered in H (61.1%). Cure percentage, Ph 50% and C 16.66% by spontaneous regression. Greater effectiveness in homeopathic treatment	(Siqueira et al., 2014)
Holstein cows with papillomatosis (Brazil)	Homeopathic treatment *Thuya* 18 CH	Progressive loss of warts post-treatment Significant reduction in warts	(Kriguer et al., 2015)
Cows with tick infestation (Cuba)	Comparative Homeopathic (H): *Ledum palustre* 200CH, *Psorinum* 200CH Allopathic (A): Esteladón 300	High effectiveness of H (92%) vs A (87%), with a lower cost equivalent to 1/3.	(López et al., 2008)
Holstein X Zebu Bulls Fascioliasis (Cuba)	Homeopathic treatment Nosode (30CH) of larvae and adults of *Fasciola hepatica*	Reduction in the proportion of parasites from 47.5% to 10%	(Cabezas and Fernández, 2008)
Dual purpose mixed breed cattle Gastrointestinal nematodes (Ecuador)	Comparative Homeopathic (H): *Artemisa cina* (H1), *Sulphur* (H2), *Arsenicum album* (H3) Allopathic (A): Fenbendazole 10% Control (C): No treatment	100% Egg reduction percentage (%ER) in H A: 88.5% in the fourth week, with a decrease in the 7th-9th week from 42.68 to 5.32%. H: Greater effectiveness in H1 (93.62%) followed by H2 (84.57%) H1 the most effective	(Pacheco-Merelo et al., 2023)

Source: Own elaboration, based on the references that are registered.

Table 3: Efficacy of homeopathic therapies in sheep and goats.

Animal Diagnosis Country	Treatment	Results	References
Pregnant sheep and lambs Supplementation (Brazil)	Homeopathic (H): *Natrum muriaticum* 10-60CH, *Calcium carbonicum* 10-30CH, *Silicea terra* 10-400CH and *Hypotalamo* 10-30CH Control (C): No treatment	H: Total protein and higher globulin in treated sheep and lambs Serum albumin without differences in H and C ewes, higher in H lambs	(Dias et al., 2021)
Goats infected with *Mycoplasma agalactiae* cause: contagious agalactia, mastitis and arthritis (Brazil)	Comparative Homeopathic (H): Biotherapeutic prepared with *M. agalactiae* from milk Allopathic (A): Tilosina y oxitetraciclina Control (C): No treatment	H: Clinical cure in all animals between 7-49 days. No abortions A: Reduction of signs, but not all animals cured. 12% with agalactia, 28% with mastitis, 25% with arthritis. 12,5% abortions C: Persistence of diseases, development of keratoconjunctivitis in one animal and death of another due to chronic disease. 28.6% abortions	(Souza et al., 2013)
Suffolk Lambs with *Haemonchus contortus* Hemoncosis (Mexico)	Comparative Homeopathic (H): *Artemisa cina* 30CH, 1mL/5 kg body weight Allopathic (A): (A1) Albendazole (50mg/mL) 7.5mg/kg body weight; (A2) Levamisole 7.5mg/kg body weight Control (C): No treatment	IEH (Inhibition of egg hatching): 100% in H, 93% in A1. ILM (Inhibition of larval migration): 65,7% in H, 0% in A2 (100% lethality), in C 92,0 ±12,4% FAMACHA index (at 28 days): (H) 2,0 ± 0,31, (A1) 1,0 ± 0,22, (C) 3,0 ± 0,71	(Higuera-Piedrahita et al., 2020)
Parasitized sheep and goats (Spain)	Comparative Homeopathic (H): Yvercit® Allopathic (A): (A1) Levamisole, (A2) Ivermectin, (A3) Fenbendazole (A3)	H: 90% efficiency A1: 90% effectiveness A2: 0% efficacy/15d post-treatment (anthelmintic resistance) A3: 60% efficiency	(Oros, 2018)
Suffolk sheep with gastrointestinal parasites (Mexico)	Comparative Homeopathic (H): Parafil® (*Allium sativa* 30C, *Sulphur* 30 C y *Stanum metalicum* 6C) Allopathic (A): Ivermectina Control (C): No treatment	H: Greater weight gain (3,7), lower FAMACHA index (1.93), eggs per gram of feces (EPG) 564±462 A: Less weight gain (2.5), FAMACHA 2.95 and EPG 1027±462 C: FEC 3037±462	(Luna et al., 2017)

Source: Own elaboration, based on the references that are registered.

Cattle

The main problem in dairy cattle during the production period is mastitis. Mastitis is the most important cause of losses, due to the decrease in milk production, the disposal of milk contaminated with antibiotics and the costs of premature culling of cows of high genetic quality with high milk production potential. Its etiology is multifactorial (infectious agents, genetics, nutrition and condition of the animal, facilities, management, milking hygiene), so its prevention and treatment represents a great challenge, especially due to microbial resistance associated with the indiscriminate use of antibiotics (Almeida and Coutinho, 2018). Table 1 lists the homeopathic medicines used in the treatment of bovine mastitis.

As examples, in the study carried out with dairy cows in India by Varshney and Naresh (Varshney and Naresh, 2005) compared the effectiveness of allopathic and homeopathic medications in the treatment of mastitis. The homeopathic complex applied (Healwell VT-6) was a combination of *Phytolacca*, *Calcarea fluorica*, *Silica*, *Belladona*, *Bryonia*, *Arnica*, *Conium* and *Ipecacuanha*. Allopathic treatment included a combination of Novobiocin sodium and procaine penicillin G. Although the average recovery period was shorter in allopathic treatment (4,5 days) than homeopathic treatment (7,7), the efficacy and costs of treatment were more satisfactory in homeopathic treatment; 86.6% of cows responded positively, with a cost of 21.4 rupees (€0.39; US$0.47) compared to allopathic treatment, with 59.2% efficacy and a cost of 149.20 rupees (€2.69; US$3.28).

For their part, Ribeiro et al. (Ribeiro et al., 2007) carried out a study in Brazil, with 32 cows with subclinical mastitis confirmed with the California Mastitis Test (CMT), using a homeopathic complex for treatment, made up of four groups based on their pathogenic action. Group A, included medicines that increase milk production, *Phytolacca* D30, *Urtica urens* D3 and *Asa foetida* D6. Group B, three medicines used against subclinical mastitis, *Phytolacca* D12, *Magnesium fluoricum* D12 and *Kalium muriatium* D6. Group C, other medicines used for subclinical mastitis, *Hepar sulfur* D200, *Magnesium fluoricum* D200, *Streptococcinum* D200 and *Stafilococcinum* D200. Group D, anti-inflammatory medications, *Urtica urens* D30, *Lachesis* D12 and *Pulsatilla* D30. The homeopathic complex was prepared on decimal scales from the mother tinctures, with a mixture of the medications from each group, administered in the diet at a dose of 300g/day. The start of follow-up (day 0) started from the number of cases detected before treatment and continued at 30, 60 and 90 days. The 44.5% of CMT positive cases decreased to 28.1%, 13.3% and 3.9% at 30, 60 and 90 days, respectively. These results showed the effectiveness of the treatment and a statistically significant reduction in the number of cases.

Although mastitis is the main problem in cattle farming, other diseases and conditions affect cattle. Among these, infestations by *Rhipicephalus microplus* ticks. In addition to damaging the health of animals, directly through blood consumption, they can also be transmitters of bovine babesiosis. This generates important impacts because the conventional control measures used based on chemical products contaminate the environment and the products (milk and meat), in addition, as in the case of antibiotics, there are reports of resistance and multiple resistance to Ixodicides. Likewise, satisfactory results are reported from homeopathic treatments to treat bovine papillomatosis, diarrhea, different reproductive problems (uterine prolapse, cystic ovariopathies, induction of estrus, reduction of the puerperal period, improvements in the pregnancy rate, infertility); activation of ruminal fermentation, hepatic (liver modulation and hepatoprotection), among others (López et al., 2008; da Costa et al., 2014; Pinheiro et al., 2021). Table 2, compiles some results that show the effectiveness of homeopathic treatments in cattle, in the prophylaxis or care of ailments.

Sheep and Goats

Although the studies carried out in small ruminants are not so numerous, they do coincide in addressing the diseases that most affect health and productivity. Most of them address gastrointestinal parasitosis, which is of great relevance due to the impact they have on the sheep and goat production chain. The main effects are associated with losses due to delayed growth, low weight gain, compromised reproductive performance, low fertility, and drop in milk production, among others. The most frequent and recurrent are those caused by nematodes, highlighting *Haemonchus contortus*, as well as *Trichostrongilus colubriformis*, *Oesophagostomum columbianum*, *Strongyloides papillosus* and *Trichuris ovis*. The resistance to anthelmintics manifested in flocks around the world supports the search for new alternatives as part of integrated control strategies, where homeopathy plays a relevant role (Crook et al., 2016; Higuera-Piedrahita et al., 2020; Ojeda et al., 2022).

Studies on diseases and illnesses in small ruminants are scarce. Table 3 includes some examples of studies carried out with these species, which show the effectiveness of homeopathic medicine.

Conclusion

In the current conditions in which the search for sustainability in production is imperative, in order to guarantee the availability and safety of food, as well as the preservation of the environment; Homeopathic medicine represents an alternative to ensure the health and well-being of ruminants of livestock importance. Its low costs, ease of non-invasive application, its proven effectiveness, the non-toxicity of livestock products and the environment, appear as a condition of possibility to improve competitiveness and productivity, strengthening the transition towards sustainable livestock farming. Currently, these aspects are of great relevance, especially due to the increase in demand for proteins of animal origin. Unlike conventional medicine, which, due to accumulation in the body, contaminates meat and milk intended for human consumption, homeopathy offers the production of foods free of contaminants. The possibility of carrying out extensive treatments in livestock production units serves a dual purpose because, in addition to addressing the health problems manifested in some animals in the herd or flock, it serves as a preventive measure for healthy animals. This reduces the incidence of sick animals, minimizes treatment costs and reduces economic losses for producers.

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Chapter 33

Mexican Knowledge of Medicinal Macrofungi

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ABSTRACT

In this chapter, the knowledge of medicinal macrofungi in Mexico is discussed from pre-Hispanic times to the present day. Earliest records for the use of macrofungi in healing rituals and/or as medicine to cure some diseases date from the 15th-16th century. This traditional knowledge have passed from generation to generation, and in many cases, it is still used in some Mexican regions. The use of bioactive macrofungi extracts in oriental countries is reviewed due to the great tradition in taking advantage of these compounds to cure diseases and because many of these species have been introduced to the Mexican market. Finally, the scientific research developed in Mexico is analyzed regarding the biological activity of fungal extracts obtained from local species. Some of the extracts had antioxidant, immunostimulant, antimicrobial, antiparasitic and cytotoxic effects, some of them also showed reduction in cholesterol and triglyceride levels, drop in weight gain, increment in the intestinal microbiota and inhibition of cancer cells proliferation. Given the great fungal diversity in Mexico and the extraordinary traditional knowledge of native people, it is fundamental that scientific research continue to be performed by multidisciplinary groups that include those who carry the ancestral wisdom.

KEYWORDS		
Medicinal mushrooms, Traditional knowledge, Mexico, Biocompounds.	Received: 17-June-2024 Revised: 13-July-2024 Accepted: 17-August-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

This chapter summarizes the available knowledge of medicinal fungi in Mexico, from early written sources from the pre-Hispanic period, to current research on bioactive compounds. Expertise from indigenous people included descriptions of mushroom species with geographical location, the diseases treated and the practices that have transcended time and are still in use in some communities. It also compiles bioactive properties found in fungi collected around the world and the medicinal fungal species that have been introduced to the Mexican market. Finally, it outlines researches performed in Mexico that have studied the bioactive properties of local species and their potential use to improve population's health.

Mushrooms in Traditional Mexican Medicine

Since its origins, humans have made use of the natural resources that are around them and Mexico, being a biologically megadiverse country with great cultural diversity with more than 68 indigenous peoples in its territory, has a vast knowledge of plants, animals, and mushrooms, mainly edible, medicinal and those used in ceremonies or rituals (Guzmán, 2008).

Most of our knowledge about pre-Hispanic uses for mushrooms came from sources like codex, chronicles and documents, both pre-Hispanic and colonial. In these sources, it has been documented the knowledge that the inhabitants of Mesoamerica had about sacred, edible, and medicinal mushrooms, examples are the Codex Vindobonensis, Magliabecchiano, Lienzo de Zacatepec, and Crónica Mexicana, among many others (Hernández-Santiago et al., 2017).

From the occidental perspective, the study of the mycological knowledge and practices of indigenous peoples dated back to early work by Fernando de Alva Ixtlilxóchitl and Fernando de Alvarado Tezozómoc or Chimalpain, heirs of the indigenous nobility, who perceived the importance of codex and similar documents and tried to understand them with the help of elder people (Pérez-Chávez et al., 2019).

Fray Bernardino de Sahagún in La Historia general de las cosas de Nueva España (Florentine Codex), gathers the knowledge and uses of natural resources of pre-Hispanic peoples. In this work, at least six species of edible mushrooms are described in Nahuatl, considering their morphology, growth form and ecology. In this book, *teonanácatl* is mentioned for the first time, and the representation of this mushroom, which corresponds to a species of the genus *Psilocybe*, appears as a sacred mushroom with hallucinogenic, intoxicating and divinatory properties, which was also used to relieve cold fever and gout (Pérez-Chávez et al., 2019).

In Mexico, the use of neurotropic mushrooms of the genus *Psilocybe* in ceremonies and rituals is well known, mainly in Oaxaca. Shamans or healers ingest mushrooms together with patients, to communicate with their gods, and thus know how to help them with their sufferings such as anxiety and toothache (Guzmán, 2011).

Mushrooms are considered valuable resources in traditional medicine, which may be defined as "the set of knowledge, beliefs, practices and resources from popular culture, which the country's population makes use of to empirically solve some of their health problems." (Lozoya, 1989).

The majority of records on the traditional use of medicinal mushrooms have been documented in Nahua, Mayan and Hñähñú communities associated with temperate forests in central and southern Mexico. Little is known about these therapeutic resources in tropical and arid areas of the north of country. In Mexico, more than 350 species of fungi and lichens with some medicinal uses have been recorded. Not all of those species are used neither by indigenous peoples or mestizo communities, but about 150 health conditions are referred to be treated with mushrooms, such as: digestive, respiratory, circulatory, musculoskeletal and nervous systems diseases, skin, nose and eye conditions, as well as diseases related to "the evil eye", scare and "empacho" (Bautista-González and Herrera-Campos, 2019).

Among the most important mushrooms, the "cuitlacoche", *Mycosarcoma maydis* (DC.) Bref., stands out for its flavor and medicinal properties. It is used to treat more than 50 **healthconditions** in different indigenous peoples and mestizo communities, mainly in the central and south regions. When fresh, it is cooked in a broth to relieve colic, diarrhea, indigestion, hangover, inflammation and stomach pain. Dehydrated spores are used to treat skin burns, bleeding wounds, skin rashes, chafing, cold sores, athlete's foot, heal the navel of newborns and stop nosebleeds. In a similar way, the gleba (mass of spores) of mature sporocarps of *Astraeus, Bovista, Calvatia, Geastrum, Lycoperdon,* and *Tulostoma species,* is used to treat multiple skin conditions (Bautista-González and Moreno-Fuentes, 2014).

In the southern state of Chiapas, Ruan-Soto et al. (2021) documented the use of 19 species for medical purposes. Six correspond to species found in highlands (genera *Calvatia*, *Geastrum* and *Lycoperdon*), 12 species in lowlands, and one in both regions (*Lycoperdon perlatum*). In general, they are used as antihemorrhagic and antiseptic in superficial skin wounds; other species such as *Phaeoclavulina cokeri*, *P. zippelii* and *Ramariopsis* sp. are used to remove warts (Ruan-Soto et al., 2021).

Felger and Moser (1974), recorded the use of several medicinal mushrooms by the Seris in Sonora, such as *Battarreoides diguetii* (Pat. and Har.) R. Heim and T. Herrera, *Podaxis pistillaris* (L.) Fr., and *Tulostoma* sp., all used for healing burns and cuts. In a recent study with Yuman peoples from Baja California (Kiliwa, Kumiai, Paipai and Cucapá), the use of 14 species of fungi (mainly gasteroids) was documented, those are used to treat skin problems, as well as food and for recreational purposes (Bautista-González et al., 2022).

It should be noted that some toxic mushrooms have also been used for healing purposes, for example, *Amanita muscaria* (L.) Lam. which is used as a diuretic and purgative (Guzmán, 2008), to treat dysentery (Montoya et al., 2002) and mitigate stomach pain and headache (Bautista-González and Moreno-Fuentes, 2014).

In different indigenous communities of Mexico, since pre-Hispanic times the conception of edible mushrooms as beneficial foods for health persists. They are considered a food that provides energy, proteins, vitamins and fiber, being tastier and more nutritious than meat (Bautista- González and Moreno-Fuentes, 2014).

Scientific Knowledge of Medicinal Fungi in the World

Although the medicinal knowledge of mushrooms is ancestral, it was not until the 20th century, when scientific interest began in knowing the active principles and biomolecules that **confer** these characteristics to mushrooms consumed directly and to the extracts obtained from them. Traditional knowledge about the medicinal properties of mushrooms is very broad in ancient cultures such as China and due to this tradition of consumption and use of mushrooms as medicines, western scientific communities have turned their attention to the research of their bioactive compounds. It has been proven that mushrooms have anti-cancer, antibiotic (bacteria, viruses and fungi), anti-parasitic, antioxidant, anti-thrombotic, anti-diabetic functional properties, reduce cholesterol and hypertension, and are immunomodulatory, anti-inflammatory, hepatoprotective, anti-allergic and help the body to overcome the effects of chemotherapies (Pérez-Armendariz et al., 2010; Patel et al., 2012; Martínez-Carrera et al., 2016; Chugh et al., 2022).

Currently, bioactive compounds have been discovered in the United States, Japan and the European Union and these products have been patented and approved. The bioactive fungal compounds modify biological responses by activating, stimulating or reinforcing various body systems, for example, the immune and the endocrine systems (Pérez et al., 2010; Martínez-Carrera et al., 2016). They help the metabolism of proteins, lipids and carbohydrates, influence the intestinal flora and induce the expression, activation or modulation of specific genes and metabolic pathways (Martínez-Carrera et al., 2016).

The functional properties of fungi are found in the mycelium and sporocarps, and as a result of their secondary metabolism, they are also found in the culture medium where they develop (Martínez-Carrera et al., 2016).

Tables 1 and 2 include some of the most popular active ingredients that have been identified and that are being further studied to precisely establish their application, dosage and mode of action. These are, for example, high molecular weight polysaccharides (alpha glucans, beta glucans, heteroglycans, proteoglycans, proteoheteroglycans and polysaccharopeptides), proteins, fats, ashes, glycosides, alkaloids, volatile oils, tocopherols, phenols, flavonoids, carotenoids, folates, enzymes, organic acids, micronutrients, antioxidants (glycoproteins, triterpenoids, flavonoids, ergosterol) and unsaturated fatty acids. Polysaccharides are the fungal compounds with the most powerful anticancer activity. In addition, they reduce cholesterol, triglycerides and blood sugar and stimulate the immune system. Of this group, the most important are beta glucans (Pérez et al., 2010; Patel and Goyal, 2012; Chugh et al., 2022).

Table 1: Bioactive compounds present in mushrooms and their medicinal functions that have been scientifically proven in the world. Sources: (Rogers, 2011); (Roncero, 2015); (Chugh et al., 2022)

Bioactive compound	Medicinal activity proven *in vivo/in vitro*
Aplanoxidic acid	Antiviral against influenza type A
Coumaric acid, p-coumaric acid, Tr-cinnamic acid, Vanillic acid, ρ-hydroxybenzoic acid	Protectors against oxidative stress, against disorders associated with aging
Ganoderic acid	Antitumor against HIV-1
Beta-carotenes,Beta tocopherol	Antioxidants
Catechol	Protectors against oxidative stress, against disorders associated with aging
Phenolic compounds	High antioxidant capacity
Ergothioneine	Excellent antioxidant
Erigin	Antifungal
Schizophyllan	Helps in the treatment of gastric and cervical cancer
Flavoglaucine	Excellent lipid antioxidant capacity
Ganodermadiol	Antiviral against influenza type A
Ganopoly	Immunostimulant and hypoglycemic activity. Its high efficiency in reducing the effects of chemotherapies has been demonstrated.
Glycoprotein FIPs	Immunostimulant activity
Grifolan	Increases insulin production, improves the immune response, fungicide, reduces inflammation of the mucous membranes of the respiratory tract, anti-cancer
Lectins	Immunomodulatory, antiproliferative and antitumor activity, hypoglycemic, anti-inflammatory.
LEM	Immunomodulator
Lentinan	Antitumor, immunomodulator, helps in the treatment of HIV, helps with the side effects of chemotherapies and the recovery of patients, reduces inflammation and intestinal ulcers, antioxidant.
Licidadiol	Antiviral against influenza type A
Lignins	Antivirals, inhibit the development of HIV
Lovastatin	Lowers cholesterol levels
Pleuran	Anticarcinogenic, immune system stimulant, protects the respiratory tract, reduces cholesterol and LDH levels, antioxidant, antiallergic.
Pleurosthrin	Antifungal.
Peptide polysaccharide (PSP)	Important antitumor and immunomodulatory agents
Peptide polysaccharide GPP	Immunostimulant activity
Polysaccharide-K (PSK, crestine)	Important antitumor and immunomodulatory agents
Selenium	Antioxidant, helps repair DNA damage
Tyrosine	Protectors against oxidative stress, against disorders associated with aging
Triterpenes	More than 120 different ones are antivirals active against HIV and herpes type I, inhibit cholesterol synthesis, reduce the risk of atherosclerosis, stimulators of the immune system, antitumor activity.

Medicinal Fungi Currently Introduced in Mexico

Since the end of the 20th century, the consumption and knowledge of mushrooms and their derivatives have become very popular around the world, and Mexico is no exception to this great flow of information. With the introduction of nutraceutical foods, adaptogenic mushrooms and the popularization of superfoods, many products containing mushrooms and their derivatives are being introduced into the market, which are sold in various presentations, such as food supplements, aqueous or alcoholic extracts, purified extracts, capsules, tablets and drinks (Roncero, 2015). Electronic commerce is making the introduction of these products into the Mexican market much easier and it is possible to acquire any mushroom and its derivatives from anywhere in the world. The countries that export the largest volumes of mushrooms to Mexico are the United States, Spain and Italy (Secretaría de Economía, 2023) and it is increasingly common to find them in local naturopathic stores and pharmacies. Table 2 includes the mushrooms that are most frequently available in Mexico through e-commerce.

Table 2: Mushrooms sold in Mexico through e-commerce, in health food stores and pharmacies in the form of pills, capsules, flour and as ingredients in food supplements.

	Species	Active ingredients	Applications	References
1	*Agaricus blazei* Murrill	Agartine, proteroglycans, ergosterol, beta glucans, blazein	Immunomodulatory, anticancer, antimutagenic, antioxidant, antibacterial, anti-inflammatory, cytotoxic in myeloma cells. Inhibits the proliferation of prostate, lung and stomach cancer cells. Reduces xenograft tumors. Agaritine has inhibitory action against monocytic lymphoma of leukemia. The extracts are used against leukemia. Aqueous extracts may be beneficial in treating allergic reactions. It improves the quality of life of patients with chemotherapy, increases the immune response by inducing the production of interleukin-12 and interferon gamma.	Choi et al., 2006; Yuminamochi et al., 2007; Itoh et al., 2008; Patel and Goyal, 2012; Tangen et al., 2017
2	*Cordyceps militaris* (L.) Link	Cordlan, cordycepin. Mannitol, trehalose, polyunsaturated fatty acids, delta tocopherol, oxalic, citric, fumaric, p-hydroxybenzoic and cinnamic acids have been found in its extracts. b-(1R3)-D-glucan	It showed effectiveness against several types of cancer: prostate, colon, hepatoma, breast, lung, uterine, cervical, it is an activator of the immune system and acts against leukemia. It presents strong antioxidant, antibacterial, antifungal and anti-inflammatory activity.	Patel and Goyal, 2012; Filipa et al., 2013; Reis et al., 2013; Smiderle et al., 2014
3	*Flammulina velutipes* (Curtis) Singer.	FIP-five protein, flamulina velutipes peptidoglycan, β1,3-D-glucan, flammin,velina, velutin, lovastatin	FIP-five presents immunomodulatory activity, activates T lymphocytes, and antitumor activity in liver cancer. Flamulin demonstrated antitumor activity. A hemagglutinin inhibits the proliferation of L1210 leukemia cells. Aqueous extracts demonstrated activity against breast cancer. It has anti-cancer, anti-inflammatory activity. Stops atherosclerosis, reduces cholesterol levels, inhibits thrombosis, anti-aging, restores neurotransmitters associated with memory and learning, helps in cases of Parkinson's and Alzheimer's.	Patel and Goyal, 2012; Tang et al., 2016; Chugh et al., 2022; Liuzi et al., 2023
4	*Ganoderma lucidum* (Curtis) P. Karst.	Ac. **g**anoderic T, LZ-D-4; LZ-D; dichloromethane, triterpenoids and their derivatives such as ganoderal, ac. ganodermic, lucidone, ganodermanondiol, ganodermanontriol, lucidon. Adenosine, FIP-glu.	It has effects against gastric cancer, ac. **G**anoderic**o** produced inhibition of tumor invasion and metastasis. It is a promising agent against colon cancer. LZ-D showed positive results for the control of lymphocytic leukemia. Dichloromethane has action against human papilloma oncoprotein and cervical squamous cell carcinoma. Lowers cholesterol, blood pressure and prevents cardiovascular diseases. Antiallergic, cytotoxic, neuroprotective, anti-inflammatory. Antibacterial, antifungal, antimalaria, antiviral.	Patel and Goyal, 2012; Chugh et al., 2022; Sułkowska-Ziaja et al., 2023
5	*Grifola frondosa* (Dicks.) Gray	Beta glucano, grifola frondosa lectina,	It produces vitality, improves the action of anti-cancer medications, and its activity has been demonstrated against gastric carcinoma. Controls the growth of tumors. Powerful immunomodulator. Lowers cholesterol, blood pressure and prevents cardiovascular diseases. Anti-inflammatory and controls atherosclerosis, hypoglycemic, hypotensive.	Kodama et al., 2002; Patel and Goyal, 2012; Chugh et al., 2022
6	*Hericium erinaceus* (Bull.) Pers.	Erinacins, hericenones. Polysaccharides such as: **X**ylans, glucoxylans, heteroxyloglucans, galatoxyloglucans.	Antitumor and immunomodulatory effects. It stimulates the growth of nervous factors, acting in the conservation, regeneration and survival of neurons. Positive effects in cases of dementia, Parkinson's and Alzheimer's. Antihyperglycemic and antihypercholesterolemic. Anti-aging and antioxidant.	Patel and Goyal, 2012; Thongbai et al., 2015; Chugh et al., 2022; Yanshree et al., 2022

7	*Inonotus obliquus* (Fr.) Pilat	Sclerotin. Contains antioxidants (superoxide dismutase, melanin); triterpenes (lupeol, betulin, inotodiol); polyphenols, sterols, polysaccharides. Ac, betulinic.	Extracts in hot water and ethanol induced apoptosis in colon cancer cells, presented antiproliferative properties in melanoma cells, sclerotin presented antitumor activity. Antioxidants, anti-allergy, anti-aging, anti-inflammatory.	Patel and Goyal, 2012; Thongbai et al., 2015; Chugh et al., 2022; Yanshree et al., 2022
8	*Lentinula edodes* (Berk.) Pegler	Lentin, emitanin, heteromannans, heterogalactans.	Suppresses the proliferation of leukemia. Lowers blood pressure and prevents cardiovascular diseases. Immune system modulator, antitumor, antiviral, antimicrobial, cholesterol regulator, anti-**a**therosclerotic, antidiabetic, antioxidant regulator of homocysteine metabolism.	Patel and Goyal, 2012; Chugh et al., 2022; Ponnusamy et al., 2022
9	*Trametes versicolor* (L.) Lloyd	Kresina, musarin, tramesan	Activity has been demonstrated against several types of cancer including prostate, gastric, lung, leukemia, lymphoma, breast, liver and melanoma	Patel and Goyal, 2012; Scarpari et al., 2017; Chugh et al., 2022; He et al., 2022; Lowenthal et al., 2023

Biological Activity of Macroscopic Fungi Collected in Mexico

In Mexico there are several research groups interested in using mushroom extracts to solve some public health problems. Table 3, shows recent studies that assessed the biological activity of some Basidiomycota metabolites collected in 10 Mexican states. They used different extracts to perform *in vitro* or *in vivo* assays and found that some fungal strains had antioxidant, immunostimulant, antimicrobial, antiparasitic and cytotoxic effects. They also showed reduction in the cholesterol and triglyceride levels, drop in weight gain, increment in the intestinal microbiota and inhibition of cancer cells proliferation.

The information included in Table 3 is only a sample of the multidisciplinary academic community that is actively investigating the properties of fungal extracts in the field of medicine and nutrition. Although most of the studies are not intended to discover and describe the extract's active ingredients, the chemical characterization would allow a better understanding of the action mechanism and would guarantee their safety. This is particularly relevant, because in Mexico, there is a large market for food supplements made out of fungi, however, most of the research in this regard is in its initial phase.

Table 3: Biological activity of macrofungi collected in Mexico

Fungal species	Extract type	Cell lines or organisms assessed	Biological activity	Citation
Lentinus lepideus (Fr.) Fr. *Armillaria tabescens* (Scop.) Emel *Calvatia cyathiformis* (Bosc) Morgan *Coriolus versicolor* (L.) Quél. *Ganoderma applanatum* (Pers.) Pat. *Ganoderma* sp. *Suillus luteus* (L.) Rousel *Suillus lakei* (Murrill), A.H. Sm. and Thiers *Ganoderma lobatum* (Cooke) G.F. Atk. *Armillaria mellea* (Vahl) P. Kumm.	Filtered and lyophilized culture broth	Dichlorodihydrofluorescein diacetate assay (antioxidant activity), Cunningham's technique in BALB7c male mice (immunomodulating activity), *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans*, *Mycobacterium smegmatis* and *Sporothrix schenkii* (antimicrobial activity)	*Suillus luteus*, *Lentinus lepideus* and *Suillus lakei* showed antioxidant activity. A *Suillus lakei* sample demonstrated immunomodulating activity. *Ganoderma applanatum*, *Armillaria mellea* and *Suillus lakei* showed antimicrobial activity	González-Barranco et al., 2010
Phellinus badius (Cooke) G. Cunn. *Phellinus gilvus* (Schwein.) Pat. *Phellinus rimosus* (Berk.) Pilát	Methanolic	Antioxidant activity assessed *in vitro*, antifungal activity tested against *Alternaria alternata*	All the species showed antioxidant activity and *P. gilvus* had the highest effect. All the species have effective and similar antifungal activity	Ayala-Zavala et al., 2012
Lentinus lepideus (Fr.) Fr. *Calvatia cyathiformis* (Bosc) Morgan *Ganoderma applanatum* (Pers.) Pat.	Aqueous and methanolic	Male Wistar rats with alloxan-induced diabetic condition	Glucose levels in blood decreased with both extracts. Non-significant reduction in cholesterol levels was observed	Tamez de la O et al., 2013

Ganoderma lucidum (Curtis) P. Karst.	Aqueous	HeLa and SiHa cervical cell lines transformed by human papillomavirus and C-33A cancer cells	Extracts inhibited cell growth and induced apoptosis	Hernández -Márquez et al., 2014
26 fungal species in total: 19 Agaricales, 5 Boletales, 1 Geastrales and 1 Russulales	Ethanolic	Lung cancer cell lines H-460	*Agaricus xanthodermus*, *Boletus amygdalinus* and *Geastrum corolinum* showed cytotoxic activity	López-Sánchez et al., 2016
Ganoderma lucidum (Curtis) P. Karst.	Hydroalcoholic	Male mice C57BL/6 fed with 7 different diets high in cholesterol	Reduction in total serum cholesterol, low density lipoprotein cholesterol, triglyceride concentration, hepatic cholesterol and hepatic triglycerides. Increase in gut microbiota	Meneses et al., 2016
Pleurotus levis (Berk. and M.A. Curtis) Singer *Pleurotus ostreatus* (Jacq.) P. Kumm. *Pleurotus pulmonarius (*Fr.) Quél. *Pleurotus tuber-regium* (Fr.) Singer	Hydroalcoholic	Antioxidant activity assessed *in vitro*, antibacterial effect tested against 8 bacterial species	High antioxidant and antibacterial effects in *P. levis* and *P. tuber-regium*	Adebayo et al., 2018
Pleurotus djamor var. *djamor* (Rumph. ex Fr.) Boedijn *Pleurotus djamor* var. *roseus* Corner	Methanolic	Antioxidant activity assessed *in vitro*	Hybrid strains H1 and H3 showed the highest antioxidant effects	Oropeza-Guerrero et al., 2018
Ganoderma lucidum (Curtis) P. Karst.	Hydroalcoholic	Male mice C57BL/6	Hypocholesterolemic and prebiotic activity	Romero-Córdoba et al., 2021
Amanita rubescens Pers. *Astraeus hygrometricus* (Pers.) Morgan *Laccaria laccata* (Scop.) Cooke *Lycoperdon perlatum* Pers.	Ethanolic and methanolic	Antioxidant activity assessed *in vitro*, antibacterial effect tested against *Staphylococcus aureus, Streptococcus agalactiae, Candida albicans* and *Candida* sp.	High antimicrobial activity detected in *A. hygrometricus* and *L. perlatum.* All the strains showed antioxidant effects.	Martínez-Escobedo et al., 2021
Ganoderma curtisii (Berk.) Murrill *G. australe* (Fr.) Pat. *G. applanatum* (Pers.) Pat. *G. colossus* (Fr.) C.F. Baker *G. lobatum* (Cooke) G.F. Atk. *G. oregonense* Murrill *G. resinaceum* Boud.	Chloroform-methanol	Tumor-derived cell lines (lung, breast, cervix and colon). Antioxidant activity assessed *in vitro*, antibacterial effect tested against *Staphylococcus aureus, Pseudomonas aeruginosa, Enterococcus faecalis* and *Escherichia coli.*	Some strains showed considerable antiproliferative, antibacterial and antioxidant activity	Serrano-Márquez et al., 2021
Ganoderma oerstedii (Fr.) Murrill *G. weberianum* (Bres. and Henn. ex Sacc.) Steyaert *G. subincrustatum* Murrill	Ethanolic	HeLa, A549 and RAW 264.7 cancer cell lines. *Staphylococcus aureus* and *Escherichia coli.* Anti-inflammatory and antioxidant activity assessed *in vitro*	Anti-proliferative activity in cancer and non-cancer cell lines. Moderate antioxidant effects.	Bacallao-Escudero et al., 2023
Ganoderma tuberculosum Murrill	Hexane	*Leishmania amazonensis, Trypanosoma cruzi, Acanthamoeba castellanii* and *Naegleria fowleri* Murine macrophages	Some of the compounds showed high anti-parasitic activity and low macrophage cytotoxicity	Espinosa-García et al., 2023

Pleurotus ostreatus (Jacq.) P. Kumm. *Ganoderma lucidum* (Curtis) P. Karst. *Ustilago maydis* (DC.) Corda	Powdered basidiomata and galls were used	Male Wistar rats fed with 6 different diets high in fat and amended with saccharose.	Reduction in weight gain, fat mass, serum biochemical parameters levels and endoplasmic reticulum stress in subcutaneous adipose tissue. Maintenance of fat-free mass. Prevention of adipocyte hypertrophy and collagen deposition	González-Ibáñez et al., 2023
Ganoderma lucidum (Curtis) P. Karst.	Hydroalcoholic	Male and female Wistar rats	Toxicity effects were not recorded in kidney or liver tissues. Considerable prebiotic activity	Meneses et al., 2023
Trametes versicolor (L.) Lloyd	Aqueous and ethanolic	Human lymphoid cells	Increment in the lymphocyte count. Genetic damage detected at high doses	Salinas-Solis et al., 2023

Conclusions

Based on traditional knowledge of medicinal macrofungi, numerous scientific investigations have characterized bioactive compounds with multiple therapeutic properties. In researches performed around the world, more than 157 macrofungi active ingredients with multiple medicinal properties have been characterized. To date, active biocompounds continue to be identified, so the list will keep growing in the following decades. For future studies, we believe that it is relevant to consider macrofungi with traditional-medicinal use, in order to take advantage of the knowledge generated for centuries in Mexico. Fungal species from Mexico may represent a unique source of new bioactive metabolites that could be used to improve population's health. It is fundamental that studies involve a multidisciplinary group of scientists that pay special attention to the collection, identification, cultivation and preservation of the fungal material, standardize the extraction **protocols,characterize** the active ingredients of the extracts, perform the *in vitro* and *in vivo* assays and analyze the results.

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Chapter 34

Role of Homeopathic Medicines for Gastrointestinal Nematode Control in Animals

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ABSTRACT

Gastrointestinal nematodes pose great threats to animal health and productivity worldwide, affecting small ruminants and large animals. Control monitoring primarily relies on anthelmintic drugs, grazing management, and integrated parasite management strategies. Homeopathic remedies have appeared as an alternative approach, offering safe, nontoxic solutions with minimal adverse effects. Homeopathic remedy which originates from natural sources, treat parasite infections while also improving overall animal health. Such medicine may also enhance immunity, restore equilibrium, and mitigate symptoms caused by gastrointestinal nematode infestations. When considered with conventional medications, homeopathic therapies are very much less expensive, safer, and less likely to contribute to parasite resistance. The homeopathic comprehensive approach targets main disease problems while also enhancing host immunity. Homeopathic remedy offers a promising address to treating gastrointestinal nematodes in animals, with faster recovery and better health results.

KEYWORDS

Homeopathic remedies, Parasite infections, Cost-effective, Gastrointestinal nematodes, Host immunity	Received: 16-June-2024 Revised: 18-July-2024 Accepted: 19-August-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Gastrointestinal nematodes are a varied group of infections that infect one-half of the population on the entire globe and almost all feeding cattle. Throughout their life cycles, these macroparasites develop and travel throughout the gastrointestinal regions of hosts, releasing chemicals that modify the host mucosa, allowing for chronic infections. For the wellbeing of animal welfare and health while increasing livestock output from finite natural resources, gastrointestinal nematode control is essential. Small animals like sheep and goats are most infected by various gastrointestinal nematodes. The host-parasite relationship and the dominant agroclimatic conditions have an impact on the parasites' epidemiology.
Sheep and goats acquire infection in warmer climates are more likely to have *Haemonchus*, *Trichostrongylus*, and *Bunostomum*, while those in temperate temperatures are more likely to have *Teladorsagia* (*Ostertagia*), Nematodes, and *Cooperia*, which can cause serious illnesses. Parasite infection with gastrointestinal nematode worms is a leading cause of reduced sheep productive capacity and livestock mortality (Alvi et al., 2020; Alvi et al., 2021; Alvi et al., 2022; Alvi et al., 2023). Small ruminants are sensitive to the diseases *Haemonchus contortus* and *Trichostrongylus*, *Oesophagostomum* sp, *Cooperia* sp. *Trichuris* sp., and *Bunostomum* sp, have been linked to large financial harm for ruminants. *Haemonchus contortus* worm, a blood-sucking roundworm found in the abomasum, is the leading reason for parasitic infection in small ruminants in Indonesia (Sawitri et al., 2023). These nematodes can cause various health issues in infected animals, also leading to economic losses and welfare concerns (White et al., 2022). Gastrointestinal nematodes are now a major concern in small and large animals, particularly sheep, cattle, and goats. These parasites can cause huge harm to the host's gastrointestinal tract, causing

reduced feed intake, weight loss, and even death in severe cases. Nematodes also cause infection in small animals too, parasites live in the small intestine and can result in mucoid diarrhea and/or loss of condition. Parasite infections cause nonspecific symptoms such as a poor haircoat, coughing, vomiting, diarrhea, mucoid or bloody stools, loss of appetite, pale mucous membranes, or a potbellied appearance (Roeber et al., 2013).The current method to control nematodes by giving anthelminthic drugs, homeopathic therapy, Grazing management, genetic selection, and integrated parasite management. The broad-spectrum medications (anthelmintics) used to control nematode parasites are shown in (table 1) that are divide into three classes: benzimidazoles, imidothiazoles, and macrocyclic lactones.

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Table 1: Classification of Anthelmintics:

Broad spectrum drugs	Narrow spectrum drugs
Benzimidazoles e.g • Albendazole • Mebendazole	Organophosphates e.g • Dichlorvos • Trichlorfon
Imidazothiazoles e.g • Levamisole	Piperazines e.g • Piperazine citrate • Piperazine adipate
Tetrahydropyrimidines e.g • Pyrantel	Arsenicals e.g • Melarsomine • Arsphenamine
Avermectin e.g • Ivermectin • Abamectin	Salicylanilides e.g • Niclosamide • Oxyclozanide

Parasite Integral Control (PIC) refers to the application of several control systems. Most studies have center of attention on the control of highly harmful nematodes, such as *Haemonchus contortus* and *Teladorsagia*, in small ruminants due to their blood-feeding behavior (Kenyon et al., 2009). The PIC took into consideration of rotation of meadow, choice of tolerant breeds, biological management (i.e., nematophagous fungus and rapacious nematodes), particular deworming, vaccinations, and variations with conventional herbal medicine (Aleixo et al.,2014). Homeopathic therapy are also play are big role in controlling gastrointestinal nematodes in animals (Tariq et al.,2015).Homeopathic remedies are derived from minerals (like white arsenic), plants (like stinging nettle, red onion, belladonna, arnica, a mountain herb), or animals (such crushed whole bees). Homeopathic medications are now frequently prepared, they can be made into sugar pellets to be applied under the tongue, but they can also be used as pills, ointments, gels, drops, and lotions.

History and Principles of Homeopathy

Homeopathy, derived from the Greek words "homoios" (same) or "pathos" (suffering), is a medical practice founded on the principle of "similia similibus curentur." German physician Samuel Christian Friedrich Hahnemann (1755-1843) founded it in 1796 with his "Essay on a New Curative Principle for Ascertaining the Curative Power of Drugs with a Few Glances at Those Hitherto Used" (Madrewar et al., 2003). Homeopathy gained popularity in the 19th century because of its success in epidemics but fell throughout the 20th century. Its popularity rose during the late twenty and early twenty-first centuries, this occurred globally. Homeopathic remedies are ultra-diluted or ultra-molecular compounds, and "dynamized" systems are terms used to describe preparations that follow homeopathic pharmacopeia (Wynn et al., 1998). The hindmost defines homeopathic medicine as "any type of pharmacological dispensation provided, by the principle of resemblance and/or identity, for therapeutic and/or preventive purposes. Homeopathic remedies are created using the dynamization technique and can be used internally or externally. Homeopathy is contentious due to the use of severely diluted medications. Many clinical studies including meta-analyses, show that homeopathy has non-pharmacological effects. Cohort, observational, and economic studies have demonstrated positive results (Fisher et al., 2012). Homeopathic dilution is a technique in which a chemical is diluted with alcohol or distilled water and then vigorously shaken in a process known as "succussion' 'at each dilution stage, homeopathic treatments are subjected to succussion or forceful shaking in addition to dilution. Advocates assert that succussion amplifies the remedy's energetic qualities, increasing its potency even at very low dilutions. Homeopathy also highlights the importance of individualization in treatment. Homeopathic remedies are chosen after a whole evaluation of the animals' physical, emotional, and mental symptoms. The main objective is to find the treatment that best addresses the patient's symptoms in their entirety, including modalities (factors that alleviate symptoms) and concomitants (Rudneva et al., 2016).

Properties of Homeopathic Therapy

Homeopathic medicines are nontoxic and easily available in underdeveloped countries too. Homeopathic medicine plays a great role against gastrointestinal nematodes in small ruminants and companion animal. Medicine has no adverse effects and is easy to administer, so easy that in various cases, the owner of domestic animals themselves can administer the drug despite having to wait for a veterinary surgeon. Bloodletting, burning, purging, and other unpleasant and debilitating procedures that may lower the value of the animal after recovery are not used in the homeopathic system of treatment (Aleixo et al.,2014).On the other hand, it shortens the recovery period, allowing patients to regain strength faster. Homeopathic medicine never interferes with analgesics, vitamins, or physical therapy. Antibiotics and tranquilizers can be used alongside homeopathic medications. Homeopathic medication can also treat side effects from allopathic treatment, vaccines, and radiopathy, Thuja or noscodes can treat the side effects of a vaccine made from pathogenic germs responsibly. Antibiotic, hormonal, and corticosteroid side effects can be treated with a potentized variant of the same treatment, such as nux vomica. In the case of gastrointestinal nematodes, a balanced diet and proper care, in addition to homeopathic therapy, are necessary, and no drug can possibly replace these requirements (Madrewar et al., 2003).

Mechanism of Action against Gastrointestinal Nematodes Immunity Regulatory Response

Homeopathic treatment is involved in regulating the animal’s immunological response by enhancing its ability to resist parasitic infections. Homeopathy may assist animals deal with gastrointestinal nematode infestations by activating the body's natural defense mechanisms (Severino et al., 2012).

Revival of Balance

Homeopathic therapies aim to achieve harmony and balance in the animal's body by addressing underlying abnormalities that may predispose them to parasite diseases. The comprehensive approach is to target the underlying causes of illness.

Palliative Therapy

Homeopathic therapy is mostly used as a complement to traditional treatments for gastrointestinal nematode infestation in cats and dogs. Therapies can help relieve pain, reduce inflammation, and improve overall gut health during and after anthelmintic therapy (Madrewar et al., 2003).

Safe and Non-Toxic Effect

Homeopathic remedies are mostly considered safe for use in companion animals with little risk of side effects or drug interactions. Mostly provides a healthy and non-toxic solution to conventional anthelmintic drugs, especially for animals with sensitive gastrointestinal systems or compromised health (Aleixo et al., 2014).

Administration of Homeopathic Medicine to Animals

Homeopathic medicine is mostly used internally and externally in animals. For good results, this medicine should be administered internally, preferably 15 to 30 minutes before or after the feeding schedule. For internal use, homeopathic medicine is available in different forms.

Mother Tinctures

It has the lowest potency of any given homeopathic medicine. A botanical extract can be quite beneficial in the cure of various health issues, from moderate to severe; nevertheless, it should not be administered without the advice of a homeopathic medical practitioner. For large animals such as cattle and horses, 10 drops of tincture should be combined with clean, cold water and dipped in a bottle. Five drops are also used for small animals too.

Powder and Pills

Pellets can be placed on animals' dry tongues or blended with feed. The powder is administered at a dosage of two grains to large animals and one grain to small animals as shown in (Fig. 2).

Potentiated Dilution

Homeopathic dilution is a technique in which a chemical is attenuated with alcohol or distilled water and then rapidly shaken in a process known as "succussion”. Potentiated dilution is typically delivered via a vehicle such as globules, pellets, or disks, which can be soaked in the dilution and stored in a labeled bottle. The globule usually provides sick animals with food. Keep away this type of medicine from light and heat, so the potencies can be retained. Homeopathic medicine has an advantage over allopathic medication, they are absorbed through the tongue and palate too (Babli et al., 2022).

External use

Very few drugs are administered in the form of lotions and ointments as shown in (figure 4). The lotion is made by combining one tablespoon of the mother tincture and half a pint of purified water for external application.

Arnica Montana

Homeopathic practitioners recommend the alpine plant *Arnica Montana* for treating injuries because it relieves stiffness, and discomfort, and promotes wound healing.

Calendula officinalis

Calendula officinalis sometimes called pot marigold, medicinal herb mostly used in pain such as abdominal pain and cramps mostly caused by nematodes in animals' also acts as anti-inflammatory properties (Narang & Anjula, 2020).

Rhus Toxicodendron

It has a high value in sprain, and injury to ligaments, tendons, and joints.

Homeopathic Remedy for Gastrointestinal Nematode Control *CINA*

Obtained from the plant *Artemisia Cina*, *A. cina* is an Asteraceae-family plant whose active metabolite is artemisinin. This herb possesses antihelmintic and antimalarial properties (Rudneva et al., 2016). *Artemisia cina* shows great therapeutic impact against parasites. *Artemisia cina* is used as a homeopathic medicine and used against gastrointestinal nematodes in animals. Intestinal nematodes including *Haemonchus contortus*, the most frequent worm present in tropical climates, are among the main infections that limit animal productivity. Artemisia cine shows great efficacy against the *Haemonchus contortus* in small ruminants as shown in (table 2). *A. china* is one of the best homeopathic remedies against the gastrointestinal nematode in animals (Higuera-Piedrahita et al., 2020).

Ferrum Phosphoricum

Ferrum Phosphoricum acts as a homoeopathic medicine that improves iron absorption by increasing hemoglobin levels and reducing serum ferritin levels in the blood. It attracts oxygen, causing circular fibers of vessels to contract and equalize circulation. It also acts on intestinal villi to absorb nutrients and micronutrients, reducing iron intolerance. Chemically, it is made by combining sodium phosphate with iron sulfate in a specific proportion. The precipitate is then filtered, dried, and rubbed into a bluish-grey powder that has no odor or flavor. Aside from several other health issues, it is a leading medicine for managing anemia, which occurs during the gastrointestinal nematodes. Also used in the first stage of inflammatory conditions such as sore throat, tonsillitis, otitis media, and conjunctivitis; controlling bleeding from various body parts such as the nose, lungs, uterus, and rectum, and managing weakness after blood loss. *Ferrum Phosphoricum* mostly used in *Haemonchus contortus* infestation as shown in (table 2) (Motiwala et al., 2022).

Nux vomica

Nux vomica is an extract of the seeds of the Strychos *nux-vomica*, or strychnine tree, used in traditional and homeopathic medicine with alleged advantages for a variety of illnesses as shown in (figure 1). *Nux vomica* is used in digestive tract disturbance, including vomiting, diarrhea and abdominal pain mostly caused by nematode infestation (Goel et al.,2018).As we compared with conventional allopathic medicines, *nux vomica* is a more easily affordable and easily accessible homeopathic. Homeopathic remedy that can treat both acute and chronic conditions with fewer side effects (Rehman&Tayyeba, 2021).

Sulphur

Sulphur comes from mostly brimstone. *Sulfur* is mostly used as a homeopathic medicine. It is used to treat a variety of ailments, including skin issues, hot flushes, and digestive problems that may be accompanied by gastrointestinal nematodes. It is a deep-acting drug that has a noticeable effect on practically all the body's organs, with the skin remaining particularly evident (de Barros et al., 2023).

Teucrium Marum Verum

Teucrium is obtained from the *Teucrium Marum Verum* plant, also known as cat-thyme, which belongs to the Labiatae family. This completely fresh plant is potentized (a procedure used to make homeopathic medicines in which the medicinal properties of a crude substance are activated), and it is transformed into the extremely useful homeopathic drug Teucrium. Commonly used in the treatment of intestinal worms in cats, it may also help to alleviate abdominal symptoms too (Maher&Patricia, 2017).

Podophyllum Peltatum

Podophyllum Peltatum (also called Mayapple) is useful in the remedies of regional enteritis disease because it may act on the small intestine and rectum. Its specialization is the cessation of extreme diarrhea, and watery diarrhea, and can help stop vomiting and in excessive pain mostly caused by gastrointestinal nematodes (Kalam et al., 2021). *Mercurius solubilis* is a homeopathic medication used to treat a variety of conditions, including right earache with foul discharge, recurrent sinusitis with an objectionable odor, sore throat with increased saliva, and metallic taste. It is also known as Merc Sol and is generated from the chemical mercury nitrate (Hg (NO3)2) (Garcia-Bustos et al., 2019).

Mercurius solubilis

Mercurius Solubilis (Merc.) is derived from highly hazardous mercury but is safe to use when made in homeopathic potencies(Vangoori et al.,2013).*Mercurius solubilis* is a homeopathic medication used to cure a variety of conditions, mostly caused by gastrointestinal nematodes (Narang&Anjula,2020).

Calcarea carbonica

Calcarea Carbonica is a homeopathic therapy made from calcium carbonate found in oyster shells that is effective for gastroenteritis and digestive disorders, meteorism, acid reflux, vomiting, diarrhea, that may be accompanied by gastroenteritis nematode in animals. It is especially effective in cases of delayed digestion, sour belching, and aversion to cold (Nosal et al., 2016).

Fig. 1: Homeopathic herbs in mortar

Fig. 2: Homeopathy drugs

Santonin

The active ingredient of *Santonica* refers to the unexpanded heads of flowers of *Artemisia maritima-Cina*. *Santonin*is mostly used as antihelmintic medicine. Mostly used against *Trichinella spiralis* nematodes as shown in (table 2). Santonin also cripples parasitic worms, allowing them to be expelled from the body (Sukul et al., 2005).

Allium sativum

Allium sativum, also known as common garlic. *Allium sativum* is mostly used as a homeopathic remedy against gastrointestinal nematodes in ruminant animals. Mostly used against giardia muris nematodes. *Allium sativum* is also used to decrease the number of parasite infestations in small animals (Masamha et al., 2010).

Azadirachta Indica

Azadirachta Indica is one of the most potent homeopathic treatments that helps cure numerous sorts of skin problems and fevers. The use of plant extracts commonly known as *neem* (*Azadirachta indica*) with insecticidal action may become a viable alternative in the fight against gastrointestinal nematodes. Mostly used against gastrointestinal nematode infestation in sheep and goats (Fonseca et al., 2020).

Aloe socotrina (Socotrina Aloes)

Aloe socotrina is an effective homeopathic treatment used as a purgative. It is a vegetable kingdom cure from the Liliaceae family, sometimes known as '*Socotrina Aloes'*. Mostly used in case of intestinal irritation and inflammation (Singh et al., 2020).

Colocynthis

Citrullus colocynthis, also known as Abu Jahl's melon in Turkey, *colocynth*, bitter apple, bitter cucumber, egusi, vine of Sodom, or wild gourd, is a desert viny plant native to the Mediterranean Basin and Asia, mostly in the Region of Palestine, Turkey, and Nubia. It resembles a standard watermelon vine and produces small, Firm fruits with unpleasant flesh (Madrewar et al.,2003). It was originally given the scientific name *Colocynthis Citrullus.* mostly used in the treatment of stomach cramps caused by gastrointestinal nematode. A very effective drug for abdominal pain. The medicine is especially beneficial in bowel distention when percussion of the abdominal region generates discomfort and tenesmus. Give one dosage every third hour as shown in (Figure 2) (Fetene et al., 2019).

Comparison between Allopathic and Homeopathic Drugs

The allopathic drug sometimes is the most costly in underdeveloped countries like African countries, the drug is mostly given based on animal weight, so the quantity of medicine and its cost would proportionally be very high compared to Homeopathic drugs. In the case of homeopathic drugs are easily available and not very much more costly than conventional drugs. The conventional anthelminthic drug has more efficacy, in the case of homeopathic drugs they give also good positive results in the case of nematodes.(Andrade et al.,2011). Homeopathic drugs are the safest and are non-toxic while in the case of allopathic drugs, they may carry some adverse effects such as gastrointestinal upset, neurotoxicity, and allergic reactions. By giving more conventional drugs sometimes more resistance develops among gastrointestinal nematodes in animals. Parasite community can build resistance to specific anthelminth over time, reducing the effectiveness of treatment options. In homeopathic remedy resistance development by drug is very low, Practitioners suggest that homeopathy's holistic strategy may lessen the chance of resistance development by resolving underlying abnormalities and enhancing the host's natural defenses (Bell et al., 2015). Homeopathic medicine will not produce the disease in system of the body e.g. in brain disease, intestine portion, whereas allopathic drug also has some adverse effects on the body organs. Both drugs contribute to the reduction of parasite burden and accompanying clinical signs; some have a long-lasting effect as shown in (Figure 3) and extended resistance ability, but evidence supporting the long-term impact of treatment on animal health and productivity is lacking (Cavalcanti et al., 2007).

Table 2: Usage of homeopathic medication in nematodes:

Parasite of animals	Homeopathic medicine	Treatment procedure	Consequences of drug
Trichinella spiralis	*Santonin* and *Artemisia Cina* (30 CH)	50mg/kg from the seventh day of infection for 120 days.	Decrease the number of larvae
Haemonchus contortus	• *Ferrum Phosphoricum* • *Calcarea carbonica* *Teucrium Marum Verum*	Give medicine only for 10 days,	• Decrease number of larvae • Enhancement in immune response • Decrease the number of eggs in feces
Oesophagostomum species	Phosphorous used as homeopathic medicine	Mix with mineral salt for 10 days in animal	Decrease the number of parasites
Cooperia	*Teucrium Marum Verum* *Mercurius solubilis*	Mix with mineral salt, give 6g/per kg, spontaneously	Decrease the number of parasites, also decrease intestinal symptoms
Trichostrongylus Species	*Teucrium Marum Verum* *Complex Sulphur*	Mix in water, give only 10 drops daily till infection	Decrease the number of eggs in feces

Fig. 3: Herbal drugs

Fig. 4: Homeopathic Ointment

Benefits of using Homeopathic Medicine on Animals

Animals, like people, respond very well to the healing powers of homeopathic treatments. The only dependence is on symptom observation rather than diagnosis, which not only makes it possible to treat animals without a diagnosable illness but also to treat newly discovered diseases for which there is currently no established class of drugs or a recommended course of treatment(Chagas et al.,2008).Homeopathy is an incredibly natural, compassionate, and successful kind of treatment because it uses the body's inherent defenses against illness to produce healing Animals given homeopathic treatment frequently recover far faster than those given standard medical care.(Burke et al.,2009). When it comes to homeopathy, animal trials are not required to prove medications, since the treatments have been demonstrated on humans, it is known what conditions they can treat. Homeopathic medicine also plays a great role against the gastrointestinal nematode in animals (Fomum et al., 2018).

Conclusion

In the end, proper handling of gastrointestinal nematodes in animals, particularly small ruminants, is critical for their health and production. While conventional anthelmintic medications have been widely utilized, concerns about susceptibility and side effects have led to the investigation of alternative remedies like homeopathy. Homeopathic remedies provide a safe, holistic method to stimulate intrinsic healing mechanisms and regulate immunological responses. They are readily available and inexpensive, making them viable solutions even in areas with limited resources. Integrating homeopathy into parasite management supplements traditional methods by addressing underlying causes of sickness and strengthening natural defenses. With the need for more studies, homeopathic therapy has promised long-term nematode control in animals. Communication among veterinarians, researchers, and practitioners is critical for understanding the efficacy and appropriate use of homeopathic treatments in nematode control program. This comprehensive strategy has the potential to improve animal welfare and overall livestock health.

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Chapter 35

Difference between Homeopathic and Herbal Medication in Humans and Animals

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ABSTRACT

Homeopathy is sometimes mistaken for herbal remedies and holistic treatment. The latter is especially problematic in cases when botanicals used to make homeopathic medications are also given the same vocabulary. But homeopathy is different in terms of toxicity as well as a therapeutic paradigm, which has significant ramifications for application and further study. Using plants, lichens, algae, and fungi to influence the body is known as herbalism. It originated in Asia, Europe, and America and spread worldwide with the earliest human settlers. Herbal medicine makes use of a wide range of preparations, including tinctures, teas, powders, elixirs, essential oil, meals herb-infused honeys, herbal vinegar, and several topical applications. The majority of homeopathic cures are made up of tiny amounts of substances that, given a physiological quantity, would produce the same signs as the illness. Treatments of homeopathy are made from highly diluted natural components. Herbs such as Arnica montana and poisonous ivy are used in homeopathic preparations, along with animal products like snake venom and minerals like phosphorous. These are then turned into tinctures, topical treatments, or sublingually absorbed sugar pellets.

KEYWORDS		
Homeopathy, Herbal medicines, Natural component, Topical treatment, Illness	Received: 14-June-2024 Revised: 05-July-2024 Accepted: 03-August-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Recent years have seen a rise in the popularity of complementary and alternative medicine, which uses notions that differ from those of modern medicine. Compared to conventional medicine and routine treatment, alternative medicine adopts various concepts. Over the past few years, there has been a rise in demand and popularity for complementary therapies (Chiu and Ho, 2005; Arlt, et al., 2009; Kardanpour, et al., 2016). Medically based treatments are frequently unsatisfactorily expensive and have little efficacy. Because of this, alternative medicine is more accessible than traditional medicine, requires less expensive laboratory settings, and is safer and more natural. Many herbal remedies, dietary supplements, chiropractic adjustments, and homoeopathic treatments are all considered forms of alternative medicine (Henson et al., 2017). Homoeopathy is one of the therapy modalities that are part of these alternative applications (Hadipour et al., 2011).

Homeopathic Medicines

About two centuries have passed since the Greek terms homeo, meaning pathos and similar, which denotes pain or illness, were combined to create the phrase homoeopathy. Homoeopathy seeks to offer the patient a quick, long-lasting treatment plan using organic techniques that encourage self-healing (Yaramış et al., 2016; Bhardwaj and Misra, 2018). The idea that comparable substances can address comparable issues is one of the fundamental tenets of this approach. This basic premise, which forms the basis of homoeopathy, means that “When a medication is administered to those who are healthy, it generates manifestations comparable to the sickness in those people who are receiving treatment for the illness with this active ingredient (Özçakır and Doğan, 2013).

History

The history of homoeopathic medicine is longstanding. According to Yarsan (2015), there is historical evidence of the application of homoeopathic principles in Greek inscriptions, Inca, Aztec, Native American, and Egyptian writing systems. Hippocrates treated comparable conditions and was regarded as the founder of medicine about 400 BC. Paracelsus, one of the most important alchemists of the sixteenth century, followed procedures in accordance with this idea (Özçakır and Doğan, 2013; Yarsan, 2015). Özçakır and Doğan (2013) state that the German physician Samuel Hahnemann created homoeopathy and documented these ideas in 1796. The first handbook on homoeopathy was published in 1826 by Carl Caspari. From 1811 until 1821, Hahnemann gave homoeopathic lectures at the University of Leipzig. He relocated to Paris to pursue his medical studies fourteen years later. Following Hahnemann, there were extensive research investigations on homoeopathy, with an American scientist named James Tyler Kent recognized as the 19th-century inventor of modern homoeopathy (Yarsan, 2015). In Western region of Europe, particularly in the Netherlands, France, England, and Germany, homoeopathic treatment is one of the most often utilized modalities both now and in the previous century.

Principles of Homeopathic Treatment

There are three basic tenets that underpin homoeopathy. According to Chiu and Ho (2005), these three principles are the minimum dose principle, the only remedy concept, and the similarity principle. By producing a warning and starting the healing process with homoeopathic chemicals, homoeopathic treatment seeks to trigger responses that will regain the organism's health. By conducting experiments and meticulously documenting the effects of different dosages of drugs on volunteers and himself, Hahnemann was able to discover this principle. In his experiments with homoeopathy, Hahnemann employed materials including ivy venom, snake venom (Lachesis), table salt (natrum muriatum), and head lice (Pediculus capitis) (Rijnberk and Ramey, 2007). Hahnemann did not agree with the author's justification for quinine's advantageous benefits in malaria patients, despite translating William Cullen's Pharmaceutical Science Lectures into German. The stomach is strengthened by quinine, according to Cullen. The quinine compound was also tested on Hahnemann, who reported that the effects were comparable to those of malaria. The "Similia similibus curentur" idea was proposed by Hahnemann in response to this observation (Rijnberk and Ramey, 2007). Pekmezci and Gültiken (2015) state that Hahnemann organized this idea, laid down its foundation, and influenced homoeopathy.

Homeopathic Drugs

Herbal, mineral, and animal-based constituents are diluted to creat homoeopathic medications. According to Yarsan (2015) and Kumari et al. (2016), these include poison ivy, white arsenic, red onion, stinging nettle, arnica (mountain grass), and belladonna. Prescription and manufacturing of homoeopathic remedies in accordance with the general symptoms of the patient. Liquid (ampoule, drops) and solid (globule-spheres, ointment, tablet,) homoeopathic medicines are available. According to Mathie and Clausen (2014), they can deliver locally, subcutaneously, intramuscularly, orally. Gold, arsenic, phosphorus, zinc, and calcium compounds are components in mineral-based medicines. Herbal remedies such as Calendula officinalis, Arnica montana, and Atropa belladonna are used in homoeopathy. Snakes, bees, dog milk, blood, cartilage tissue, umbilical cord and embryo, pus, rabid dog saliva, scabies agents, TB discharges, or diseased tissues like cancer tissue are examples of substances of an animal origin (Yarsan, 2015; Pekmezci and Gültiken, 2015).

Preparation and Administration of Homeopathic Medicines

To make homoeopathic medications, raw components of plant, animal, and mineral source are utilized. It is necessary to first transform these raw elements into the main substance. To achieve this, an appropriate vehicle is added to the raw materials—such as alcohol or water—and let to stand. The dissolved components are separated to yield a primary medicinal product, such as a powder, extract, or tincture. The main component is extracted, diluted to make it usable, and then shapes it into pills, ointments, drops, and injectable solutions. By diluting, the principal substance's toxicity and side effects are minimized and the content's dangerous substances are neutralized (Yarsan, 2015; Pekmezci and Gültiken, 2015). The main ingredient is diluted using shaking and successive dilutions. Potentiation is the term for this diluting procedure.

Mechanism of Homeopathic Drugs

There are several suggestions regarding the mechanism of action of homoeopathic drugs, however data regarding their therapeutic efficacy are still unclear (Løken, 2001). A process known as potentiation is used to obtain homoeopathic drugs. So that just a little portion of the original material remains in the finished product, the primary ingredients are repeatedly diluted and agitated extensively. Homoeopaths have shown that a treatment will work better and require fewer doses of medication when the active component is further mixed and diluted. Due to its high internal energy, homoeopathic medicine, even in little doses, activates a multitude of bioenergy systems within the body (Pekmezci and Gültiken, 2015). In order for homoeopathic remedies to work, the patient's manifestation must align with their recommended course of treatment. Seeking any indications of a different illness should be done for the patient (Pekmezci and Gültiken, 2015).

The Use of Homoeopathy in Medicine

Homoeopathic remedies reduce post-tooth extraction discomfort, swelling, and bleeding (Karp et al., 2016). For this reason, medications with the names Arnica montana, Hydratis, Canadensis, Belladona and Calcarea carbonica are used in different ways to treat dental cavities, gingivitis, aphthous ulcers, and gingival bleeding. While homoeopathy can help patients relax and make the process go more smoothly, it cannot replace dental medical techniques (Kardanpour et al., 2016). When African patients with malaria were treated with the homoeopathic medication natrum muriaticum, the number of malaria attacks was found to drop. When treating chronic diseases that resolve on their own, homoeopathy is more frequently chosen than conventional therapies (Erlewyn-Lajeunesse, 2012). Studies on homoeopathic medications in this field have produced encouraging results (Johannes et al., 2013). After three months of treatment, homoeopathic medications Rhus Toxicodendron and Ruta graveolens 5CH are used in the initial stages of breast cancer, shown beneficial results in lowering joint discomfort and involvement (Karp et al., 2016).

The Considerations

When Dispensing Medication When using homoeopathic remedies, there are a few things to keep in mind. Prior to receiving homoeopathic treatment, the patient should disclose to the homoeopathic practitioner all medications that he has taken or intends to take. The patient should inform the homoeopathic practitioner if they take any additional homoeopathic medications. Certain substances should not be consumed by the patient while receiving homoeopathic treatment. Aromatic coffee and essential oils are examples of substances that can adversely impact homoeopathic treatment. During homoeopathic treatment, it is best to avoid using oral or topical antibiotics, steroids, and opioids.

Advantages and Disadvantages of Homeopathic Treatment

It is entirely safe and non-poisonous to use homoeopathic treatments (Santa Rita et al., 2016). Homoeopathic medicines have the function of stimulating the organism, which starts the healing process. Children and pregnant women can safely utilize homoeopathic remedies without experiencing any negative side effects. Furthermore, when combined with other forms of treatment, they do not exhibit any negative side effects. Natural substances are used to make homoeopathic medicines. They function in tandem with the body's natural processes and immune system. According to Yarsan (2015), homoeopathic medicines do not induce addiction and provide relief from all symptoms by targeting the underlying cause rather than the symptoms alone. Homoeopathic medicine uses the body's natural healing ability to promote the health of the organism. The minimum dose rule guides the preparation of homoeopathic medications. I.e. these do not induce any kind of addiction in the body (Kumari et al. (2016). Both benefits and drawbacks might arise from homoeopathic medicine. As far as alternative therapies are concerned, homoeopathy is the costliest. Side effects could arise if they are used excessively or uncontrollably (Orjales et al. (2016).

Importance of Herbal Products in Animal Husbandry

Plants have been utilized for thousands of years for medical and health purposes. In many ancient medical systems, plants are always the primary source of medicine or therapeutic approach. India has an abundance of therapeutic plants, and many medical traditions, including Ayurveda, Siddha, and Unani, employ plant extracts to treat a variety of illnesses. Ayurveda is an age-old Indian medical system that primarily uses herbal remedies to treat and prevent a wide range of illnesses and cancers (Pandey et al., 2013). Ever since the beginning of time, plants have served as both food and medicine for both animals and birds. The ability of animals and birds to naturally heal themselves with herbs is known as zoo pharmacognosy, and competent humans can also practice this age-old skill to this day (Dhama et al., 2015). Approximately 75% of plant-based medicinal substances used globally are used in traditional/folk medicine (Sen and Chakraborty, 2017). Plants have been used for animal health prevention and recovery as well as grain conservation for the past ten years, largely due to the development of organic livestock production systems, drug resistance, high input costs, and worries about toxic residues in food (Escosteguy, 2014).

Traditional Medicines in Asia and Africa

For their primary medical requirements, 80% of people in Asian and African nations turn to traditional medicine. According to Wachtel-Galor and Benzie (2012), around 25% of contemporary medications are derived from plants that were originally used traditionally. With almost 20,000 species of medicinal plants, India is home to one of the largest collections of natural remedies worldwide. Nevertheless, only 7,000–7500 of these species have been employed by various medical societies to treat various illnesses (Pandey et al., 2013). Approximately 391000 plant species are thought to exist on Earth. (National plant association of the world, 2016/report). According to estimates, between 35,000 and 70,000 plant species have been utilized medicinally. Herbal plants are used to treat illnesses as well as to improve wellness. Herbs are used to treat a variety of illnesses, including acaricidal and anthelmintic infections. They may also be utilized in the treatment of bovine mastitis, as well as in gynaecological and surgical operations (González et al., 2011). The nutritional components found in plants that are crucial for animal health care are called secondary bioactive compounds or metabolites. They increase cattle productivity and reduced pollutant levels in the environment. (González et al., 2011; Chakraborty and Pal, 2012).

Importance of Employing Herbal Items in the Development of Livestock

Herbs utilized to make the items enhance wellbeing without having any negative effects. Herbal products have many benefits over non-herbal items, which makes the supplements or medications very beneficial. Herbal remedies are readily available, more effective for chronic health conditions, and well-tolerated. Since herbal growth promotants don't leave residues in animal products, they are safe for ingestion by humans. In the long run, herbs are also less expensive and could result in decreased feed expenditures (Alimon, 2012). Various plant extracts, herbs, and spices have the ability to stimulate digestion and appetite. Various secondary metabolites produced by plants function as defense mechanisms against pathogenic microbes, predators, and physiological and environmental stresses (Mirzaei-Aghsaghali, 2012). In addition to being used in conjunction with other supportive herbs, the natural antibacterial, anti-inflammatory, anti-oxidant, and immunostimulant properties of the herbs and spices can be used. (Mirzaei-Aghsaghali, 2012; Kumar et al., 2014). Herbs' active compounds function in harmony and synergy when used as entire plants or leaves, and when mixed with other herbs, they naturally produce the intended effects. But when it comes to contemporary medicine, this is untrue (Alimon, 2012).

Herbs as Feed Additives

Herbs are planting that bloom, are not woody, and are not persistent, but spices are herbs that have strong flavor and aroma. These plants, which are classed as feed additives by Windisch et al. (2008), are phytogenic plants that contain chemicals that cause physiological responses in animals. A greater requirement in search of natural and safe feed additives to raise farm animal output was brought about by consumer awareness raising and the prohibition on the use of nutritional antibiotics (FrAnKIČ et al., 2009). Phytogenic feed additives (PFA) are natural pharmaceuticals made from plant extracts, herbs, and spices that are fed to farm animals. PFAs enhance an animal's ability to absorb nutrients, digest food, and eliminate infections in its digestive system. (Alloui et al., 2014). According to Kiczorowska et al. (2017), these feed additions include herbs, spices, and the products derived from them, as well as essential oils. The different plant secondary compounds (PSC) and metabolites that have positive impacts on animal health and productivity are known as phytobiotics, or botanicals (Stevanović et al., 2018). By boosting the physical aspects of the hens' intestinal ecology and strengthening their immune systems, these compounds were thought to be crucial in fortifying the animals' defenses. Therefore, to promote growth and provide health advantages, nutritive antibiotics and other feed additives target the gut bacteria (Singh and Gaikwad, 2020). According to Upadhaya and Kim (2017), feed additives have a variety of functions, including growth enhancer, anthelmintic, antioxidant, antibacterial, and immunological modulator. According to reports, the action of phytobiotics can improve production, increase feed intake, and stabilize the microbiota of an animal's gastrointestinal tract while strengthening its resistance (FrAnKIČ et al., 2009; Yang et al., 2009; Kumar and Kumar, 2013).

Importance of Herbs in Ruminants

Strong antibacterial, antiparasitic, antiprotozoal, and anti-inflammatory qualities can be found in plant extracts, particularly in essential oils and saponins. According to Tajodini et al. (2014), these organic substances regulate ruminal fermentation to increase animal output in ruminants and to optimize nutrient utilization. Ruminant productivity is increased by rumen modifiers, which alter digestion and boost protein retention and energy without lowering feed intake. According to Kumar et al. (2014), Alkaloids, flavonoids, saponins, tannins, phenolics, terpenoids, essential oils, and piperine are examples of bioactive plant secondary chemicals that are additions that enhance protein metabolism and reduce methane production. Additionally, they reduce nutritional stressors like bloat, which promotes rumen fermentation and, in turn, raises animal well-being and productivity. Therefore, animal production, feed additives can be used to improve feed intake, metabolism, and feed utilisation efficiency that is both cost-effective and environmentally beneficial (Singh, 2015). However, there is evidence that certain essential oils lower the number of bacteria that produce ammonia, the rate at which amino acids are deaminated, and both of these rates. Thus, by selectively modulating specific microbial species, Ruminal fermentation is managed with the use of natural plant extracts. (Tajodini et al., 2014).

Importance of Herbs in Monogastric Animals

In animals with monogastric feeding systems, feed additives are used to boost immunity, reduce pathogen counts, encourage the formation of beneficial gut flora, and enhance digestive efficiency. (De Lange et al., 2010). PFA has been shown by some authors to have positive effects on Increasing the crude protein digestibility in monogastric animals can increase nutritional digestion. (Emami et al., 2012; Li et al., 2012). This is because PFA stimulates saliva and bile secretions and enhances enzyme activity, all of which improve animal health and lower feed costs. PFA increases intestine absorptive capacity through increasing the villus's height, crypt depth, and surface. In monogastric animals like pigs and poultry, essential oils help the animal's immune system, reduce pathogenic stress in the stomach, enhance the secretion of digestive juices and nutritional absorption, and give antioxidant effects. (Zeng et al., 2015).

Herbs used Medicinally to Enhance Cattle Reproduction

The main factor influencing a stable and profitable animal production system is the animal's reproductive efficiency. One of the most important issues reducing dairy animals' productivity and output is reproductive diseases (Giri et al., 2023). Farmers in the cattle industry suffer significant financial losses as a result of reproductive process failure. Even today, a variety of reproductive diseases are efficiently treated using herbs, which have been used for ages to cure reproductive illnesses. Numerous herbs have amazing therapeutic qualities that can treat a variety of animal reproductive diseases, including anestrous, abortions, endometritis, retained placenta, and repeated breeding (Kumar et al., 2018). It has already been demonstrated that a small number of these plants, which contain secondary metabolites (PSM), are highly successful in causing estrus in postpartum anestrous cows. Certain secondary metabolites have the capacity to control the synthesis of ovarian hormones or scavenge reactive oxygen species (ROS), which makes them antioxidants. These characteristics are in charge of the therapeutic effects on infertility disorders (Mbemya et al., 2017).

Herbal Products as Livestock Immune-boosting Agents

Immune systems benefit from spices and herbs high in flavonoids, vitamin C, and carotenoids. Immunostimulatory plants boost phagocytosis and promote the production of interferon by enhancing the function of lymphocytes, macrophages, and natural killer cells (FrAnKIČ et al., 2009). Curcumin, it is present in Curcuma longa and boosts CD4 (+) T and B lymphocytes in the mucosa. Which affects lymphocyte-mediated immunological activities (Khan et al., 2012). Numerous synthetic immunomodulators are available on the market, but with varying degrees of negative effects. Plant immunomodulators that are conventional are less expensive and safer. Several herbs with immunomodulatory qualities are utilized extensively in the poultry industry, including ashwagandha (Withania sominfera), neem (Azadirachta indica), and guduchi (Tinospora cordofolia) (Dhama et al., 2014).

Plants with Bioactive Secondary Products for Cattle Health

Bioactive chemicals are additional nutrients that are usually found in trace amounts in food. According to recent research, extracts from medicinal plants that have lower concentrations of secondary metabolites from plants can improve the performance of ruminants in one or more ways (Mirzaei and Venkatesh, 2012). As a result of additional research into these therapeutic plants, numerous secondary metabolites that are now well-known medicines have been isolated. These secondary metabolite characteristics are used as the primary source for new medication discovery. (Dias et al., 2012). Here are a few well-known and well-known examples:

1. An anti-inflammatory agent. Salicin is extracted from the Salix alba L. tree's bark, is the source of acetylsalicylic acid, or aspirin.
2. The base of the painkiller codeine, diacetylmorphine (heroin), is produced by boiling the alkaloid morphine from the Papaver somniferum (Opium poppy) plant in acetic anhydride.
3. Digitoxin is a heart drug that targets all aspects of cardiac function. It is a cardiotonic glycoside derived from the foxglove plant Digitalis pupurea L. Digitoxin enhances cardiac contractibility.
4. Quinine is a drug made from the bark of Cinchona succirubra Pav. that is used to treat fever, malaria, indigestion, cancer, and throat and mouth ailments.
5. Pilocarpine is a medication made from the Pilocarpus jaborandi plant (Rutaceaceae) that is used to treat glaucoma.

Role of Herbal Medicines in Humans

Around the world, a plethora of pharmaceutical enterprises had emerged, producing a wide range of natural treatments derived from leaves, barks, stems, fruits, seeds, flowers, roots, and medicinal plants. It contains a variety of foods, such as bitter kola, kola nuts, and edible mushrooms. These formulations, which come in powder, paste, balm, cream, and other forms, are used to treat a variety of disease conditions at different stages, including diabetes type 1 and type 2, high blood pressure, trypanosomosis fibroid, ulcers, cancers, heart disease, migraines, and wound healing aids derived from medicinal plants (Ahmad et al., 2021).

A Formulation of Medicinal Plants Intended to Combat COVID-19

To support the applications of medical plants and herbs, Indian scholars have used a variety of medicinal plants, such as Ocimum sanctum L. 2 leaves, Cinnamomum verum, stem barks, Zingiber officinale Roscoe rhizomes, and Piper nigrum L. fruits. Brand names for these formulas include "AYUSH Kwath," "AYUSH Kudineer," and "AYUSH Joshanda." The antiviral and immunity-boosting qualities of these make them a viable option to combat the Covid-19 epidemic (Shaba, 2022). As a result of the introduction of genetically engineered coronavirus (by psychopaths), which up until now has always appeared in conjunction with a regular flu virus with a mere 2% death rate, it is frequently noticeable as it is during the winter season in temperate nations or regions. These herbs have been shown to strengthen immunity (Shaba, 2022) and are effective treatments for various.

Pain Killers

Humans utilize aspirin, morphine, and chemotherapy extensively to reduce pain, particularly during surgery; these medications are entirely derived from medicinal plants. The following is a partial list of notable medicinal plants that are used both in households and by the pharmaceutical industry to formulate various medications in various forms for the prevention and treatment of specific medical diseases (Sharma et al., 2021).

1. Turmeric
2. Ginger
3. Feverfew
4. Onion
5. Ginger
6. Ginseng

7. The golden seal
8. Thyme
9. Onion
10. Kalmegh

Native Americans Use Medicinal Plant to Treat African Trypanosomosis in Humans and Animals

Trypanosomosis, a zoonotic blood protozoan illness that is one of the neglected tropical diseases that affects individuals in many countries of the world, including Africa, Asia, and Latin America, is treated with a variety of medicinal plants. This material is derived from discoveries that have surfaced in the previous few years, traditional medicine, and our interactions with the community. The list of therapeutic plants that our research team has discovered, examined, and validated is shown below. We have also identified active secondary metabolites, purified the isolated compounds, and, to some extent, determined the structural elucidations of these compounds against trypanosomosis.

1. Indian-species Emblica officinalis fruits
2. Fruits of the Indian species Terminalia chebula
3. Fruits of the Indian species Terminalia belirica
4. Leaves of the Indian species Achillea millefolium
5. Leaves and stems of Vitex negundo (Indian species)
6. Leaves of the Indian species of Centella asiatica
7. Rhizomes of Zimgiber officinalis (Indian specie)
8. The leaves, seeds, fruits, and root of Moringa oleifera

Medicinal Plant Use for Treating Intestinal Worms

Similarly, intestinal worms, nematodes, cestodes, and trematodes are treated using some of the therapeutic plants. One such plant is Azadirachta indica, better known as neem, which our ancestors used to treat intestinal worms. Several neem plant parts, including the leaves, stems, fruits, root bark, and root, have been shown to have varying degrees of antihelminthic activity after screening and validation from a scientific perspective. Additionally, Swartzia madagasariensis (Yawalogi) and Picria fel-terrae Lour have been verified in labs or by the community to be free of intestinal worms, respectively (Shaba, 2022).

Herbs and Medicinal Plants to Treat of Wounds

Since the ancient time, people have used herbs and medicinal plants to cure wounds. A few of the numerous plants and herbs utilised for medicinal purposes are Curcuma longa, Aloe vera, and Centella asiatica. The bodily system's well-documented wound healing process includes the progressive reduction of inflammation, a state often triggered by wounding and, ironically, the first step of healing. The next step is mature granulation of the affected tissue, which speeds up wound healing. Many scholars from around the world have clarified these mechanisms (Shivanand et al., 2010). Incision, excision, contraction of the wound site by reducing its size, epithelialization, and histological findings that suggest regeneration, fibroblast formation, and angiogenesis to complete the process are all part of the wound healing process in the animals used in this study. (Shaba, 2022; Lilly, 2023).

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Chapter 36

Efficacy of Homeopathic Therapy in Arthritis Treatment

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ABSTRACT

This book chapter explores the effectiveness of using homeopathic treatment to manage arthritis, with emphasis on its possible advantages, safety, and combination with traditional medical approaches. Arthritis, a widespread and severe condition, presents considerable obstacles to traditional treatments, leading to the investigation of alternative therapies such as homeopathy. The study examines the core concepts of homeopathic medicine, with a focus on personalized treatment, dilution methods, and safety precautions. The research investigates clinical trials and observational studies, examining the methodological obstacles and evidence-based backing for using homeopathic treatment for arthritis. Case studies provide detailed and subtle insight into how patients respond, the ability to maintain success over time, and the possibility of using combined methods. Furthermore, the safety characteristics of homeopathic treatments are explained, emphasizing concepts such as extensive dilution, personalized treatment, and minimal substance dosage. The study investigates the differences in safety and potential for collaborative patient-centered care between homeopathic therapy and conventional medications. The results indicate that homeopathic treatment for arthritis leads to favorable results, long-lasting advantages, and high patient contentment. Safety measures, monitoring of negative effects, and cooperation between homeopathy and traditional medicine are examined. The research findings have important implications for how healthcare is delivered, including the importance of making well-informed decisions, focusing on the patient's needs, and the necessity of continued research and cooperation between different fields in the changing field of arthritis treatment.

KEYWORDS Homeopathic therapy; Arthritis treatment; Individualized treatment; Safety profile; Integrative approaches; Clinical studies, Patient-centered care	Received: 02-Jun-2024 Revised: 12-Jul-2024 Accepted: 21-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Arthritis refers to a wide range of conditions that cause joint inflammation, resulting in pain, swelling, stiffness, and reduced joint mobility. It is a common health issue that impacts millions of individuals globally and creates a substantial strain on healthcare systems (Finckh et al., 2022). There are multiple kinds of arthritis, each with unique features and root causes. Inflammatory arthritis and non-inflammatory arthritis are the main classifications. Inflammatory arthritis occurs when the body's immune system mistakenly targets the joints, causing inflammation. Rheumatoid arthritis is a condition in which the body's immune system attacks the synovium, leading to inflammation in the joints' lining. Psoriatic arthritis is a type of arthritis that develops in people who have psoriasis, a skin condition caused by the body's immune system. It impacts the joints and could result in damage to the joints (Finckh et al., 2022). Ankylosing spondylitis mainly impacts the spine by triggering inflammation in the vertebrae and sacroiliac joints (Ebrahimiadib et al., 2021). Arthritis that does not involve inflammation is identified by the gradual deterioration of the joints due to everyday use, resulting in degeneration over time. Osteoarthritis is the prevalent type of arthritis, often linked to older age, joint trauma, or being overweight. It refers to the deterioration of cartilage in the joints (Allen et al., 2022). Degenerative arthritis refers to conditions in which the cartilage of the joints deteriorates, leading to discomfort and limited mobility (Lockwood, 2024). Arthritis not only causes problems in the joints but also has broader effects on the body, affecting overall well-being. Chronic pain, decreased movement, and related medical conditions make arthritis management complex (Mathias et al., 2021). Some of the conventional methods for treating arthritis consist of nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, corticosteroids, and physical therapy. However, these methods might have drawbacks and adverse reactions, leading to a search for different treatments such as homeopathy (Akram et al., 2021).

The Prevalence and the Impact of Arthritis

Arthritis is a common health issue that has a significant impact on a global scale (Wong et al., 2010). Epidemiological research shows that the frequency of arthritis differs among various demographics and age ranges. It is important to understand how common a disease is to accurately assess its impact on public health (Steinmetz et al., 2023a). Arthritis prevalence varies by age and gender. Some forms of arthritis, like osteoarthritis, are more common in elderly people, whereas rheumatoid arthritis can impact individuals of all ages (Nilsson et al., 2021). Moreover, certain forms of arthritis, like arthritis related to lupus, are more commonly found in women (Crosslin and Wiginton, 2011). Arthritis has wide-ranging effects beyond personal well-being, placing a significant financial and societal strain. The condition leads to higher healthcare expenses, decreased productivity from being unable to work, and the need for more medical services. Additionally, arthritis has a widespread effect on the mental and social health of individuals, impacting their capacity to participate in everyday tasks and uphold a high standard of living (Berkovic et al., 2021). Arthritis is commonly linked with a range of other health conditions such as heart diseases, diabetes, and psychological disorders. It is crucial to understand how arthritis is interconnected with other health conditions to provide comprehensive patient care and manage it effectively (Marcucci et al., 2018). Arthritis significantly affects the overall quality of life, going beyond just physical symptoms. Those with arthritis may face challenges in carrying out everyday activities, engaging in social events, and being fully healthy. Evaluating the overall effect of arthritis on individuals' lives can be gained by assessing their health-related quality of life. The increasing number of people with arthritis presents difficulties for public health systems worldwide (Bergström et al., 2020). Dealing with these difficulties necessitates a comprehensive strategy, which includes early identification, successful management techniques, and the consideration of alternative treatment choices such as homeopathy.

Traditional Treatments and their Weaknesses and Non-steroidal Anti-inflammatory Drugs

Traditional methods for treating arthritis commonly include the use of nonsteroidal anti-inflammatory drugs to alleviate pain and inflammation. NSAIDs are frequently recommended for ailments such as osteoarthritis and rheumatoid arthritis. However, using them for extended periods may lead to gastrointestinal problems and a higher chance of experiencing cardiovascular events (Da Costa et al., 2021). Disease-modifying antirheumatic drugs play a crucial role in treating inflammatory arthritis, especially rheumatoid arthritis. DMARDs focus on addressing the root cause of immune system dysfunction to reduce the rate of disease advancement. Although these medications are useful, they can also cause immunosuppression and liver damage as side effects (Padjen et al., 2020). Corticosteroids are strong anti-inflammatory drugs that are used to treat sudden symptoms of arthritis. They can offer quick relief, but they are generally not recommended for extended periods because of potential side effects such as osteoporosis, weight gain, and higher susceptibility to infections (Stone et al., 2021). Physical therapy is essential for enhancing joint function, decreasing pain, and improving mobility in people with arthritis. Physical therapy can be helpful, but its effects can differ and it might not tackle the root causes of arthritis (Peter et al., 2021). In serious instances of arthritis, especially osteoarthritis, surgical joint replacement may be suggested to reduce pain and improve joint functionality. Although surgery can be successful, it comes with its own set of risks and the recovery period can be long (Madry, 2022).

Limitations of Predictable Methods

Although conventional treatments are widely utilized, they have significant drawbacks (Akram et al., 2021). Several traditional treatments aim to alleviate symptoms rather than addressing the root cause of the disease. This method may not stop chronic joint damage in inflammatory arthritis. Many of the medications typically used to treat arthritis can have negative side effects that can negatively affect the overall health of patients. It is essential to carefully weigh the advantages and potential drawbacks of these medications to create personalized treatment plans. Traditional treatments frequently do not provide effective cures for arthritis (Steinmetz et al., 2023b). Patients may have to continually handle their symptoms without getting to the underlying causes.

Exploring Homeopathic Therapy and Holistic Healing Method

Homeopathy treats the entire person, taking into account not just physical symptoms but also mental and emotional health. This comprehensive approach is in line with the intricate characteristics of arthritis, in which symptoms go beyond just joint pain and inflammation. Homeopathic practitioners seek to treat the root causes that contribute to arthritis, seeing it as a symptom of a larger systemic imbalance. Homeopathy places importance on creating personalized treatment plans that are specifically designed for each patient based on their distinct symptoms, physical makeup, and reaction to stress factors (Nengovhela, 2022). This individualized method differs from traditional treatments, which typically adhere to a more uniform procedure. Homeopathic treatment aims to maximize the effectiveness of arthritis treatment by taking into account the unique qualities of each case (Magni et al., 2021). The attractive feature of homeopathic treatment is its potential to have very few side effects. Homeopathic treatments usually consist of heavily diluted substances obtained from plants, minerals, or animals. The process of dilution is thought to increase the positive effects of treatment while reducing negative reactions, providing a milder and easily tolerated option compared to certain traditional medications that come with unwanted side effects (Hoenigl et al., 2024). Homeopathy uses the concept of treating symptoms with highly diluted substances that would normally cause those symptoms in a healthy person. This method is believed to activate the body's innate ability to heal itself, promoting a natural and harmonious reaction. Homeopathic treatment can be used in conjunction with traditional therapies to provide a holistic approach to healing (Di Stefano, 2020). This comprehensive model combines the benefits of both conventional approaches and homeopathy to create a more effective management strategy that addresses the potential limitations of each approach. The scientific foundation of homeopathy is a subject of debate, but some research and clinical findings are indicating possible advantages in the treatment of arthritis symptoms. Studying the current research and clinical evidence offers valuable insights into the effectiveness of homeopathic treatment as a component of a comprehensive approach to treating arthritis.

Comprehending Homeopathy and the Essentials of Homeopathic Medicine

The basic idea behind homeopathy is that a substance that can cause certain symptoms in a healthy person can also help the body overcome those same symptoms when highly diluted and given to a sick person (Ling, 2020). This principle is known as "like cures like". This idea is the foundation for choosing homeopathic treatments that are customized to fit the individual's specific symptoms (Rizvi, n.d.). The Law of Minimum Dose highlights the importance of using very small amounts of a substance to reduce the risk of harm and side effects while still improving the effectiveness of the treatment. Homeopathic treatments are created by repeatedly diluting and vigorously shaking a substance, a process known as succession (Kalliantas et al., 2020). This method is thought to transfer the therapeutic qualities of the substance onto the water or alcohol solution. Homeopathy acknowledges the presence of a vital force or energy that brings life to living organisms. Illness is believed to stem from imbalances in this essential energy (Ling, 2020). Homeopathic treatments are believed to impact the vital force, bringing back equilibrium and enhancing the body's natural capacity to heal. Homeopathic medicine is tailored to each individual, considering not only the distinct symptoms of the illness but also the personal traits of the patient. Homeopaths take into account the psychological, emotional, and physical components of a person's well-being to choose the most fitting treatment (Masuku, 2022). This customized method sets homeopathy apart from more uniform medical treatments. Potentization is the term for the method of preparing homeopathic remedies through serial dilution and succession (Kalliantas et al., 2020). The gradual dilution process, typically indicated by potencies like 6C or 30X, leads to highly diluted solutions. Oddly, homeopathy proposes that the therapeutic effectiveness of the remedy strengthens as it becomes more diluted (Berghian-Grosan et al., 2024).

Modified Treatment Method

The fundamental aspect of homeopathic therapy involves a comprehensive evaluation of the patient (Jain and Kapoor, 2024). Homeopathic practitioners thoroughly interview their patients to gain a comprehensive understanding of not just the physical symptoms of their illness, but also their mental, emotional, and lifestyle characteristics. This thorough assessment enables the recognition of specific qualities that influence the choice of a personalized solution (Nengovhela, 2022). Homeopaths gather detailed information and then use repertories, which are thorough reference books that list symptoms and the corresponding remedies. Repertorization involves comparing the patient's symptoms with the remedies listed in the repertory to find a suitable match. This methodical examination assists in identifying the most appropriate solutions to be taken into account. Constitutional remedies in homeopathy are chosen according to the patient's comprehensive makeup, including their physical, mental, and emotional characteristics (Grollmann and Maurer, 2021). These treatments are specifically selected to target the root causes that are contributing to the patient's health problems. Choosing the right constitutional remedy involves a thorough understanding of the patient's unique characteristics and the principles of "like cures. Homeopathy acknowledges the existence of miasms, which are inherited tendencies that impact a person's vulnerability to specific illnesses. The consideration of miasms is important in choosing the right treatment, as it is thought to help with long-term healing by addressing underlying miasms (Vithoulkas and Chabanov, 2023). Homeopathic treatments can be given individually or as part of a combination of remedies to address a variety of symptoms. The decision to use a single remedy or a combination of remedies is based on the intricacy of the situation and the concept of tailoring treatment to the individual (Haider et al., 2024). Aside from recommending homeopathic treatments, practitioners also offer advice on how lifestyle and dietary choices can affect the patient's well-being. This comprehensive approach recognizes how physical, mental, and environmental factors are interrelated and impact overall health.

Safety Information about Homeopathic Medicines

The safety of homeopathic remedies is largely attributed to their extremely diluted form. The method of potentization entails repeatedly diluting and shaking a substance, leading to remedies with the original substance typically present in very minimal amounts (Borkens et al., 2024). The process of dilution is intended to reduce the material effects of the substance while preserving its energetic properties. Because of the high levels of dilution, homeopathic treatments are usually perceived as safe and easily tolerated (Stub et al., 2022). One key benefit is the lack of harmful side effects, particularly when compared to certain standard medications that pose the risk of negative reactions, organ damage, or interactions with other drugs. Homeopathy uses a personalized approach when determining which remedies to prescribe.

The choice of a homeopathic treatment depends on the individual's symptoms and overall health. This customized method aims to tailor the treatment to each person, thus minimizing the risk of negative effects that can result from one-size-fits-all therapies. Homeopathic treatments are generally believed to be able to be used alongside traditional medications (Silveira et al., 2020). They do not hinder the effects of pharmaceutical drugs, thus enabling them to be combined with customary medical treatments. This feature makes homeopathy an appealing alternative for people looking for a comprehensive approach to their health. Homeopathic treatments are usually seen as safe for use during pregnancy and in children (Illamola et al., 2020). The diluted nature of the remedies greatly reduces the potential harm to the unborn fetus or young children. Pregnant individuals and parents must seek guidance from a qualified homeopath or healthcare provider before utilizing any remedies.

Table 1: Plants used for the treatment of arthritis

Sr.No	Plant Name	Constituents	Effect of Plants on Arthritis	Target Site	References
1	Turmeric (*Curcuma longa*)	Curcuminoids	Anti-inflammatory, Analgesic	Joints, Inflammation	(Zeng et al., 2022)
2	Willow Bark (Salix spp.)	Salicin	Analgesic, Anti-inflammatory	Joints, Connective Tissues	(Lin et al., 2023)
3	Devil's Claw (Harpagophytum procumbens)	Harpagoside	Analgesic, Anti-inflammatory	Muscles, Joints	(Gxaba and Manganyi, 2022)
4	Ginger (Zingiber officinale)	Gingerol	Anti-inflammatory, Analgesic	Joints, Muscles	(Mutthuraj et al., 2020)
5	Boswellia (Boswellia serrata)	Boswellic acids	Anti-inflammatory	Joints	(Karlapudi et al., 2023)
6	Nettle (Urtica dioica)	Flavonoids, Quercetin	Anti-inflammatory, Analgesic	Joints, Immune System	(Abd-Nikfarjam et al., 2022)
7	Cat's Claw (Uncaria tomentosa)	Alkaloids, Oxindole	Immunomodulatory, Anti-inflammatory	Joints, Immune System	(Coelho and do Nascimento, 2020)

Natural Treatments for Arthritis and Remedies that are often used

Arnica montana is commonly used as a homeopathic treatment for arthritis, especially when there is bruising, tenderness, and a sensation of being battered or bruised. It is commonly advised for arthritis resulting from physical damage, accidents, or excessive strain. Arnica is thought to alleviate pain, decrease swelling, and reduce inflammation (Raza, 2021). The prominent remedy Rhus toxicodendron, which comes from poison ivy, is often used for arthritis characterized by stiffness and pain that gets better with movement (Mbatha, 2020). It is often advised for conditions like rheumatoid arthritis and osteoarthritis, where joints may initially feel stiff but become better with ongoing movement. The treatment could also be advantageous for arthritis caused by being in wet or chilly environments. Bryonia alba is recommended for arthritis cases with severe, sharp pains that are aggravated by movement. People who require Bryonia often experience relief when they rest and apply pressure to the affected joint. This treatment is linked with a lack of moisture and a need for calmness in order to relieve discomfort. One might recommend it for arthritis that is worsened by cold and aggravated by touch (Sakthi1and2 et al., n.d.). The homeopathic remedy Apis mellifica, made from the honeybee, is often recommended for arthritis accompanied by a feeling of stinging, burning pain, and inflammation. Inflamed joints can appear red, warm, and enlarged, and the symptoms tend to worsen with warmth and improve with cold therapies (Çelik and Aşgun, 2020). Many people believe that Apis can be beneficial for treating arthritis accompanied by swelling and may also provide relief for rheumatoid arthritis (Nipate and Bhandarkar, 2020). Pulsatilla is a commonly used treatment for arthritis characterized by joint pain that moves and changes location (Pushkar, 2022). People who need Pulsatilla may find comfort in mild movement and fresh, cool air. It is often advised for arthritis characterized by fluctuating symptoms, where the pain can shift from one joint to another. When determining the appropriate use of Pulsatilla, emotional characteristics like sensitivity and tendency to cry should also be taken into account (Jason and Adams, 2023).

Requirements for Choosing Homeopathic Treatments

The main factor in choosing a homeopathic treatment for arthritis is the unique set of symptoms exhibited by the patient. Homeopaths carefully evaluate the specific qualities of the joint pain, stiffness, and related symptoms. Various aspects such as the timing of symptoms, triggers, and the individual's mental and emotional state all play a role in creating a comprehensive picture of symptoms. When prescribing homeopathic treatments, consideration is given to the patient's overall traits, which encompass physical, mental, and emotional aspects. Constitutional remedies seek to restore the overall well-being and energy of the individual by addressing their state and bringing back equilibrium. Furthermore, taking into account miasms, inherited predispositions, or diatheses can aid in pinpointing underlying imbalances that contribute to the arthritis condition. It is important to comprehend the various ways and factors that worsen arthritis symptoms to choose the most effective treatment (Teut et al., 2020). If joint pain intensifies in cold and damp weather, Rhus toxicodendron could be a potential option (Kanchinkoote, 2020). On the other hand, if the symptoms get better with cold treatments, Apis mellifica may be a better choice. Identifying the exact circumstances that make symptoms better or worse can narrow down the options for treatment (Chotaliya, n.d.).

Arrangements and Formulations

In the practice of homeopathy, combination therapies refer to the mixing of multiple individual remedies to create a single formulation. These mixes are frequently created to target various symptoms linked to a particular ailment, for instance, arthritis. Combination treatments are a convenient option for people with a variety of symptoms, as they aim to take a more holistic approach to address multiple health issues (Kayne, 2021). Combination treatments seek to utilize the combined effects of different remedies, thus creating a solution that targets various elements of the condition. For people with multiple symptoms, combination treatments provide a simplified solution by removing the requirement to match each symptom with different remedies (Stub et al., 2022). Arthritis can present with different symptoms, and combination treatments aim to address a wider range of symptoms, potentially offering relief to more patients. While combination treatments seek to cover a wide range of symptoms, homeopaths stress the significance of tailoring treatments to each individual even within these combinations. Homeopaths understand that arthritis symptoms vary for each patient, so they may select a combination remedy that best matches the patient's overall symptoms (Edwards et al., 2023). This specific blend of treatments may contain ingredients such as Rhus toxicodendron for stiffness that gets better with motion (Kanchinkoote, 2020), Bryonia alba for increased pain when moving (Riley, 2022), and Arnica montana for feelings of soreness and bruising (Bartolomei et al., 2022). Blends created to support the joints and muscles might consist of treatments like Ruta graveolens for joint discomfort (Rathod et al., 2023), Calcarea fluorica for joint inflexibility (Sakthi1and2 et al., n.d.), and Kalmia latifolia for fluctuating pains (Hulekar and Poolya, 2022).

Medical Studies, Research, and Reviewing of Trials for Patients

Randomized Controlled Trials (RCTs) are widely regarded as the highest standard in clinical research and are specifically crafted to evaluate the effectiveness and safety of interventions, such as homeopathic remedies for arthritis. In randomized controlled trials, participants are assigned to receive either a homeopathic intervention or a placebo/conventional treatment in different groups through a random process. Using random assignment helps to minimize potential biases and ensures that any observed outcomes are directly linked to the intervention (Baig and DiRenzo, 2020). A randomized controlled trial found that Arnica montana was effective in reducing pain and stiffness in osteoarthritis patients when compared to a group receiving a placebo. The research indicated that Arnica could potentially have a beneficial effect on alleviating symptoms in individuals with osteoarthritis (Das et al., n.d.). Another randomized controlled trial examined the effectiveness of Rhus toxicodendron in treating rheumatoid arthritis and observed that the group receiving the treatment experienced reduced joint pain and improved physical function compared to those receiving a placebo. This implies that Rhus toxicodendron could potentially help alleviate symptoms linked to rheumatoid arthritis (Khadim et al., 2023).

Analyzing Medical Research, Conducting Studies, and Evaluating Trial Results for Patients

One of the main obstacles in researching homeopathy is the personalized approach required for homeopathic treatments (Fønnebø et al., 2007). Homeopathy focuses on providing individualized treatment tailored to the specific symptoms and characteristics of each patient. The customization of treatments makes it difficult to create standardized interventions that are appropriate for traditional research methods such as randomized controlled trials (RCTs). Homeopathic studies frequently encounter challenges in establishing consistent treatment protocols (Jonas et al., 2001). Homeopathic treatments are tailored to each individual and are prepared through a potentization process that results in highly diluted solutions. The lack of standardization in remedy composition and the variability introduced by the potentization process makes it difficult to achieve consistent results in different studies (Prajapati et al., 2023; Walach et al., 2005). This variation can present challenges in comparing results across trials and reproducing discoveries. Homeopathic treatments frequently utilize greatly diluted substances, leading to inquiries about how they work and whether any benefits are due to the placebo effect (Ullman, 2021). Creating research studies that successfully prevent participants and researchers from knowing the treatment conditions can be difficult, particularly when it comes to homeopathic remedies which have unique characteristics that may be identifiable. This challenge could impact how results are interpreted in both controlled trials and observational studies (A. Dutta, 2023). Arthritis includes a wide variety of conditions, such as osteoarthritis, rheumatoid arthritis, and other inflammatory problems affecting the joints. The diversity of arthritis symptoms makes it challenging to study, as various forms of the condition may react in varied ways to homeopathic remedies. Customizing interventions for different types of arthritis may be essential, but it can also make study designs more complicated (Sharma and Goel, 2023). Despite facing methodological difficulties, a few randomized controlled trials (RCTs) examining homeopathic remedies for arthritis have found promising results. Research has found that homeopathic treatments have led to enhancements in pain management, joint function, and the general health of those who receive them. The positive results seen in some randomized controlled trials add to the evidence that supports the potential efficacy of homeopathic treatments for managing arthritis (Feng et al., 2021).

Integrative Homeopathy with Conventional Treatments and Rationale for Integration

An integrative approach to arthritis management acknowledges the potential advantages of incorporating homeopathic remedies alongside traditional treatments. This collaborative effort is focused on delivering holistic care for arthritis, encompassing the different facets of the condition such as managing symptoms, modifying the disease, and enhancing overall health. The incorporation of homeopathy with traditional treatments is based on the idea of personalized and comprehensive patient care. Homeopathy and traditional treatments can work together to provide comprehensive care for arthritis (Gupta, 2023). Homeopathic treatments can be customized to target specific sets of symptoms, providing relief from pain, rigidity, and inflammation. This focused symptom control enhances the overall effectiveness of traditional medications. Traditional medications, like disease-modifying anti-rheumatic drugs (DMARDs), aim to alter the progression of arthritis (Han et al., 2022). Homeopathy focuses on providing personalized treatment based on an individual's unique constitution, which could help address fundamental imbalances and aid the body's self-regulation. Homeopathy takes into account emotional and mental aspects, leading to better overall well-being through a holistic approach. Blending homeopathy with traditional treatment acknowledges the significance of addressing the psychological and social aspects of arthritis. The homeopathic treatment Rhus toxicodendron, often used for arthritis accompanied by stiffness that eases with movement, can be combined with nonsteroidal anti-inflammatory drugs (NSAIDs) to provide greater pain relief during periods of inflammation (Kanchinkoote, 2020). Arnica montana, known for its ability to alleviate pain and bruised sensations, can be used alongside pain-relieving medications to help manage sudden pain episodes in arthritis (El Gendy et al., 2024). The holistic approach of homeopathic constitutional treatment can be combined with DMARDs to effectively address both the symptoms and underlying causes of arthritis (Sakthi1and2 et al., n.d.).

Treating Arthritis using many Different Methods

A holistic approach to managing arthritis involves multiple disciplines and recognizes that the condition affects not just physical symptoms, but also emotions, psychology, and lifestyle. This comprehensive strategy seeks to meet all the different facets of a person's arthritis experience, promoting their overall health and ability to function at their best. Traditional medical methods such as medication, rehabilitation, and surgery are essential for treating arthritis (Akram et al., 2021). These interventions target the alleviation of symptoms, alteration of the disease course, and enhancement of joint functionality. Homeopathy brings a distinct viewpoint as it provides personalized treatment according to the principle of "like cures like". Homeopathic treatments target particular sets of symptoms and the inherent characteristics of a person, potentially improving their overall health. Rehabilitation and physical therapy are essential for preserving joint flexibility, preventing abnormalities, and maximizing functional capacity (Shahid et al., 2023). Customized workout routines, such as resistance training and stretching exercises, are crucial for effectively managing arthritis. A diet that is balanced and provides all the necessary nutrients is crucial for managing arthritis. Nutritional support focuses on reducing inflammation, improving joint health, and promoting overall physical wellness. One possible dietary approach involves incorporating foods and supplements with anti-inflammatory properties (Nikiphorou and Philippou, 2023). Arthritis has a strong emotional and psychological effect. Receiving psychosocial support such as counseling, participating in support groups, and learning stress management techniques can assist individuals in managing the difficulties of living with arthritis and improve their overall mental health (Batko, 2020).

Patient Education and Permission

Effective management of arthritis involves educating patients about their condition as a key component (Nikiphorou et al., 2021). Patients who are knowledgeable and confident in their understanding of their health are more prepared to be actively involved in their treatment, make well-informed choices, and adopt healthy habits that support their overall health and wellness. Education helps individuals feel more empowered, less anxious, and better equipped to manage the difficulties related to arthritis. Offering detailed information on the particular form of arthritis, its causes, and its potential effects on the joints and overall well-being aids individuals in understanding the nature of their ailment. Teaching patients about different treatment options such as traditional medications, homeopathic treatments, physical therapy, and lifestyle changes allows them to make knowledgeable decisions that match their personal preferences and beliefs (Carluzzo et al., 2022). By elucidating the fundamental concepts of homeopathy, its personalized methods, and its possible contribution to symptom relief and overall health, patients can gain a better understanding of this complementary form of treatment. Equipping individuals with effective techniques for self-care, safeguarding their joints, and adjusting their lifestyles encourages them to take proactive steps in managing their arthritis symptoms. This incorporates advice on physical activity, diet, and coping with stress (Wainwright et al., 2023). Emphasizing the advantages of physical therapy in preserving joint function, averting deformities, and enhancing mobility adds to a complete comprehension of the interdisciplinary method of treating arthritis (Peter et al., 2021). Highlighting the significance of arthritis on mental and emotional health highlights the crucial need for psychological and social assistance, therapy, and involvement in support communities (Park et al., 2020).

Homeopathic Treatments are safe with Minimal Side Effects. It follows basic safety principles

Homeopathic treatment is typically considered safe when practiced by experienced practitioners following established principles. There are multiple aspects that contribute to the safety of homeopathic remedies. Homeopathic treatments go through a potentization process, which includes multiple dilutions and vigorous shaking. The resulting highly diluted levels reduce the possibility of the original substance causing harm (KANUPRIYA, 2021). Homeopathic remedies are customized to match the specific symptom profile of each patient. This individualized method seeks to tailor the treatment to the particular symptoms, thereby decreasing the chances of negative side effects. The principle of minimal material dose in homeopathy involves administering remedies in highly diluted forms to reduce the concentration of the original substance. This decreases the likelihood of experiencing unwanted effects linked to higher amounts of the medication (Ullman, 2021).

Safety of Popular Homeopathic Remedies

Arnica, often utilized for bruising and injury, is generally considered safe when applied topically or taken in homeopathic dilutions (Yalgi, 2022). Nevertheless, it is advisable to refrain from applying undiluted forms to broken skin or consuming them orally. This treatment, recommended for arthritis characterized by stiffness that gets better with movement, is deemed safe when prepared by homeopathic principles. Negative effects are uncommon when used by instructions. Bryonia is a well-tolerated homeopathic remedy used for arthritis with intense stitching pains that are aggravated by movement (Limping, n.d.). Healthcare providers take into account the specific traits of each patient to decide whether a particular treatment or intervention is appropriate. Obtained from the venom of honeybees, Apis is utilized to treat arthritis characterized by pain, inflammation, and burning sensations. When used in homeopathic preparation, it is generally regarded as safe and carries a low likelihood of causing negative reactions (Çelik and Aşgun, 2020). Pulsatilla, recommended for changing joint pain, is typically considered safe in homeopathic dilutions. One must take into account the unique sensitivity of each individual to the treatment (S. Dutta et al., 2022).

The Surveillance and Documentation of Negative Outcomes and the Significance of Such Surveillance

Monitoring for negative effects is a crucial part of ensuring the safety of homeopathic treatment. Although homeopathic treatments are typically safe, oversight enables practitioners to quickly detect and deal with any unforeseen reactions or exacerbations. This proactive method helps in continually enhancing patient care and safety standards in the homeopathic community. Possible negative effects of homeopathic treatment may consist of temporary worsening of symptoms or unforeseen reactions (Stub et al., 2022). Healthcare professionals must be observant and quick to notice any changes in the patient's health, thoroughly assessing the symptoms and their duration, and acknowledging the potential for a reaction to the treatment.

The Categorization of Adverse events in the Practice of Homeopathy

Temporary increases in current symptoms, also referred to as aggravations, may occur as a part of the homeopathic healing journey (Bell, 2020b). It is important to be able to differentiate between a minor annoyance and a more serious negative response to effectively address the situation (El-Manstrly et al., 2021). Occasional unexpected reactions, such as the appearance of new symptoms or a worsening of unrelated health issues, can also occur. Healthcare professionals must evaluate if these effects are consistent with the anticipated reaction to the treatment and make modifications to the treatment plan if needed (Busse et al., 2021). Although uncommon, some individuals can experience allergic reactions to certain treatments or dilution substances. Professionals need to pay close attention to indications of allergic reactions, like skin irritations, inflammation, or breathing issues (Murodovna and Zayniddinovna, 2024).

Comparison of Traditional Medicines

Recognizing differences in the way homeopathic remedies and conventional medications work, how they are made, and how they are regulated is essential when comparing their safety profiles.

Homeopathic treatments are made by diluting substances and undergoing a potentization process. Their focus is on individualizing treatments, using minimal doses of materials, and matching symptoms closely (Bell, 2020a). This results in a safety profile that emphasizes tailoring treatment to the individual and using small amounts of substances. Negative incidents usually occur infrequently, and treatments are generally easy for the body to handle. Traditional drugs used for arthritis, such as NSAIDs, DMARDs, and corticosteroids, may have a wider range of impacts (Akram et al., 2021). Although they are created to control symptoms and slow the progression of the disease, they may come with side effects and possible long-term risks. Traditional drugs used to treat arthritis can have certain adverse effects and dangers (Wang et al., 2021). Gastrointestinal problems, cardiovascular issues, and renal complications are common side effects of NSAIDs. Extended use or the consumption of large amounts may heighten the likelihood of experiencing negative effects (Domper Arnal et al., 2022). Disease-modifying drugs for rheumatoid arthritis are successful in treating the condition, but they may also lead to a weakened immune system, liver problems, and a higher likelihood of getting sick. Prolonged use of corticosteroids can result in decreased bone density, a higher risk of infections, and other overall body effects (Miravitlles et al., 2021).

Conclusion

Valuable insights have been gained from the investigation of homeopathic therapy for treating arthritis. Several randomized controlled trials and observational studies have found that homeopathic interventions have resulted in positive effects, such as decreased pain, improved joint function, and overall better health in individuals. According to long-term studies and research on specific age groups, it is indicated that homeopathic remedies could result in lasting improvements for patients, leading to continued symptom relief and improved overall well-being. Safeguarding safety in homeopathic practice requires following established guidelines, keeping an eye out for any negative effects, and maintaining open communication with patients. Professionals should be actively involved in continuous safety monitoring, contribute to reporting systems, and be part of ongoing efforts to improve quality. Homeopathic treatment provides a personalized and comprehensive strategy for treating arthritis. Through the analysis of individual symptom patterns, overall constitution, and emotional aspects, homeopathy assists in providing a thorough and holistic approach to understanding and treating arthritis. In the future, arthritis care could incorporate greater teamwork and blending of homeopathic and conventional medical approaches. This cooperative strategy acknowledges the wide range of resources for arthritis management and strives to enhance results by providing coordinated, patient-focused treatment. Homeopathic therapy plays a diverse role in treating arthritis, involving continued research, personalized care for patients, and cooperation between various methods to create a comprehensive approach to managing arthritis. The quest for exploration and improvement persists, aiming to improve the quality of life for people with arthritis.

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Chapter 37

Homeopathic Medicines used to Treat Various Internal, Muscular, Joint and Skin Diseases in Equines

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ABSTRACT

There are multiple problems treating in various muscular, joints, skin, and internal diseases of equines with synthetic drugs. To avoid all the contraindications and complications of the synthetic drugs, natural remedies are the best alternative solution. Among all the alternative methods to treat the diseases of the equines, homeopathy is the best suitable option. Homeopathic treatment has the least side effects, and it is the least toxic. Homoeopathy is secure, it is based on three principles: infinitesimal individualization of the cases, and similarity. Homoeopathic treatments, when used alone or in combination with antibiotics, are effective in treating bacterial infections in both humans and animals. In this chapter, we will discuss the different internal, muscular, joints, and skin diseases of equines and their treatment with homeopathic medicines.

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Homeopathy, Homeopathic medicine, Equines, Problems, Treatment	Received: 05-Jun-2024 Revised: 21-Jul-2024 Accepted: 05-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Homoeopathy is a natural method used for both acute and chronic horse illnesses that helps in the restoration of the animals' health (Bergh et al., 2021). The name "homoeopathy" comes from the Greek terms "pathos," which means suffering, and "homoios," which means "like" (Goswami and Dey, 2022). Although the initial purpose of homoeopathy was to heal equine, it was created in 1796 by Samuel hahnemann that animals would probably also benefit from homoeopathic treatment (Avcıoğlu and Boyacıoğlu, 2024). Homoeopathy is secure, it is based on three principles: infinitesimal individualization of the cases and similarity (Ijaz, 2020). Studies have indicated that homoeopathic treatments, when used alone or in combination with antibiotics, are effective in treating bacterial infections in both humans and animals (Nayak and Varanasi, 2020; Varanasi and Nayak, 2020; Yalgi, 2022; Aditya et al., 2023). It is applied generally, much like remedies as we are aware, human and equine muscle physiology is identical, used in the therapy of muscles (Lage et al., 2020; Reis et al., 2024). In addition, it is used to improve their growth and production and to cure a variety of bacterial, viral, and parasite illnesses as well as nutritional inadequacies and stress (Bergh et al., 2022; Datta, 2020; Lingeswaran and Mohan, 2024). Numerous inflammatory conditions, such as persistent gingivitis, both acute and chronic diarrhea, respiratory ailments, renal insufficiency, behavioral issues, and more, can also be treated with it (Alex, 2020). They are also used together with allopathic medications to minimize side effects (Aphale and Sharma, 2022; Patel and Patel, 2022). Maximum outcomes are achieved by the internal management (Siddique et al., 2023). Equine homoeopathic remedies *Pulsatilla, silicea, lycopodium, calcarea flurica,* and *ledum* are frequently used (Fleming, 2002).

Natural Remedies for Internal Problems

Immune System

Many herbs and natural products are used to treat different immune problems in equines (Williams and Lamprecht, 2008; Elghandour et al., 2018). *Echinacea* spp. are the most commonly used natural products used as immunomodulatory agents (Senchina et al., 2011; Eldin et al., 2021). It is also known as Coneflower (Petrova et al., 2023). There are 9 species of Echinacea, but *Echinacea purpurea, Echinacea angustifolia,* and *Echinacea pallida* are tested and proven effective in boosting the immune system (Fu et al., 2021; Burlou-Nagy et al., 2022; Kakouri et al., 2024). There are multiple uses of these plant products, but mainly they are used as supportive therapy for treating respiratory tract infections and common colds (Willcox et al., 2020). Results have shown that Echinacea has a very wide scope for pharmacological activities (Burlou-Nagy et al., 2022). It reduces the severity of the ailment and the duration of symptoms of the problem (Xu et al., 2021). Echinacea activates the innate immune cells and improves immunity. Sulphur is another naturally occurring compound which enhances the immune mechanism of the body (Tadele and Zerssa, 2021). Research shows that compounds containing sulphur have significant effects on the humoral immune system (Lesyk et al., 2022; Pozzi et al., 2022). The highest effect on the stimulation of immune system is observed by a sulphur compound Diallyl disulfide (DADS) (Jikah and Edo, 2023; Sonaji et al., 2024). According to results from another research shows both an increased number of plaque-forming cells and increased titer of antibodies (Park et al., 2022).

Liver

Liver plays a significant role in detoxification and metabolism (Esteves et al., 2021). Any damage to the liver can lead to numerous health problems or severe ailments (Devarbhavi et al., 2021). Dandlion, a natural product, is a very good hepatoprotective agent (Mahboubi and Mahboubi, 2020; Pfingstgraf et al., 2021). Dandelion has a significant role in the detoxification of the liver (Wang et al., 2022). It is present as ad libitum in the grazing tracts of the horses (Schlittenlacher, 2022). Leaves of Dandlion help in the digestion and increase of appetite (Li et al., 2022). Other functions of this natural product include antioxidant properties, detoxification of gallbladder, and improves kidney function (Kour et al., 2020; Mahboubi and Mahboubi, 2020; Li et al., 2022). It also has diuretic properties which ultimately help in removal of water and salts from the kidney (Suljević et al., 2022).

Poisoning

Poisoning is caused by ingestion of toxic plants (Okereafor et al., 2020; Awuchi et al., 2021). It happens mostly when the horse has nothing else to eat, so they eat harmful poisonous plants, herbs, or forages (Cappai and Aboling, 2020; Aboling, 2023). Most prone equine specie to poisoning is the donkey because of its management and environment habitat (De Santis et al., 2021; Furtado et al., 2022). Some of the poisonous plants include *Digitalis* spp*., Juglans nigra, Acer rubrum,* and *Ranunculus* spp. (McCullough, 2022; Singhurst et al., 2022). If the horse has taken any of the poisonous compounds, it can be treated by various natural products (González and Vallejo, 2021). Ginger, aloe vera, turmeric, and peppermint can be used against poisoning (Yassin, 2023). Ginger has very good digestive, anti-inflammatory, antioxidant, anti-thrombotic, and anti-bacterial properties (Williams and Lamprecht, 2006). Hence, used as an agent against poisonous products (Yassin, 2023). The major constituents of ginger are gingerol, myoga, and paradol (Deng et al., 2022).

Natural Remedies for Treatment of different Joints and Muscle Problems

Arthritis

Arthritis is the common condition of the bone in equines, which causes stiffness, pain and decreases functionality (McIlwraith et al., 2020). It mostly affects the quality of life of adults and older adults. Most common problem which occurs due to arthritis is lameness and horse cannot be used in any game or competition, results in retirement (Holmes and Brown, 2022). Lameness can be corrected with the help of exercise. Rhus Tox is a naturally made product which has been proven very effective in the treatment of arthritis (Goswami et al., 2022). Rhus tox increases the expression of COX-2 and decreases NO formation, which will ultimately have anti-inflammatory response (Khalil et al., 2021). It also acts as an immunomodulator, it consists of urushiol (Ghosh et al., 2024).

Muscle Stiffness

Major cause of the disability in equines are muscle disorders, which include mainly the muscle stiffness in the back muscle of the horses (Story et al., 2021). Muscle stiffness is caused by the deficiency of Vitamin E, sodium or calcium (Raskh, 2020). Blood of horses may exhibit the increased activity of the enzymes which work in the muscle (Arfuso et al., 2022). Correcting dietary deficiencies and metabolic imbalances may cause relief from muscle stiffness. Ruta graveolens, also known as Rue, is used as anti-inflammatory medicine and has proven helpful against muscle stiffness. Rhus tox is also used for the treatment of muscle stiffness (Vinita et al. 2024).

Natural Remedies for the Treatment of Skin Related Problems

Equines are important for different activities, so we need healthy animals having a good skin coat

Warbles

It is caused by *Hypoderma Bovis* and *Hypoderma lineatum* which causes painful and large swelling on skin (Jamil et al., 2023). It can be treated by incising tumor and then by application of Sulpurous acid 3 times a day (McClure, 1917).

Lice

Damalinia equi and *Haematopinus asini* infest equines. *H. asini* is present around the tail base, above fetlock hairs which causes itching. Animals feel irritation and scratch their body, which damages skin. For treatment or eradication of louse wash harness with hot water. Apply olive oil to damaged skin. Sulphur ointment can also be used. If an eruption occurs, use Arsenicum thrice a day (Alipour and Goldust, 2015).

Scabies

It is caused by *Dermatodectes equi, Sarcopies equi, Symhiotes equi* also known as itch or mange. Mites burrowed in skin causes irritation and eruptions. Always wash your whole body with warm water and soft soap and then dry the skin. Zinc, neem, tea tree oil, clove oil, turmeric, aloe vera and cayenne pepper are used for killing of these mites. Sulphur ointment can also be used (Nasir et al., 2023).

Erythema

Friction between skin folds causes erythema. Clean the affected part, dry it properly, dust with fuller's-earth. If it is caused by saddle/collor pressure to remove the saddle collar and apply Arnica Lotion. To treat sit fast, remove affected hard skin and dress wound with Calendula Lotion. Cracked heels can be treated by clipping hairs and poultice with bran. Sulphorus acid is used to treat ulceration and also give 10 drops of Arsenicum. Application of Sulphurous acid by a camel's-hair pencil heals chapped teat (Williams, 2024).

Hives, Stings and Bites

Apis Mellifluca is used for treating swelling and itching caused by bites and stings of insects, spiders, snakes, scorpions, and honeybees. Rhus Tox is useful for treating hives. Ledum palustre prevents and treats reactions caused by bites of insect (Sīle, 2021).

Warts, Tumors, Sarcoids, Papular Eruptions and Reactions

Warts or sarcoids are tumors of skin which can reoccur caused by Bovine papillomavirus (BPV), primarily types 1 and 2. Thuja is used for treatment of styes, tumors, sarcoids, warts, skin tags and reaction at injection site or due to vaccination. Belladonna, Arsenicum and Sulphur treat paular eruptions (Pudale, 2022).

Ringworm

Ringworm is caused by keratinophilic fungi mainly by Trichophyton species and Microsporum species. It is major health concern among human and animals. Bacillinum 200 per month is given for treatment. Kali arsenicum 200 restores normal skin and is given daily for seven days (Husain, 2020). Before giving a bath to animals, apply hot mustard oil.

Mud Fever

It is seborrheic dermatitis of the lower limbs, which is chronic in nature. Also known as scratches. Wash and clean with lukewarm water and glycerin, then dry it with cloth. Poultice with turnips and boiled carrots if there are scabs or discharge. Sulphurous acid Lotion and Arsenicum 10 can be used (Kalaghatagi, 2020).

Adverse Effects

Homeopathic medicines are usually safe and without significant adverse effects, since they consist of only a small amount of a highly diluted substance (Hawke et al., 2022). So, the chances of causing direct toxicities are less. Many homeopathic products are being used to treat different diseases and conditions in horses. However, if any homeopathic products have not been reviewed by the drug regulatory authority (like the FDA) for safety or effectiveness in treating, curing, preventing, or elevating any diseases or conditions, they can impose serious effects on animal health. Adverse effects can occur if a combination of different homeopathic medicines is given to a horse, which are antagonists and can disrupt the normal body function of the horse. We think homeopathic products are natural, and they don't produce adverse effects on the animal's body. 'Natural product' does not mean a lack of adverse effects. Homeopathic medicine can cause fatal effects on equine health if it is present in higher quantities or if the horse is allergic to any ingredient present in that particular medicine. Some homeopathic products were identified as containing higher doses or ingredients other than those listed on the label. There is also less research work in the field of veterinary homeopathy. Common adverse effects induced by homeopathic medicine include hypersensitivity, dermatitis, abnormal intestinal motility, and allergic reactions. Nux vomica, Rhus tox, arsenic, Arsenic, and chmomilla are commonly used ingredients in different homeopathic products and can cause Acute pancreatitis, melanosis, keratosis, skin lesions, severe swelling, bleeding, and rashes Tincture of aconite contains aconitum, which is used to treat fear, anxiety, restlessness, and acute sudden fever in horses. Aconitum intoxication causes severe bradycardia, a reversible panconduction defect, hypotension, and syncope in horses (Chung, 2004).

Conclusion

Homeopathic medicine has been proven very effective against multiple diseases of equines. Natural remedies have been in use since long. These drugs have a potential to treat various diseases and problems in equine family. Homeopathic medicines have multiple medicinal properties out of which their immune boosting activity is the most helpful for the treatment and prevention of different diseases and disorders. In this chapter, we have concluded that the herbal or homeopathic medicines have very positive effects in the treatment of internal, muscular, joints, and skin problems. However, the safety index of some drugs should be monitored by conducting multiple experimental designs.

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Chapter 38

Management of Food Allergies and Intolerance using Traditional and Advanced Methods

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ABSTRACT

Food allergies and celiac disease are examples of adverse food reactions with an immunological basis. A food allergy is an adverse immune-mediated reaction that always arises when exposed to a specific food and goes away when it is avoided. Food allergies affect between 0.5 to 9% of the population overall and have a negative impact on health, particularly in young people. Milk and milk products, wheat products, shellfish, tree nuts, eggs and egg products, peanuts, fish and fish products these are the common foods that trigger food allergy. Foods associated with intolerance are gluten- containing products, chemicals and foods with additives and dairy products. Immunoassays, ELISA, Lateral flow immunoassay, xMAP techniques. These methods are used to detect food allergens. The majority of commercially accessible foods may contain chemicals that cause allergies or intolerances as an unidentified ingredient.

KEYWORDS		
Food Allergies, Intolerance, Traditional, Advanced Methods	Received: 01-June-2024 Revised: 23-July-2024 Accepted: 06-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Food allergies and celiac disease are examples of adverse food reactions with an immunological basis. Food intolerances, on the other hand, are examples of adverse food reactions without an immune base. Despite being a T-cell mediated (Type 4 hypersensitivity) immunological response to gluten, celiac disease is not typically considered a food allergy (Turnbull et al., 2015).

What is Food Allergy?

A food allergy is an adverse immune-mediated reaction that always arises when exposed to a specific food and goes away when it is avoided. To diagnose food allergies, one must find evidence of sensitization and unique symptoms after consuming a particular meal. IgE-mediated, non-IgE-mediated, or a mix of the two types of immune responses can be brought on by food allergies. Food allergen sensitization—the formation of a serum-specific IgE antibody to a food allergen—and the manifestation of symptoms upon exposure to the food allergen are prerequisites for IgE-mediated food allergies. T-cell-mediated mechanisms are predominant in non-IgE-mediated food allergies, and histological evidence of an underlying immunological process, such as eosinophilic inflammation of the gastrointestinal tract, may be present (Turnbull et al., 2015).

What is Food Intolerance?

Dietary intolerances refer to several categories of unwanted dietary reactions. The immunological system is not involved in these non-allergic food reactions. A lack of an enzyme that breaks down lactose results in lactose intolerance, one example of a dietary intolerance involving an organic pathophysiological process. Nevertheless, a number of dietary intolerances observed in people with irritable bowel syndrome (IBS) cannot be easily explained by currently recognized organic mechanisms (Turnbull et al., 2015).

Food allergies affect between 0.5 to 9% of the population overall and have a negative impact on health, particularly in young people. All the following are major food allergies: milk, eggs, peanuts, tree nuts, shellfish, wheat, soybeans, fish, and other food products that either directly or indirectly include these allergens (Boye, 2012). Ninety percent of food allergy cases globally are linked to these foods, according to the US Food and Drug Administration. In addition to the top eight allergens, a number of foods have a high potential to cause allergy reactions, such as corn, sesame, pork, celery, honey, fruits, and vegetables (Fu et al., 2019).

Common Foods that Trigger Allergies

1-Milk and Milk Products

Milk is a staple food consumed by people worldwide, even young toddlers and babies. It is the incredibly nourishing nourishment that postpartum female mammals' mammary glands make. For newborns between the ages of five and six months, breast milk is their only nutritional source. Other foods are gradually introduced after that. It fulfills the essential nutrient requirements for newborn growth and development as the major source of nutrient supplements (Walsh et al., 2016). Milk is an essential part of every adult's diet, including babies and young toddlers. It is the incredibly nutritious material that postpartum female mammals' mammary glands generate. For a newborn between the ages of five and six months, breast milk is their only dietary source. One food at a time after that is added. It fulfills the essential nutrient requirements for the growth and development of neonates and is the main source of vitamin supplements (Ramachandran et al., 2020). All adults, even infants and young toddlers, eat milk as a staple diet. It is the extraordinarily nourishing substance produced by the mammary glands of postpartum female mammals. Breast milk is the only food that newborns between the ages of five and six months may consume. After that, other foods are added one at a time. As the primary source of vitamin supplements, it satisfies the vital nutrient requirements for the growth and development of newborns (Pilolli et al., 2020). Furthermore, a variety of vegan milk alternatives are offered for sale as a fast-growing trend to replace cow's milk (Elsabie and Aboel Einen, 2016). To extract milk, vegan milk sources including rice, almond, soy, oats, hemp, coconut, etc. are soaked in water for a few hours, crushed, and then filtered. Additionally, vegan milk meets all of the nutritional requirements of conventional milk, and fortification is a method that may be used to further improve the nutritional profile. In the rare event of an allergy, heated or baked milk products are typically advised as safe (GRAS). The heat process denatures or modifies the proteins in milk, making it impossible for the immune system to identify them as allergens (Upton and Nowak-Wegrzyn, 2018). The greatest defense against newborn milk allergy is breastfeeding. It is vital to note that lactose intolerance and milk allergy have completely different pathophysiologies and are frequently undiagnosed.

2- Wheat Products

Roughly 75% of wheat-based products are thought to be utilized as dietary food for humans, with the remainder going toward animal feed and non-food uses (Bird and Regina, 2018). Gluten, globulins (salt soluble), and albumins (water soluble) are the three types of wheat proteins. The main protein found in wheat is gluten, which is further divided into two types based on solubility: gliadin, which is soluble in ethanol, and glutenin, which is soluble in acid or alkali. IgE-mediated food allergies are triggered by gluten, and depending on the dosage consumed, the symptoms can be minor to severe (Cabanillas, 2020). Dermatitis, rashes, and skin redness are the most common allergic reactions. Skin, lip, and throat irritation are also common, as are digestive issues such as diarrhea, vomiting, abdominal pain, and nasal congestion, as well as severe wheat-dependent exercise-induced anaphylaxis. The latter takes place right after consuming wheat or its products and is contingent upon how long the exercise is performed following the ingestion of wheat, often lasting between 10 and 60 minutes (Cianferoni, 2016).

3- Shellfish

The symptoms of shellfish allergy can range from mild to severe and are typically an onsite reaction. After tree nuts and peanuts, it is the third allergy that can result in anaphylaxis. The primary allergen causing shellfish allergies is tropomyosin, a muscle protein found in shellfish (Gupta et al., 2019). It's crucial to understand that, despite their shared misconception, fish allergy and shellfish allergy are quite distinct from one another. Allergy reactions induced by shellfish are unpredictable because even a small amount of the substance might result in symptoms like hives, itching, swelling, breathing difficulties, diarrhea, and unconsciousness. Allergy responses can also be brought on by handling procedures and steam inhalation during clam cooking (Pedrosa et al., 2015). It is preferable to prepare and eat shellfish at home rather than dining out, where there is a greater risk of cross-contamination.

4- Tree Nuts

Tree nuts are edible seeds that are used as a vegan milk substitute and as a small-scale garnish for cooked food. They also have a strong flavor. Most tree nuts are 50–60% fat and enhanced with important nutrients (Vanham et al., 2020). But they are a strong and common food allergy that causes unfavorable health effects that are rarely fatal. A person who has an allergy to one type of nut need not have an allergy to all nuts. Walnut, hazelnut, cashew, and almond allergens can induce life-threatening reactions. Numerous seed storage proteins, including vicilin, legumins, albumins, and others, are abundant in tree nuts and function as major allergies; guard proteins and profilins, on the other hand, are regarded as minor allergens (Geiselhart et al., 2018). Oral or pollen food allergy syndrome is the name given to the mild symptoms that arise from the cross-reactivity of birch pollen and tree nuts (Wangorsch et al., 2017). Tree nuts are an ingredient in many commercial products, such as baked goods, candies, cereals, soup mixes, high-energy bars, and homemade meals. Allergic responses can be caused by these products (Eigenmann et al., 2017).

5- Egg and Egg Products

Eggs are a cheap, easily accessible food that's rich in vitamins, proteins, and lipids. As stated by Godbert and colleagues (2019). They help regulate weight loss and enhance the strength of the heart, muscles, brain, skin, eyes, and immune system. Although chicken eggs have many beneficial health impacts, they are categorized as one of the top eight food allergens. The main allergens identified in the egg yolk are vitellus, apoprotein B, and alpha-livetin; ovalbumin, ovomucoid, conalbumin, and lysozyme enzymes are present in the egg white. Chicken serum albumin, or alpha-livetin, is the main allergen source that contributes to cross-reactivity (Hemmer et al., 2016). Egg whites trigger more allergic reactions than egg yolks because of their higher protein content. The proteins found in egg whites are heat-labile and retain their allergenic qualities even after processing (Onoda et al., 2020). Anaphylaxis, breathing difficulties, skin rashes and hives, and digestive issues are among the symptoms of egg allergy that appear right after ingestion (Ballmer-Weber et al., 2016).

6- Peanuts

The legume family that includes peanuts is widely utilized as an ingredient and part of our daily diet in a variety of forms, such as a single nut, filler, and alternative to more costly food items. The flour made from peanuts is typically used to make chocolate bars, baked goods, and other culinary products since it is high in protein and low in carbohydrates. Nut oils are derived from peanuts and employed in nutritious cooking methods (Akram et al., 2018). But among the eight common dietary allergen sources that cause severe allergic reactions, peanuts are one. According to (Chan et al., 2019), some of the linked allergy symptoms include inflammation, tingling of the tongue, itching in the mouth and throat, breathing difficulties, and low blood pressure. Anaphylactic shock is a potentially fatal condition. It is possible for pregnant women to eat peanuts, however, avoiding peanut-containing foods during pregnancy can limit the risk of exposure to the fetus. According to some research, applying peanut oil topically to the skin to treat wounds may also cause allergic reactions (Palladino et al., 2018). While highly processed oil from peanut is safe to eat, crude peanut oil is thought to cause allergies since it contains the majority of the allergens in the final product (Blom et al., 2017).

7- Fish and Fish Products

Eating fish and fish products is essential for human nutrition and can help prevent shortages in certain micronutrients. They have increased protein content, vitamins and minerals that are fat-soluble, good fats like eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA) that are necessary for a balanced diet (Kvasnicka et al., 2019). Fish with fins can produce a variety of allergic reactions, including the deadly anaphylaxis. In areas where fish and fish products are consumed in large quantities, the allergic reactions have a higher prevalence rate. About 40% of adults suffer from allergies connected to fish, which is typically a chronic illness. Various fish species' muscle, skin, bone, blood, and bodily fluids include allergens (Kobayashi et al., 2016). There have been reports that food processing procedures, such as applying physicochemical techniques, can reduce fish's allergenicity; however, the exact mechanism at work is yet unknown (Fernandes et al., 2015).

Foods Associated with Intolerance

1- Gluten-containing Products

A gluten-free diet cannot include bread, cereals, or similar products made with wheat, oat, dinkel, barley, triticale, kamut, or rye flour. The bulk of processed food items, such as cheese, pasta, pizza, hot dogs, cream sauces, salad dressings, and soup mixes, contain thickeners and fillers made from gluten derivatives (El Khoury et al., 2018). Unexpectedly, malt-based products such as malt extract, malt flavoring, or malt vinegar, licorice, beer, broth, soy sauce, and imitation crab meats can all contain gluten. Furthermore, consuming various forms of wheat—including spelt, cracked wheat, wheat germ, wheat bran, emmer, farina, einkorn, faro, graham flour, and so on—is not advised (Jnawali et al., 2016). In addition, those who adopt a gluten-free diet need to take precautions to prevent gluten from contaminating food in their own kitchens and other eating locations. Bread, biscuits, soups, cookies, bagels, cakes, pasta, and other frequently consumed foods are made of wheat and contain gluten. But avoiding these goods would require a complete lifestyle adjustment, which may not be feasible for all people with gluten intolerance. These restrictions are driving up demand for gluten-free goods. It is important to stress, nonetheless, that the nutritional profile of gluten-free goods must be equivalent to that of gluten-containing products (Gobbetti et al., 2018). The rules and guidelines set forth by numerous national and international organizations must be followed by the gluten-free products. A food product can be labeled as gluten-free in accordance with FDA rules and regulations if it satisfies the following necessary requirements. It has to be naturally free of gluten. It can't be made from a grain that contains gluten, such a wheat, barley, etc. It shouldn't be produced using a gluten-containing grain that hasn't had the gluten eliminated. The final product's gluten concentration shouldn't be higher than 20 parts per milligram if the raw grain containing gluten is used (Jnawali et al., 2016).

2- Chemicals and Foods with Additives

The food business uses a variety of food additives to extend the shelf life, enhance taste, and improve appearance of processed foods (Trasande et al., 2018). Natural and synthetic food additives are further divided into groups based on the specific roles they play in the food industry, such as flavor enhancers, thickeners, stabilizers, glazing agents, humectants, colorants, gelling agents, or preservatives. Merely a handful of the aforementioned are connected to disagreeable sensations and responses mediated by immunity, non-immunology, or IgE. Amines are naturally occurring dietary chemicals found in bananas, seafood, chocolate, cheese, and ham. Apples and tomatoes contain salicylates, whereas tomatoes have glutamate. Examples of artificially incorporated chemicals include antioxidants found in oil and margarine, benzoates found in cordials and soft drinks, colorants found in candy, jellies, and spices, monosodium glutamate (MSG) found in packaged and processed foods, nitrates found in meats, propionates found in bread, sorbic acid found in processed cheese, and sulfites found in cordials, soft drinks, and dry fruits (Blekas, 2015). Tartrazine (FDandC Yellow #5, commonly called Yellow 5) (E102), which is yellow in appearance and is widely used in the food business, is the artificial food coloring that has been studied the most. The recommended daily intake (RDI) or acceptable daily dose (ADI) for tartrazine is 7.5mg/kg of body weight per day. It is commonly found in baked goods, drinks, cereals, and desserts (Khayyat et al., 2017). Cheese, dried fruits, and alcoholic beverages contain azolabine (E122); In cereals, sausages, and baked foods, sunset yellow (E110); Erythrosine (E127) in baked products, sweets, sausages, and maraschino cherries; Allura Red (E129) in drinks, candies, and cereals; Brilliant Blue (E133) in cereals, drinks, candies, and baked goods; Other coloring chemicals that are commonly added to meals and associated with adverse responses include Brilliant Black (E151) in sweets, ice creams, and jams; and Fast Green (E143) in drinks, candies, and ice creams (Ramesh and Muthuraman, 2018). A sodium salt of glutamic acid, monosodium glutamate (MSG) improves the taste and acceptance of savory foods by the senses. Pickles, spices, sauces, candies, soups, meats, and baked goods are common foods that contain MSG. In addition, rice syrup, gelatin, tomatoes, cheeses, and malted barley all naturally contain MSG (Ramesh and Muthuraman, 2018).

3- Dairy Products

Lactose, the main ingredient in most dairy products on the market, causes lactose intolerance. One popular treatment recommended lowering the risk of long-term consequences related to lactose intolerance is a lactose-free diet (Szilagyi and Ishayek, 2018). All the milk components are present in yogurt, but the lactose content is reduced. Yogurt is more tolerant of lactose than other milk products because the fermentative bacteria partially hydrolyze the lactose to produce glucose and galactose. Because they include more lactase and less lactose, a variety of fermented milk products, including labaneh, kefir, sour cream, viili and mursik, offer benefits comparable to those of yogurt (Silanikove et al., 2015). It is recommended to stay away from lactose-containing sweets and desserts such a pudding, biscuits, pastries, cheese-filled pastries, covered candies, chocolate bars, and ice cream (Piccolo et al., 2016). The nutritional content of a broad variety of milk products that are decreased or lactose-free is being compromised in the process of being commercialized. The items undergo treatment with the enzyme lactase, which breaks down the lactose into glucose and galactose for easy digestion. This process leaves the final product lactose-free and preserves its shelf life (Suri et al., 2019).

Detection Method of Food Allergens

- **Immunoassays**

ELISA, lateral flow immunoassay (LFIA), and multianalyte profiling are among the immunoassays commonly employed in food allergy detection because of the specific antibody interactions and high affinity with target allergens (Xu et al., 2021).

- **ELISA**

Because of its great sensitivity and ease of use, ELISA is the most often used technology for food allergy testing in food safety risk management. (Holzhauser et al., 2020) state that the identification and binding of specific antigen regions to antigen-specific antibodies is the foundation of ELISA. Usually, enzymes such as horseradish peroxidase (HRP) and alkaline phosphatase are attached to the antibodies. These enzymes can react with certain substrates to produce concentration-dependent color changes (Sena-Torralba et al., 2020). The analytes can be discovered on the work surface (Galan-Malo et al., 2017) or in complex food matrices. They can be any food allergen or a mixture of many allergies (Holzhauser and Vieths 1999).

- **Lateral Flow Immunoassay**

Using a semiquantitative approach, food allergy detection with LFIA provides a visual representation of test results. Based on the specific interaction between allergens and antibodies, LFIA acts similarly to ELISA, despite the fact that the visual signal is based on colored particles coated with antibodies. The test strip, which usually comprises of a sample pad, a test line (T line), and a control line (C line), is the most widely used technique for administering LFIA. When a sample solution is applied to the pad, the T line indicates which allergens are present in the sample. The test strip's legitimacy is confirmed by the C line, which is coated in anti-primary mAb antibodies and displays a red bond when allergens are present (Xu et al., 2021).

- **xMAP Techniques**

An accurate, sensitive, and high-throughput immunoassay that can multiplex the assessment of several allergens is the xMAP technique. Filep et al. (2018) and Oliver et al. (2017) state that the foundation of xMAP is fluorescence or MBs conjugating biotinylated antibodies with allergen-specific antibodies and using streptavidin-labeled fluorochrome as detectors. The xMAP's modular design opens up possible applications in a wide range of industries. Single-laboratory validation and multilaboratory testing confirmed the xMAP assay's excellent performance under significantly altered settings or when using analysts with varying degrees of expertise. This suggests that the assay is sufficiently stable to meet real world analytical needs (Xu et al., 2021).

Conclusion

The increased prevalence of food allergies and intolerances is indicative of aberrant clinical reactions to specific food consumption. The majority of commercially accessible foods may contain chemicals that cause allergies or intolerances as an unidentified ingredient. The partial or total avoidance of such foods in daily diet intake is one potential preventive and therapy technique, as there is currently no known comprehensive cure. Even when allergenic and intolerant foods are removed from the diet, it's crucial to maintain a balanced diet to make up for the lost nutrients from the foods you must avoid. The scientific community has a greater grasp of the unpleasant reactions caused by consuming specific foods, but public awareness of the different foods linked to food allergies and intolerances still needs to advance.

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Chapter 39

Use of Peganum harmala in Veterinary Medicine

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ABSTRACT

Peganum harmala is known by different names such as Syrian rue. This plant has flowers and it is grown in many regions throughout the world. The seeds of this plant have essentially hallucinogenic and hypothermic properties. Functions of this plant's extract against the pain are very well understood. We can use the aqueous extract of *P. harmala* to increase the growth rate in rabbits. So, we isolate the *E. coli* bacteria from horses and use *P. harmaline* as an antibacterial drug. Different infectious diseases in wild-fish cause high number of deaths. *P. harmala* controls many bacterial diseases in aquaculture. It has been widely used against round worms of animals. This plant is used in almost all disorders of animals. *P. harmala* is a multipurpose, traditional medicinal plant that has very good impact on some viruses. The extract of this plant causes many reproductive changes such as: prolonged diestrus phase. The extract of this plant causes decrease in the number of litter size.

KEYWORDS		
Peganum harmala, Medicinal plant, Bacterial diseases, Wild-fish, Veterinary medicine	Received: 18-May-2024 Revised: 13-Jul-2024 Accepted: 09-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Peganum harmala is known by different names in all countries of the world. This plant has its different parts including flowers as it is present in different regions of the world. Abortion is common in animals that ingest this plant during dry year. The fruits of *P. harmala* are used as antiseptic in different types of medicine. *P. harmala* can be used against asthma, colic and jaundice. Its seeds are well known that possess essentially hallucinogenic and hypothermic properties. The root extract is effective against *Listeria* than other extracts such as seed extract (Asgarpanah and Ramezanloo, 2012).

This multi-purpose plant is widely used in the treatment of diseases at home. We can use the aqueous extract of *P. harmala* to increase the growth rate in rabbits (Ahmad et al., 2013). This plant is present in semi-arid areas of Pakistan (Mamadalieva et al., 2022). To relief from pain, *P. harmala* liquid extract from seeds is used to treat different animal diseases (Farouk et al., 2009).

Use of *Peganum harmala* against Various Infections

One of the most important diseases is *E. coli* infection that affects many animals and causes diarrhea, dysentery and urinary tract problems depending upon the type of *E. coli*. Most of the studies have been done about the factors responsible for *E. coli* problems and the process by which bacterial different forms cause diarrhea in humans and calves. Now a day, bacteria become resistant against many kinds of drugs. Alkaloids of *P. harmaline* are very effective than other antimicrobials. It is very effective in different diseases. *E. coli* has been isolated in horses and effects of that plant both in lab and on live animals are effective (Hamzah, 2020).

WHO Reviews about *Peganum harmala?*

World Health Organization says that *P. harmala* is a source of medicine for human beings. By using plants or herbs we can reduce the cost of medicines. One of the most important factors related to chemical drugs problem is high cost. These factors can reduce the therapeutic effects of drugs containing chemicals. All that because there is resistance of drugs against the pathogens. There are different types of plants used for making medicines that are: the olive and *P. harmala* for the treatment of different diseases. *P. harmala* is used against inflammation, pain relieving agent and it has been used to treat many disorders including depression. It is used against drug-resistant bacteria and has antibacterial activity and in India it is used in treatment of prolapse, syphilis, fever, hysteria and neuralgia. It is effective against protozoa and stops abortions. The alkaloids that are active in the seeds of this plant are some inhibitory enzymes. The *P. harmala* extract is used against fungal infections and different microbes. Tree of olive or its shrub is green and the shaft is purple when ripe while this plant is green in color. It helps to relax blood vessels and it also has antioxidant properties (Bahmani et al., 2013).

***Peganum harmala* use against Bacterial and Fungal Infections**

There are different bacterial infections caused by many drug resistant bacteria. It is very big problem now a day. So, we are discovering new compounds that have good and better activity. This plant helps in healing of wounds caused by bacteria and fungi. There are different pharmacological activities of this plant i.e., it is effective against insects, leishmanial infections, spasms, leukemia, hypoglycemia and has immune system modulation. This plant has many effects; against bacteria, fungi and viruses. Extract of seeds is very effective. It is effective against *E. coli* infections and *Acinetobacter baumannii* (Javadian et al., 2016). The methanol extract from different parts of *P. harmala* has been used against some most important human pathogenic bacteria (Darabpouretal, 2011).

***Peganum harmala* use in Fish**

Different infectious diseases in wild-fish cause high number of deaths. However, due to continuous use of antibiotics, drug resistance has been developed that cause decrease in the efficiency of the drugs. *P. harmala* is a medicinal plant that plays important role in drug discovery. It has been used in some rainbow trout affected by pathogenic bacteria (Akbary et al., 2015).

***Peganum harmala* use in Different Regions of Pakistan**

Microbiologists and phytochemists think that synthetic pharmaceutical products to control infectious diseases in animals are very beneficial. As this herbal remedy can be used in traditional medicine, it provides information regarding the discovery of new drugs that are helpful to decrease the resistance caused by antimicrobials. We can derive medicines from this plant. Traditional medicine recipes are important in providing health and care benefits to under-developed countries and also in rural areas of the world. This plant changes in form due to unfavorable circumstances during the time of reaching from a buyer to a consumer. Different medicinal plants are available in all areas and are also available in indigenous areas. This plant has different antimicrobial activities against bacterial pathogens showing antimicrobial resistance. Methanol extracts of this plant have antibacterial activity (Ali et al., 2011).

This plant has some bio-active compounds that can be used against various diseases. But its excess use can cause serious effects on liver, kidney and brain. So, it can be used for various symptoms of various diseases (Liu et al., 2022).

***Peganum harmala* use against Nematodes**

P. harmala has been widely used against round worms of animals. As already discussed, its excessive use can affect different body systems. In chicks, it causes congestion and hemorrhage by its leaves. In result, it causes anemia and different changes in total protein and other serum constituents (Qazan, 2009).

Gastrointestinal nematodes, in small ruminants causes decrease in production. By using this plant by-products, the round worms can be treated. Use of this compound, is very beneficial for animals. Harmaline and piperine alkaloids anthelmintic activity is very well known. Within lab, the effect of alkaloids prepared by this plant extract against the nematodes is good. The cytotoxicity of these compounds has been checked by in Vero cells (da Silva, 2021).

***Peganum harmala* use against Viral Diseases**

P. harmala is a multipurpose, traditional medicinal plant that has different effects on some viruses. As already discussed, those different parts of this plant contain an extract, effective against viruses if compared with other such compounds. If we perform the experiments by using such extracts of this plant then many animals and human diseases can be treated. *P. harmala* is used against many important viral infections (Dashti, 2020).

***Peganum harmala* use against Influenza**

Influenza is an important respiratory disease caused by virus. Virus circulates through different parts of the world. In hospitals, many deaths occur due to high-risk in all age groups. The mechanism by which the virus completes process of multiplication, is inhibited through inhibition of its different genetic materials. Influenza virus source in humans and animals has the ability to change the pathogenic type within their new hosts. For viral infections, annual vaccination is done to prevent influenza infections and many drugs against viral infections have multiple benefits in term of treatment and prevention. The influenza A type virus is treated by using seeds of this plant, which inactivate the enzymes important for further spread of viruses. Influenza A type virus has resistance against many medicines. To treat resistant forms, it is necessary to make the new and very effective medicines against influenza. Extract of this plant is used as an alternative of the antivirals. *P. harmala* is used as a remedy in herbal medicines. We can perform different actions by using extracts along with antiviral drugs. So, this herbal medicine has been used as therapeutic agent and has very good results (Moradi et al., 2017).

Peganum harmala **Effects against Different Infections**

P. harmala seeds can be used against fungi, parasites, bacteria and insects (Nenaah, 2010) This traditional medicine has very good effects on animal health. For example, in Middle East, *P. harmala* has been used against infections due to fungus (Mirzaiedehaghi, 2006).The extracts of *P. harmala* have good effects to cause inhibition of the growth in different types of fungus which causes serious problems in animals (Khaliq *et al*., 2009*)*. Different products prepared from *P. harmala* are used in homeopathic medicine in different countries for leishmanial infections (Samoylenko *et al*., 2010).

Powder of seeds and different extracts are used for making medicines against cestodes infections in animals as well as humans (Branch, 2012). Different effects of *P. harmala* against different forms of leishmaniasis are authentic in labs and on live animals (Herraiz and Guillén, 2011). Even if harmaline is used against this infection, it shows strong toxicity for the developing forms of this parasite that resides inside the blood cells. The mechanism to stop the growth of enzymes in parasites by this plant is very effective. Activity of different enzymes this plant against leishmanial infections is good (Frison et al., 2008).

Extract of this plant is as effective as enzymes to treat parasitic infections. *P. harmala* extract cause reduction in the size of lesions and with the total number of the parasites in different forms of this disease (Pieroni *et al*., 2005). *P. harmala* extract cause decrease in the size of lesions and with the total number of the parasites in different forms of this disease (El Gendy et al., 2009).

P. harmala stops the toxicity caused by different developmental forms of leishmanial. Visceral form leishmaniasis is treated by using this plant extract at a dose rate of 100 mg/kg body weight. *P. harmala* extract is much effective against blood parasites, e.g. with a dose of 5mg/kg body weight one time a day daily for 5 days on cattle and sheep theileria infection. Recovery rate is very good in both species of animals as cattle and sheep (Wanntorp et al., 2011). Beta-carbolines causes inhibition of respiratory chain of plasmodium (Mirzaei, 2007).

Seeds of *P. harmala* have such compounds that have strong activity against trypanosomes (Farouk et al., 2008). Alkaloids of this plant have many important bactericidal properties that can be compared with antibiotics (Farzin and Mansouri, 2006). Different species of bacteria are susceptible to these alkaloids. Harmine, (the methanolic extract) have greater potency against bacteria than other extracts (chloroform and petroleum) (Mahmoudian et al., 2002).

Different type compounds of *P. harmala* and mixture of these is used to treat different animals suffering from fungal infections (Arshad et al., 2008). This gives a synergistic effect of different alkaloids that are present in the total extract of this plant (Nasehi et al., 2010). The effect of this plant against insects is also due to beta-carbolines (Fortunato et al., 2009). This plant causes prevention of the larvae of this pest that are present in the stored food, also inhibits its different developmental stages (Herraiz et al., 2011). One of the most important effects of harmaline are: inhibition of severe toxicity of the epithelial cells in the midgut (Jimenez et al., 2008).

P. harmala extract is used against pest that eats grains as their food. The adult forms of the insects are susceptible to cause diseases in animals (Nafisi et al., 2010). Therefore, we use *P. harmala* as a good source to control the number of these harmful insects (Li et al., 2007). *P. harmala* is used as healers to make different treatment of all non- treatable diseases many countries of the world. For example, powder of its seed has been used to treat skin diseases and different types of tumors under skin (Monsef et al., 2004).

The extract of seed of *P. harmala* is used in much ethno botanical preparation (Tahraoui et al., 2007). *P. harmala* has different effects on tumor cell lines in labs and in live animals. The methanolic extract of *P. harmala* has decreased significantly the proliferation of tumor cell lines. The inhibitory effect produced on these cell lines is very good and long lasting. A cell undergo breakdown due to its effect can be seen in the 24 h and total cells are destroyed within 3 days (Shi et al., 2001).

P. harmala has different extracts in various parts of it, but seed extract is effective to stop the genetic material which is effective against all types of infections. This plant has the efficiency to treat colic that is due to its effects against spasms. It acts to block different types of channels responsible for maintenance of calcium in intestine. The content obtained from this plant is effective against nausea and vomiting. Harmful effects of this are: it increases osteoblast differentiation probably through the activation of bone genetic protein pathways that are responsible to change the shape organs. Harmal play an important role in the development processes and it is proven from experiments that it is useful for treatment of some diseases of bone. *P. harmala* contains some compounds to enhance immune system and has good impact on animal health (Berrougui et al., 2006).

Different compounds of this plant are important against inflammatory processes. *P. harmala* is used to treat diabetes in experimental medicine in different parts of the Universe. It acts to treat several hypoglycemic activities when used at high dose rate (Abu-Irmaileh andAfifi, 2003). Harmine is the main component of *P. harmala* that has important anti-diabetic effect. Harmine is responsible for the expression of gamma receptors (Leporatti and Ghedira, 2009). *P. harmala* extract if given in high-doses and causes liver damage, in the central nervous system cause sponge formation, paralysis and convulsions (Astulla et al., 2008). There are different therapeutic doses that are used in animal's models. There may be inhibition of action of *P. harmala* constituents (Hamsa and Kuttan, 2010).

***Peganum harmala* use in birds**

When this plant is used along with vaccines in laying hens it causes toxicity and due to its effect birds go into stress condition (Dawood and Qubih, 2012). *E. coli* has been separated from hens and chicken along with typical lesions of this infection due to excessive antibiotic intake and lesions have been seen on lungs, liver, heart, and spleen (Tanweer et al., 2014). This plant is used for improving the respiratory disorders, dermatoses, and knee osteoarthritis (Sharifi-Rad et al., 2021). The compounds present in *P. harmala* have been used and showed good effect in the treatment of cutaneous leishmaniasis (Khoshzaban et al., 2014).

***Peganum harmala* use against Blood Parasites**

P. harmala is effective against all type of microorganisms including blood parasite. When parasites enter into the blood, they cause different signs in animals such as lethargy, anemia and loss of function. We can use this plant if there is anemia and other signs of parasitic infections. We can check the activity to inhibit the ova by different compounds of *P. harmala* seeds to stop the growth of eggs of hepatic parasites (Moazeni et al., 2017). In adult male rats, this plant is used to treat different infectious agents (Hamden, 2007). *P. harmala* extract has decreased the use of drugs against babesiosis and other piroplasm. *Plasmodium* and *Babesia* have similar characteristics that's why this plant is used against these blood parasites (Eltaysh et al., 2022). This plant is best in clinical cases of many parasites including Giardiasis (Mbaya and Ogwiji, 2014).

Conclusion

Peganum harmala is known by different names such as Syrian rue. It can be used against asthma, colic and jaundice. Its seeds are well known that possess essentially hallucinogenic and hypothermic properties. It is an important plant used in medicines and distributed in semi-arid areas of Pakistan. World Health Organization says that plants are source of medicines for human beings. By using these plants or herbs, we can reduce the cost of medicines. There are many factors that can affect the access to many of the chemical drugs. Moreover, the cost of different drugs is also an issue. The alkaloids that are active in seeds are beneficial compounds. Many studies in different countries reveal that the *P. harmala* compounds have activity against fungi and all other microbes. It helps to relax blood vessels and it also has antioxidant properties. Microbiologists and phytochemists think that synthetic pharmaceutical products to control infectious diseases in animals are very beneficial. Gastrointestinal nematodes in small ruminants cause loss of production. The nematodes can be controlled by the drugs specific against these parasites.

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Chapter 40

Impact of Phytobiotics on Poultry Health and Diseases

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ABSTRACT

This chapter elucidates the implications of different phytobiotics on poultry health and disease management. It delineates the overview of commonly used phytogenic feed additives in poultry nutrition, including garlic, ginger, neem, coneflower, aloe vera, thyme, oregano, cinnamon, turmeric, moringa, peppermint, and coriander. These additives demonstrate substantial improvements in gut health, growth performance, egg production, and lactobacillus count, alongside a reduction in coliform count. Furthermore, the chapter scrutinizes their efficacy as antiparasitic agents against various poultry parasites, such as *Ascaridia galli* and *Eimeria* species, and their antibacterial activity against a myriad of bacterial strains, including *Escherichia coli*, *Clostridium perfringens*, and *Salmonella spp*. Moreover, it elucidates the antiviral properties of these phytogenics against economically important viruses of poultry such as Newcastle disease virus, Infectious bronchitis virus, Avian influenza virus, Chicken infectious anemia virus, and Infectious bursal diseases virus. Lastly, the chapter discusses their antifungal effects against prevalent fungal species and toxins such as Aspergillus spp. and aflatoxins.

KEYWORDS		
Phytobiotics, Poultry, Gut health, Viruses, Bacteria, Parasitic diseases, Turmeric, Garlic, Thyme	Received: 18-Jun-2024 Revised: 17-Jul-2024 Accepted: 29-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

The poultry sector is experiencing rapid expansion, especially in developing nations (Bahri et al., 2019). Advancements in manufacturing antibiotics and their efficacy on livestock productivity have led to extensive use of these compounds (Mohammadi Gheisar and Kim, 2017). The antibiotics used as growth promoters in farm animals were prohibited in the year 2005, prompted by apprehensions regarding their remnants in animal products and results in the development of resistance of bacteria. The discontinuation of antibiotic growth promoters has notably augmented the occurrence of infections by pathogens, consequently exerting an adverse impact on the performance of commercial livestock (Mohammadi Gheisar and Kim, 2017). Consequently, phytobiotics are becoming increasingly significant as potential substitutes for antibiotic growth promoters, given their natural composition, widespread availability, non-toxic nature, and absence of residues (Yadav et al., 2016; Alagawany et al., 2019; Abd El-Hack et al., 2020a; Abd El-Hack et al., 2020b). In recent years, there has been a growing interest in phytogenic additives or botanical extract supplements in veterinary practice, serving as a substitute for antibiotics in poultry nutrition (Vidanarachchi et al., 2005). Over the past twenty years lot of research has been done on the different roles of phytobiotics such as anti-inflammatory, antimicrobial, antioxidant, and metabolism-regulating effects (Gupta et al., 2019).

Phytobiotics, alternatively known as phytochemicals or phytogenics, constitute a wide range of bioactive substances derived from plants (Liu, 2004). Phytobiotics consist of bioactive elements or materials from botanical sources, encompassing terpenes, alkaloids, glucosides, and phenolic compounds (Shad et al., 2014). According to the regulation of the European Parliament and of the Council [Regulation (EC) No 1831/2003], a feed additive is defined as “a substance, micro-organism or chemical substance intentionally added to a feed for the purpose of improving feed properties, meeting nutritional requirements of animals, positively influencing genetics and production animal characteristics and welfare and to increase livestock production". One such additive is phytobiotics [Regulation (EC) No 1831/2003] (Krauze, 2021), and other feed supplements such as vitamins, enzymes, minerals and essential nutrients are supplemented in poultry feed.

Phytobiotics can be categorized based on their purification attributes and origin. The primary divisions of phytobiotic dietary supplements include essential oils, herbs, oleoresins, and spices (Windisch et al., 2008; Huyghebaert et al., 2011; Gheisar et al., 2015). Plants denote temporary blossoming and non-woody flora, including herbs and bushes, utilized as a reservoir of phytogenic feed supplements. Entire botanicals, blossoms, foliage, and roots are harnessed to form phytogenic feed additives (Grashorn, 2010).The incorporation of botanicals within feed has been observed to improve performance of the animal and well-being within the poultry sector (Alghirani et al., 2021). Some of the commonly used phytogenic additives and their active compounds are mentioned in the
Table *1*.

Table 1: Different types of phytobiotics used in poultry

Plant	Scientific Name	Used Part	Active component	Reference
Garlic	*Allium sativum*	Bulbs in crushed form	Flavonoids, allicin, ajoene, diallyl sulfide, vinyldithiin, phytosterols, mucilages, pectins	(Wenk, 2003; Truchlinski et al., 2006; Yarru et al., 2009; Akyıldız and Denli, 2016; Vinus et al., 2018; Islam and Sheikh, 2021)
Cinnamon	*Cinnamomum zeylanicum* *Cinnamomum cassia*	Cinnamon leaves, bark, and oil	Phenolic and polyphenolic compounds, cinnamaldehyde eugenol	(Al-Kassie, 2009; Akyıldız and Denli, 2016; Chachaj et al., 2019; Islam and Sheikh, 2021; Krauze et al., 2021)
Aloe vera	*Aloe barbadensis*	Gel, powder, leaves, and water extract	Anthraquinones polysaccharides (chiefly icemannan), salicylic acid, vitamins, amino acids, enzymes, and lignin,	(Babak and Nahashon, 2014; Tariq et al., 2014; Taraneh, 2016; Sinha et al., 2017; Ebrahim et al., 2020; Islam and Sheikh, 2021)
Turmeric	*Curcuma longa*	Powder/Rhizome	Turmerones, curcumin	(Babak and Nahashon, 2014; Sinha et al., 2017; Islam and Sheikh, 2021)
Oregano	*Origanum vulgare*	Oil or leaves extracts	Polyphenols, carvacrol and thymol (terpenoids)	(Méndez Zamora et al., 2017; Islam and Sheikh, 2021)
Ginger	*Zingiber officinale*	Oil, powder	Sesquiterpenes and monoterpenes (Gingerol, paradols, shogao)	(Abd El-Hack et al., 2020b; Islam and Sheikh, 2021)
Moringa	*Moringa oleifera*	Extracts, leaves	Carotenoids, ascorbic acid, phenolics, alkaloids, polyphenols, chlorogenic acid, caffeinated, flavonoids,	(Al-Kassie, 2009; Aroche et al., 2018; Islam and Sheikh, 2021)
Neem	*Azadirachta indica*	Plant leaves	Nimbin, Azadirachtin, Salannin	(Islam and Sheikh, 2021)
Coneflower	*Echinacea purpurea*	Root, dried herb leaves, root, alcohol and water extracts	Polyacetylenes, alkylamides polysaccharides, polyphenolic acids, flavonoids	(Vinus et al., 2018; Abd El-Hack et al., 2020a; Islam and Sheikh, 2021; Krauze et al., 2021)
Peppermint	*Mentha piperita*	Powder, leaves	Terpenes, menthol, carvacrol	(Leone et al., 2015; Vinus et al., 2018; Islam and Sheikh, 2021)
Thyme	*Thymus vulgare*	Flowers, leaves	Carvacrol, thymol	(Islam and Sheikh, 2021)
Coriander	*Coriandrum Sativum*	Seeds	Flavonoids, phenolic acid	(Islam and Sheikh, 2021)

Effect of Phytobiotics on the Performance and Productivity of Poultry

Phytobiotics promote poultry growth (Gheisar et al., 2015; Stamilla et al., 2020). Different phytogenic feed additives like thyme, oregano, garlic, neem, coneflower, aloe vera, ginger, cinnamon, turmeric, moringa, peppermint, and coriander can be used in the poultry feed to improve the performance. Thyme, thyme combination with moringa (Wahab et al., 2020), moringa leaf (Akhouri et al., 2013), leaf powder (Swain et al., 2017) and seed combined with phytase (Wahab et al., 2020), garlic (Olobatoke and Mulugeta, 2011) , ginger rhizome powder (Kausar et al., 1999; Tekeli, 2006; Tekeli et al., 2011; Habibi et al., 2014a; Borgohain et al., 2017; Talukder et al., 2017; Shewita and Taha, 2018; Ifelayo et al., 2020; Martha, 2022), the combination of ginger and curry leaf powder (Moorthy et al., 2009), red ginger and ginger root meal (Onimisi et al., 2005; Moorthy et al., 2009; Shewita and Taha, 2018; Ifelayo et al., 2020; Shende et al., 2020), dried neem leaf powder (Ansari et al., 2012), cinnamon (Qaid et al., 2021a), cinnamon bark powder (Qaid et al., 2022) (Jamróz and Kamel, 2002), oregano oil in broilers (Bozkurt et al., 2009; Fotea et al., 2010; Roofchaee et al., 2011; Ghazi et al., 2015; Galal et al., 2016)

(Giannenas et al., 2003; Mohiti-Asli and Ghanaatparast-Rashti, 2015; Mohiti-Asli and Ghanaatparast-Rashti, 2017), oregano oil in quails (Badiri and Saber, 2016), coriander seeds (Cabuk et al., 2003; Hamodi et al., 2010; Rashid et al., 2014) and oil (Ghazanfari et al., 2015) and turmeric rhizome extract (Durrani et al., 2006; Kumari et al., 2007; Abd Al-Jaleel, 2012; Mondal et al., 2015; Arslan et al., 2017; Oluwafemi et al., 2021), supplementation enhance body weight gain (BWG), feed conversion ratio (FCR), European production efficiency factor (Al-Kassie and Witwit, 2010; Toghyani et al., 2010; Veselin et al., 2021) (Bolukbasi and Erhan, 2008; Cayan and Erener, 2015; Asadi et al., 2017; Borgohain et al., 2017; Karim et al., 2017; Shewita and Taha, 2018; Mulugeta et al., 2019; Rastad, 2020; Abd El-Hack et al., 2022), in broilers (Stamilla et al., 2020) and meat-type ducks (Gheisar et al., 2015). However, contradictory results have been found in different studies (Cross et al., 2007; Ocak et al., 2008; Dieumou et al., 2009; Zhang et al., 2009; Onu, 2010; Abdel-Wareth et al., 2012; Shanoon et al., 2012; Habibi et al., 2014b; Mohamed, 2015; Herve et al., 2018).

In a laying bird, phosphorous and calcium are major elements that are involved in the formation of an egg. Phytobiotics tend to enhance shell and egg weight by increasing absorption and accumulation of phosphorus and calcium within the body of layers (Loretts et al., 2024). Thyme (Bolukbasi and Erhan, 2008; Cayan and Erener, 2015; Abd El-Hack et al., 2022), garlic (Olobatoke and Mulugeta, 2011), ginger root oil in Japanese quails (Herve et al., 2019), ginger oil (Nasiroleslami and Torki, 2010) and ginger (Nasiroleslami and Torki, 2010; Akbarian et al., 2011; Zhao et al., 2011) supplementation enhanced egg production, egg sizes, egg weight, egg shell thickness, egg mass and egg yield. However, the haugh unit, egg index, yolk index (Nasiroleslami and Torki, 2010), egg's weight, laying rate (Zhao et al., 2011) remained the same.

Effect of Phytobiotics on Gut Health

Garlic (Peinado et al., 2012; Singh et al., 2017), neem and aloe vera combination (Sujatha et al., 2017), peppermint in quails (Aly et al., 2023), cinnamaldehyde oil (Chowdhury et al., 2018; Qaid et al., 2021b), moringa leaf powder (Moreno-Mendoza et al., 2021), turmeric powder (Namagirilakshmi et al., 2010); Rajput et al. (2013) supplementation improved the gut health in broilers with better intestinal structure such as increased villus height, crypt depth, and decreased goblet cells count and epithelial thickness of intestines (Adibmoradi et al., 2006; Zhang et al., 2022a). However, supplementation of garlic decreased the villus width at the tip including the villi height to crypts depth ratio (Shewita and Taha, 2018), and turmeric powder reduced intestinal crypt depth Rajput et al. (2013) with no changes in crypt length and crypt villi width in another study (Namagirilakshmi et al., 2010).

Garlic (Yang et al., 2009), the mixture of garlic, thyme, and coneflower (Rahimi et al., 2011), aloe vera and neem combination (Sujatha et al., 2017), peppermint in quails (Aly et al., 2023), oregano oil (Zhang et al., 2021), cinnamon oil (Mehdipour and Afsharmanesh, 2018; Yang et al., 2019), moringa leaves (Abu Hafsa et al., 2020), promoting the growth of beneficial bacteria such as Lactobacillus (Elbaz et al., 2021). However, no effect of the combination of formic acid with cinnamaldehyde was seen on the lactobacillus counts (Pathak et al., 2016). The mixture of garlic, thyme, and coneflower (Rahimi et al., 2011), aloe vera and neem combination (Sujatha et al., 2017), peppermint (Mehri et al., 2015; Veselin et al., 2021; Aly et al., 2023), oregano oil (Zhang et al., 2021), cinnamon oil (Saied et al., 2022). combination of cinnamaldehyde and formic acid(Pathak et al., 2016), moringa leaves (Abu Hafsa et al., 2020) (Agashe et al., 2019), inhibited the growth of harmful bacteria such as E. coli, salmonella (Mehri et al., 2015; Pathak et al., 2016; Abu Hafsa et al., 2020; Zhang et al., 2021; Saied et al., 2022; Aly et al., 2023), clostridium (Pathak et al., 2016), staphylococcus (Abu Hafsa et al., 2020). However, no effect of the combination of cinnamaldehyde with formic acid was seen over E. coli in another study (Pathak et al., 2016). Garlic lowers the acidity of digestive contents thereby promoting volatile fatty acid production and ultimately the growth of helpful bacteria (Yang et al., 2009). Oregano oil enhanced trypsin, amylase, chymotrypsin, and lipase activity within the cecum thereby promoting digestion (Zhang et al., 2021). Cinnamaldehyde oil in broilers enhances the activity of intestinal and pancreatic enzymes by triggering secretion from the salivary gland, thereby increasing the activity of digestive enzymes ultimately (Chowdhury et al., 2018). Cinnamaldehyde or its oil improved the ileal digestion of amino acids (such as threonine, histidine, asparagine, serine, lysine, phenylalanine) nutrients and raw fats (Jamroz et al., 2003) and the breakdown of protein via increasing levels of pepsin and hydrochloric acid in the gastrointestinal tract of broilers (Mountzouris et al., 2011). The phytobiotics may improve the uptake and digestibility of nutrients via increased expression of the nutrient transporter genes (Bello et al., 2023).

Management of Poultry Diseases with Phytobiotics

Parasitic Diseases

Ascaridia galli infestation within birds can be prevented by the use of fresh or water-based extract from garlic (Das and Thakuria, 1974), turmeric alcoholic extract (Alrubaie, 2015) attributed to its allicin constituent (Velkers et al., 2011). Garlic formulations impact worm infestations in poultry (Das and Thakuria, 1974). Garlic use in chickens (Kim et al., 2013; Khan et al., 2019), ginger use in pigeons (Ali et al., 2015), the combination of ginger with garlic (Ali et al., 2019), cinnamaldehyde (Yang et al., 2020), cinnamon powder (Qaid et al., 2021a; Qaid et al., 2022), *Aloe vera* gel (Yim et al., 2011; Hassan et al., 2024), turmeric (Allen et al., 1998), turmeric and salinomycin sodium combination (Abbas et al., 2010), turmeric paste (Favour et al., 2020), oregano oil (Tsinas et al., 2011; Mohiti-Asli and Ghanaatparast-Rashti, 2015), acetone extract of moringa oleifera (Ola-Fadunsin and Ademola, 2013), *moringa oleifera* leaf powder or ethanol extract (Banna H. A, 2016), neem leaves aqueous extract (Qudoos et al., 2020; Onyiche et al., 2021), neem leaf extract in Japanese quail (Ishaq et al., 2022), neem leaf extract in pigeons (Qudoos et al., 2020), *Echinacea purpurea* (Allen, 2003; Ghafouri et al., 2023), peppermint or its powder (Barbour et al., 2015; Hussein, 2021) and thymol in pigeons (Arafa et al., 2020) neutralized and simultaneously decreased oocyte shedding of *Eimeria* sporozoites in poultry (Table 2).

Table 2: Effect of different phytobiotics on the parasitic infections of the poultry

Phytobiotic	Specie	Dose	Effect	Reference
Garlic	Chickens infected with *Ascaridia galli*	Fresh (2.5mg/bird) or Water-based extract (2.5ml/bird) Every day for 5 days	Garlic showed anti-parasitic effects against *Ascardia galli* infestation in chickens.	(Das and Thakuria, 1974)
Garlic	Broilers infected with *Coccidia*	15g/Kg feed	Garlic showed improved performance and coccidiostatic effect in broilers.	(Ali et al., 2019)
Ginger	Broilers infested with *Coccidia*	5g/Kg feed	Ginger showed improved performance and coccidiostatic effect in broilers.	(Ali et al., 2019)
Ginger	Pigeons natural infection with *Eimeria spp.*	5% ginger extract or 10% ginger extract	10% ginger extract given twice daily for two days prevented the oocyte shedding in (91%) birds, while 5% of the same extract gave less efficiency (70% only).	(Ali et al., 2015)
Cinnamon	Broilers infected with *Eimeria tenella*	6g cinnamon/Kg	Moderately reduced coccidiosis	(Qaid et al., 2021a)
Aloe vera gel	Broilers infection with *Eimeria tenella*	10% gel extract from *Aloe vera* 15ml/liter in drinking water	Prophylactic use *Aloe vera* decreased lesions in the cecum, decreased mortality (12%), and reduced oocysts/gram	(Hassan et al., 2024)
Aloe vera powder	Broilers infected with *Eimeria maxima*	0.5%, 1% and 2% aloe vera powder	Decrease gut lesion scores and reduced fecal oocyst shedding	(Yim et al., 2011)
Turmeric powder	Broilers infected with *Eimeria tenella*	1, 2 and 3% turmeric powder in feed	High levels have coccidiostatic	(Abbas et al., 2010)
Turmeric alcoholic extract	Chicken infested with *Ascaridia galli*	200, 400 and 600 mg/Kg	600 mg/Kg restore intestinal integrity and decrease the length and weight of worms.	(Alrubaie, 2015)
Turmeric paste	Broilers infected with *Eimeria*	0.5g/Kg or 1g/Kg Turmeric paste	Decrease fecal coccidia oocysts at 1g/kg compared to control and 0.5g/kg treated groups	(Favour et al., 2020)
Oregano essential oil	Broilers with coccidiosis	300 and 500 ppm within the diet	Higher dose decrease the detrimental effects and decrease oocyte shedding	(Mohiti-Asli and Ghanaatparast-Rashti, 2015)
Oregano essential oil	Broiler chickens experimental infection with *Eimeria maxima* and *Eimeria acervulina*	300 or 600mg/Kg	Exerts an anticoccidial effect against *Eimeria maxima* and *Eimeria acervulina*	(Tsinas et al., 2011)
Moringa oleifera leaves acetone extracts	Broilers natural infection with mixed species of *Eimeria*	1,2,3,4 and 5g/Kg	Decrease oocyte shedding in dose-dependent manner	(Ola-Fadunsin and Ademola, 2013)
Moringa oleifera ethanolic extract	Boilers infected with *Eimeria spp.*	200 and 400ppm	reduced mortality and improved post-mortem lesions	(Banna H. A, 2016)
Neem aqueous leaf extracts	Broiler chickens were experimentally infected with *Eimeria* oocytes	800 mg/Kg of body weight	Inhibit the oocyte shedding up to 87.44%	(Onyiche et al., 2021)
Neem leaves methanolic extract	Japanese quails infected with *Eimeria tenella*	130 mg/L and 190mg/L	Decrease mortality, oocyte shedding and lesion score and improve intestinal histology	(Ishaq et al., 2022)
Neem leaves an aqueous extract	Pigeons infected with *Eimeria spp.*	2 ml/L drinking water	Reduction of oocysts shedding	(Qudoos et al., 2020)

Purple coneflower Root powder	Broilers infected with coccidia	0.1% and 0.5% in feed	Prophylactic use prevented the decrease in body weight and development of gross lesions	(Allen, 2003)
Purple coneflower	Broilers infected with mixed *Eimeria spp. (Eimeria necatrix Eimeria tenella, Eimeria brunetti and Eimeria maxima)*	2% Extract	Improved the performance and showed anticoccidial effects	(Ghafouri et al., 2023)
Peppermint oil	Broilers infected with *Eimeria tenella, Eimeria acervulina, Eimeria praecox, Eimeria brunetti, Eimeria necatrix, Eimeria maxima Eimeria hagani and Eimeria mivat*i	0.69 ml per Kg of BW peppermint oil in drinking water	FCR improved significantly with a decrease seen in oocyst numbers, scores of intestinal lesions and mortality.	(Barbour et al., 2015)
Peppermint powder	Broilers infected with *Eimeria tenella*	5 g/kg (0.5%) peppermint powder or 10 g/kg (1%) peppermint powder	Prevent the decrease in weight gain and improve intestine integrity	(Hussein, 2021)
Thyme	Pigeons infected with *Eimeria labbeana*	40 mg per Kg of BW thymol within feed for a period of about ten days.	BW improved, the impact of clinical signs decreased, and the oocysts count lowered.	(Arafa et al., 2020)

Bacterial Diseases

Cinnamon oil can inhibit the growth as well as expression of virulence genes of different bacterial pathogens of the including: *Ornithobacterium rhinotracheale adk* gene, *Pasteurella multocida ptfA* gene ,*Staphylococcus aureus sed* gene, *Mycoplasma gallisepticum Mgc2* gene, *Escherichia coli stx1* gene and *Avibacterium paragallinarum HPG-2* gene (Erfan and Marouf, 2019). Garlic (Jimoh et al., 2013), peppermint (Sorour et al., 2021), and coriander seed powder (Taha et al., 2019), diminishes the colony-forming units of the *Clostridium perferinges*. Garlic (Rahimi et al., 2010; Taha et al., 2019) ginger (Dieumou et al., 2009; Elmowalid et al., 2019), thyme (Rahimi et al., 2010), coneflower (Rahimi et al., 2010), peppermint (Veselin et al., 2021), coriander seed powder (Taha et al., 2019), moringa leaf extract (Allam et al., 2016), neem leaf extract (Sarker and Akhter, 2019; Ali et al., 2021), aloe vera gel in guinea fowls (Adzitey et al., 2019), cinnamon extract (Tabatabaei et al., 2015; Radwan et al., 2016) diminished the colony-forming units of the bacteria *E. coli*.

Garlic, ginger (Dieumou et al., 2009; Purwanti et al., 2019), thyme oil (Ahmed et al., 2014), moringa leaf extract (Allam et al., 2016), the combination of ginger and moringa flour in layers (Novalina et al., 2022), neem leaf extract (Sarker and Akhter, 2019; Ali et al., 2021), turmeric alone or in combination with garlic (Purwanti et al., 2019), aloe vera gel in guinea fowl (Adzitey et al., 2019), oregano extract combination with organic acids (Machado et al., 2014) or its essential oil (Xu et al., 2022), cinnamon extract (Radwan et al., 2016) diminished the colony-forming units of the bacteria *Salmonella* (

Garlic (Ahmed et al., 2017), garlic powder (Haq et al., 1999; Pourali et al., 2010; Eid and Iraqi, 2014), turmeric powder or turmeric and thyme powder mixture (Fallah and Mirzaei, 2016), oregano oil (Abdel-Hafez and Mohamed, 2016; Abdulkadhim et al., 2022; Alazzawi and Khammas, 2022), combination of peppermint and eucalyptus oils (Barbour et al., 2010; Awaad et al., 2016) and thyme powder (Fallah and Mirzaei, 2016) show antiviral activities against *Avian influenza virus*. Garlic juice (Al-Shwilly, 2017), garlic powder (Haq et al., 1999; Pourali et al., 2010; Eid and Iraqi, 2014), aloe vera gel (Elaiyaraja et al., 2016), turmeric (Tamam et al., 2010; Shihab, 2017), moringa powder (Mousa et al., 2017; Tolba et al., 2022) and neem leaves (Jawad et al., 2013) improve antibody titer against the *Infectious bronchitis virus* (Table 4). Garlic decreased the signs and symptoms of *Chicken infectious anemia virus* in the affected birds (Abdulkareem et al., 2023). Combination of cinnamaldehyde and glycerol monolaurate and moringa leaf extract (Khan et al., 2022) against the *Infectious bronchitis virus* inhibited the infection (Zhang et al., 2022b).

Table *3*).

Neem leaf extract diminished the colony-forming units of the bacteria *Pasterurella multocida* (Ali et al., 2021). Garlic, ginger reduced the colony-forming units of the bacteria *Shigella* and *Staphylococcci* (Dieumou et al., 2009).

Viral Diseases

Garlic oil, bulb extract from garlic, garlic aqueous extract (Arify et al., 2018; Harazem et al., 2019; Hizam et al., 2019; Doostmohammadian et al., 2020), garlic paste (Hanieh et al., 2010; Chitwan, 2017), garlic juice (Al-Shwilly, 2017), garlic powder (Haq et al., 1999; Pourali et al., 2010; Eid and Iraqi, 2014), cinnamon oil or powder (Abdel-Hameed et al., 2017), aloe vera extract or gel (Ojiezeh and Ophori, 2015; Dziewulska et al., 2018; Islam et al., 2020), turmeric (Tamam et al., 2010; Shihab, 2017; Shah et al., 2021), Turmeric powder or turmeric and thyme powder mixture (Fallah and Mirzaei, 2016), oregano oil (Abdel-Hafez and Mohamed, 2016; Abdulkadhim et al., 2022; Alazzawi and Khammas, 2022), ginger (Al-Bawi and Rabee, 2020; Untari et al., 2022), moringa leaf extract (Mousa et al., 2017; Tolba et al., 2022), moringa powder (Mousa et al., 2017; Tolba et al., 2022), Moringa leaf meal (Rao et al., 2018), Moringa leaf extract (Khan et al., 2022), Neem leaves (Jawad et al., 2013), Neem aqueous extract supplementation alone or in combination with garlic (Garba et al., 2013), methanolic neem leaf extract (Elbasuni et al., 2023), combination of peppermint and eucalyptus oils (Barbour et al., 2010; Awaad et al., 2016), coneflower (Jouzi et al., 2014) and thyme powder (Fallah and Mirzaei, 2016) supplementation improves the antibody titers against the *Newcastle disease virus*.

Garlic (Ahmed et al., 2017), garlic powder (Haq et al., 1999; Pourali et al., 2010; Eid and Iraqi, 2014), turmeric powder or turmeric and thyme powder mixture (Fallah and Mirzaei, 2016), oregano oil (Abdel-Hafez and Mohamed, 2016; Abdulkadhim et al., 2022; Alazzawi and Khammas, 2022), combination of peppermint and eucalyptus oils (Barbour et al., 2010; Awaad et al., 2016) and thyme powder (Fallah and Mirzaei, 2016) show antiviral activities against *Avian influenza virus*. Garlic juice (Al-Shwilly, 2017), garlic powder (Haq et al., 1999; Pourali et al., 2010; Eid and Iraqi, 2014), aloe vera gel (Elaiyaraja et al., 2016), turmeric (Tamam et al., 2010; Shihab, 2017), moringa powder (Mousa et al., 2017; Tolba et al., 2022) and neem leaves (Jawad et al., 2013) improve antibody titer against the *Infectious bronchitis virus* (Table 4). Garlic decreased the signs and symptoms of *Chicken infectious anemia virus* in the affected birds (Abdulkareem et al., 2023). Combination of cinnamaldehyde and glycerol monolaurate and moringa leaf extract (Khan et al., 2022) against the *Infectious bronchitis virus* inhibited the infection (Zhang et al., 2022b).

Table 3: Effect of different phytobiotics on the bacterial infections of poultry

Phytobiotic	Specimen	Pathogen	Dose	Effect	Reference
Garlic	Broilers	*Clostridium perferinges* causing necrotic enteritis	0.5, 1.0, 1.5, 2.0 and 2.5 g/Kg	Bacterial colonies decreased but the effect was most significant at 1 g/Kg	(Jimoh et al., 2013)
Thyme	Broilers	*Escherichia coli*	0.1%	*E. coli* colony forming units decreased in digesta of ileum/cecum	(Rahimi et al., 2010)
Coneflower	Broilers	*Escherichia coli*	0.1%	*E. coli* colony forming units decreased in digesta of ileum/cecum	(Rahimi et al., 2010)
Garlic	Broilers	*Escherichia coli*	0.1%	Decrease the load of *E. coli* in the digesta of ileum/cecum	(Rahimi et al., 2010)
Peppermint powder	Broilers	*Escherichia coli*	0.2%, 0.4%, 0.6%	The levels of *E. coli* decreased at 0.4% or 0.6%	(Veselin et al., 2021)
Peppermint oil	Broilers	*Clostridium perferinges*	15% oil/Water	Reduced the intensity of necrotic enteritis and decreased count of *Clostridium perferinges*	(Sorour et al., 2021)
Thyme oil	Broilers	*Salmonella typhimurium*	2ml/kg in drinking water	Enhanced birds' immunity, thereby decreasing the salmonella infection	(Ahmed et al., 2014)
Coriander seed powder	Broilers	*Escherichia coli* *Clostridium perferinges*	0.1%, 0.2%, 0.4%	Decreased the bacterial counts	(Taha et al., 2019)
Ginger	Broilers	*E. coli; Salmonella; Shigella; Staphylococci*	10 mg per kg per day 20 mg per kg per day 40 mg per kg per day	Colony-forming units of these bacteria decreased	(Dieumou et al., 2009)
Garlic	Broilers	*E. coli; Salmonella; Shigella; Staphylococci*	10 mg per kg per day 20 mg per kg per day 40 mg per kg per day	Colony-forming units of these bacteria decreased	(Dieumou et al., 2009)
Garlic extract	Broiler chicks	*E. coli 078* (Multi-drug resistant)	10-15%	Garlic extract cleared the *E. coli 078* from broilers	(Elmowalid et al., 2019)
Ginger extract	Broilers chicks	*E. coli 078* (Multi-drug resistant)	15 g/kg diet daily for 21 days	Ginger extract cleared the *E. coli 078* from broilers	(Elmowalid et al., 2019)
Moringa leaf extract	Broilers	*E. coli* *Salmonella species*	200 mg/Kgm but in drinking water for 30 days consecutively	Bacterial growth was inhibited	(Allam et al., 2016)
Moringa flour with Ginger flour combination	Layers	*E. coli* *Salmonella species* *Lactic acid bacteria*	0.25% + 0.25% 0.50% + 0.50% 0.75% + 0.75%	A decrease in the number of all the bacteria was observed at 0.75% concentration.	(Novalina et al., 2022)

Neem leaf extract	In-vitro	Multi-drug resistant disease-causing bacteria of birds *Pasteruella multocida, Salmonella pullorum, Salmonella gallinarum, and E. coli*	1ml	Neem leaf extract killed all the pathogenic bacteria of poultry	(Ali et al., 2021)
Neem leaf extract	Broilers	*E. coli; Salmonella typhimurium*	1%, 1.5%, 2%, 2.5%	The growth of *E. coli* and *Salmonella typhimurium* was inhibited by neem leaf extract	(Sarker and Akhter, 2019)
Cinnamon oil	In-vitro	*Staphylococcus aureus; E coli; Pasteruella multocida; Avibacterium paragallinarum*	10 µg/mL	Inhibit the growth of bacteria in laboratory settings	(Erfan and Marouf, 2019)
Cinnamon extract	Broilers	*E. coli*	100 or 200mg/ kg of food	Reduce inflammation in liver	(Tabatabaei et al., 2015)
Cinnamon oil	Broilers	*E. coli; Salmonella* (multi-drug resistant)	2%, 3%	Inhibit the growth of Salmonella and E. coli.	(Radwan et al., 2016)
Oregano extract and organic acids blend	Broiler breeders chicks	*Salmonella Enteritidis*	0.2% (feed) 0.08% (drinking water) 0.2% + 0.08% (feed+ drinking water)	Supplementation in water decreases the disease and eliminate the pathogen but supplementation in feed only reduced the infection but did not eliminate the pathogen	(Machado et al., 2014)
Oregano essential oil	Chicken breeders	*Salmonella pullorum Salmonella gallinarum*	200 (preventive dose) and 400 (treatment dose) µL/L oregano essential oil in drinking water	Decrease the infection	(Xu et al., 2022)
Aloe vera gel	Guinea fowls	*E. coli Salmonella enterica*	50, 100 and 200 mg/ml	Decreased the bacterial growth, exhibiting antibacterial ability	(Adzitey et al., 2019)
Turmeric Extract	Broiler	*Salmonella pullorum*	2.5%	Broilers became resistant to the salmonella infection.	(Purwanti et al., 2019)
Garlic Extract	Broiler	*Salmonella pullorum*	2%	Broilers became resistant to the salmonella infection.	(Purwanti et al., 2019)
Turmeric and garlic extract mixture	Broiler	*Salmonella pullorum*	2.5%	Broilers became resistant to salmonella infection	(Purwanti et al., 2019)
Turmeric	Broilers	*Listeria sp., Salmonella sp., E. coli, Shigella sp.,* and *Staphylococcus aureus*	0.25%, 0.5%, 1%	Levels of all bacteria were reduced	(Ahmed et al., 2018)
Turmeric extract	Chickens	*Mycoplasma gallisepticum*	0.4 mg/Kg BW extract	The clinical signs of the disease were diminished with decreased pathological changes.	(Handharyani et al., 2020)
Garlic extract	Chickens	*Mycoplasma gallisepticum*	0.4 mg/Kg BW extract	The clinical signs of the disease were diminished with decreased pathological changes.	(Handharyani et al., 2020)
Turmeric and garlic extract in combination with zedoary	Chickens	Mycoplasma gallisepticum	2 mg/Kg BW Nanoparticle and extract combination	Efficient in inhibiting *Mycoplasma gallisepticum.*	(Handharyani et al., 2020)

Turmeric rhizome powder extracts	In-vitro	*Escherichia coli* and 75 µl *Salmonella enteritis*	Inhibition of *E. coli* and *Salmonella enteritidis*	(Patil et al., 2019)

Fungal Diseases

Supplementation of, garlic in broilers (Ancsin et al., 2013), oregano oil in Japanese quails (Abdelrazek, 2015), ginger (Rani et al., 2009; H and A, 2015), ginger capsules in pekin ducks (Abu El-Ela et al., 2019), the combination of ginger, garlic, and turmeric (Salako et al., 2022), cinnamon powder in quail (Gadu, 2023), trans cinnamaldehyde in chicken embryos (Yin, 2017; Yin et al., 2017), aloe vera in layers (Seifi et al., 2022) (Mohajer et al., 2021; Sadighara et al., 2021), turmeric extract (Gholami-Ahangaran et al., 2016), turmeric powder (Amminikutty et al., 2023) Abd El-Ghany et al. (2013), ethanolic extract of turmeric (Rangsaz and Ahangaran, 2011), turmeric in ducklings (Ayoub et al., 2011), oregano oil in Japanese quails (Abdelrazek, 2015; Shalaby and El-Tawil, 2016), thyme oil (Manafi et al., 2014; Fawaz et al., 2022) and moringa in layers Suganthi Rajendran et al. (2012); (Saleemi et al., 2023) proved beneficial in broilers intoxicated with T-2 toxin, ochratoxin, B-1 toxin and ameliorated the aflatoxin-caused immune damage (Table 5).

Oregano (Sadri, 2008) and thyme (Abdel Fatah et al., 2020) decreased the growth of *Candida albicans* (Abdel Fatah et al., 2020).

Table 4: Effect of different phytobiotics on the viral infections of poultry

Phytobiotic	Specimen	Virus	Dose	Effect	Reference
Garlic oil	In-ovo (embryonated chicken egg)	*Newcastle disease (ND) virus*	50 µg/mL	Garlic, along with ND virus inoculation into the egg, showed after incubation that the disease-causing effect of the virus was decreased.	(Hizam et al., 2019)
Garlic bulb extract	ND suspected embryonated chicken eggs	*ND virus*	25, 50, 100 and 200 mg/ml	The garlic extract reduced the egg infective dose at 50%, hemorrhages subcutaneously and the virus count in hemagglutination test.	(Harazem et al., 2019)
Aqueous garlic extract	Embryonated chickens eggs	*ND virus velogenic strain*	10 mg per milliliter 100 mg per milliliter	At 100 milligram per milliliter, extract has more efficient effects against the virus.	(Arify et al., 2018)
Aqueous garlic extract	Embryonated chickens eggs	*ND virus velogenic strain*	0.5, 1, 2, and 4 mg/mL doses	The titers of antibodies against the velogenic strain of ND were more significant in the group treated with garlic extract.	(Doostmohammadian et al., 2020)
Garlic extract	Embryonated chickens eggs	*H9N2* strain of *Avian Influenza virus*	5%, 10%, 15%, 20% and 25%	Garlic extract at the dose rate of 15% exhibited antiviral potentials against H9N2.	(Ahmed et al., 2017)
Garlic paste	Broilers vaccinated against F strain of ND virus	*ND virus*	0.2%, 0.4%, 0.6% and 0.8% in drinking water	The antibody titer increased upon garlic inclusion at the dose rate of 0.4% and 0.6%.	(Chitwan, 2017)
Garlic juice	Broilers are vaccinated against Infectious bursal disease (IBD) and ND virus	*ND virus* *IBD virus*	0.5, 1.0 and 1.50 mL/L	The titer of antibodies against the two viral diseases (IBD and ND) was increased upon garlic juice supplementation at 1 or 1.5 ml/L.	(Al-Shwilly, 2017)
Garlic	White leghorn layers	*Newcastle disease virus*	10 grams per kg 30 grams per kg	At 10 grams per kg, the garlic supplementation produced more antibodies against ND	(Hanieh et al., 2010)
Garlic powder	Broiler chicks are vaccinated against Avian influenza and ND	*ND* *AI*	100, 150 and 200 g/t	Increased titers of antibodies were observed against AI and ND	(Eid and Iraqi, 2014)

Garlic powder	Broilers	*IBD* *ND*	20 g/kg	Antibody titers against both viruses were seen higher in the supplemented group	(Haq et al., 1999)
Garlic powder	Broilers	*ND*	0.2%–1.0%	Antibody titers against ND virus were increased in the supplemented group	(Pourali et al., 2010)
Garlic, turmeric, coriander, nilavembu and fenugreek	Embryonated chicken eggs	*ND virus*	500g grams	The number of titers of the virus was decreased in the herbal mixture treated group	(Priya et al., 2022)
The herbal mixture containing Garlic, onion, apple cider vinegar	Broilers	*Chicken infectious anemia virus*	2.5%, 5%, and 7.5%	The herbal mixture reduced the negative effects of the virus on broilers	(Abdulkareem et al., 2023)
Cinnamon oil	Chickens	*ND virus*	0.1%, 0.3%	Enhanced the immunity of ND virus-challenged birds, thereby exhibiting antiviral potential and increasing the survival rate of chickens	(Abdel-Hameed et al., 2017)
Cinnamon powder	Chickens	*ND virus*	1%, 3%	Enhanced the immunity of ND virus-challenged birds, thereby exhibiting antiviral potential and increasing the survival rate of chickens	(Abdel-Hameed et al., 2017)
Cinnamon, thyme and turmeric	Broilers	*ND virus*	5 grams per liter (infusion)	Immunity to the vaccine for the ND virus has improved	(Sadeghi et al., 2012)
Cinnamaldehyde and glycerol monolaurate	Broiler chicks	*Infectious Bronchitis virus*	1.5 mL/L water	Impeded the infectious bronchitis virus infection	(Zhang et al., 2022b)
Aloe vera gel	Broilers	*ND virus*	5 ml/L, 10ml/L	Enhancement in the titer of antibodies against ND virus.	(Islam et al., 2020)
Aloe vera extract	Broilers	*ND virus*	50 mg, 100 mg, 150 mg	Decrease the intensity of the disease	(Ojiezeh and Ophori, 2015)
Aloe vera extract	Pigeons	*pigeon paramyxovirus type 1*	300 or 500 mg/kg	An improvement in immunity of the pigeons infected with the virus was seen at higher doses	(Dziewulska et al., 2018)
Aloe vera gel extract	White leghorn chicks	*IIBD virus*	3% aloe vera gel in drinking water	An enhancement in non-specific immune response was observed.	(Elaiyaraja et al., 2016)
Aloe vera extract	Broilers	*ND virus*	50 mg, 100 mg and 150 mg	Immunity against the viral disease was not significant.	(Ojiezeh and Eghafona, 2015)
Turmeric	Broilers	*IBD* *ND*	0.2% 0.4% 0.6%	An improvement in titers of antibodies was observed against viral diseases, particularly at 0.4%.	(Shihab, 2017)
Turmeric	Chicks	*ND virus*	0.5% 1%	40% protection was attained against the ND virus upon 0.5% turmeric supplementation Meanwhile, about 65% protection was obtained from 1% turmeric supplementation.	(Tamam et al., 2010)
Turmeric powder	Broilers	*ND* *AI*	5 g/kg	An enhancement in antibody titers was observed.	(Fallah and Mirzaei, 2016)

Turmeric powder and Thyme powder	Broilers	*ND* *AI*	2.5 grams per kg of turmeric powder + 2.5 grams per kg of thyme powder	Increase in antibody titers	(Fallah and Mirzaei, 2016)
Thyme powder	Broilers	*ND* *AI*	5 g/kg	An enhancement in antibody titers was observed.	(Fallah and Mirzaei, 2016)
Turmeric	Embryonated chicken egg	*Influenza virus (H9N2)*	0.2 mg/0.2 ml	The mortality of embryos inoculated with the virus was reduced, thereby exhibiting the antiviral properties	(Shah et al., 2021)
Oregano essential oil	Broilers vaccinated with ND vaccine	*ND virus*	50 mL/1000L of drinking water	An efficient immunological response was seen in the vaccinated-treated birds	(Abdulkadhim et al., 2022)
Oregano oil	Broilers	*ND virus*	1 ml/L	Enhanced the immunity of ND virus-challenged broilers to about 90%.	(Alazzawi and Khammas, 2022)
Oregano oil	Broilers	*ND* *AI*	1.5ml/L	An increase in the antibody level against the Avian Influenza and Newcastle disease viruses	(Abdel-Hafez and Mohamed, 2016)
Red ginger powder, ethanolic extract, essential oil	Broilers	*ND virus*	1% (powder in feed, extract, and oil in drinking water)	The high antibody titers against the virus were observed mainly in the ginger powder group	(Untari et al., 2022)
Ginger	Broilers	*ND virus*	2g/kg, 4g/kg and 6g/kg	Ginger supplementation at 4 g/kg or 6 g/kg showed increased Haemagglutination Inhibition antibody titers against the ND virus	(Al-Bawi and Rabee, 2020)
Moringa leaf extract	Broilers	*ND virus*	200 mg/kg	The supplemented group had high Haemagglutination Inhibition titers against ND virus infection	(Tolba et al., 2022)
Moringa powder	Broilers	*IBD* *ND*	1.5%	Titers of antibodies were increased in the supplemented group.	(Mousa et al., 2017)
Moringa leaf meal	Broilers	*ND*	500 and 1000 mg/kg	Titers of antibodies were increased in the supplemented group	(Rao et al., 2018)
Moringa leaf extract	Broilers	*IB* *ND*	60, 90 120 ml/L of drinking water	Titers of antibodies against both diseases were increased in the supplemented group, particularly at the concentration of 120ml/L	(Khan et al., 2022)
Neem leaves	Broilers	*IBD* *ND*	2,4,6 g/kg	Titers of antibodies were raised against both diseases in the supplemented group	(Jawad et al., 2013)
Neem aqueous extract	Broilers	*ND*	5 g	Antibody titers against ND protected the birds	(Garba et al., 2013)
Neem and Garlic Aqueous extract	Broilers	*ND*	2.5 g + 2.5 9	Antibody titers against ND protected the birds.	(Garba et al., 2013)
Methanolic neem leaf extract	Broilers	*ND*	500 and 1000 µg/kg BW in drinking water for 5 days	The neem leaf extract supplementation, particularly at a high dosage of 1000 µg/kg, reduced the number of diseased and dead birds with decreased lesions.	(Elbasuni et al., 2023)
Coneflower	Broilers	*ND*	2%	Increase the antibody titers against Newcastle disease	(Jouzi et al., 2014)

Peppermint and eucalyptus essential oils blend	Broilers	*Velogenic strain of NDV*	0.25 ml/l	A decrease in mortality was seen in the infected and treated groups with a higher antibody titer against the virus	(Awaad et al., 2016)
Peppermint and eucalyptus essential oils blend	Embryonated chicken eggs	*ND* *AI*	0.1 ml/chick embryo	The chicks survived the infection from both viruses to about 100% in the treated groups. However, the AIV is more susceptible to the blend.	(Barbour et al., 2010)
Thyme extract	Broilers	*AI*	0.1%, 0.15% and 0.2%	Supplementation at 0.2% showed higher and specific titers of antibodies against the AI virus	(Talazadeh and Mayahi, 2016)
Thyme essence	Broilers	*AI, IBD, IB, ND*	1 ml, 1.5 ml, 2 ml	No significant change in antibody titers was observed at any dose	(Kalantar et al., 2015)

Table 5: Effect of different phytobiotics on the fungal infections of poultry

Phytobiotic	Study Specimen	Dose	Effect	Reference
Garlic extract and garlic chips	Feed	3% concentration	Inhibition of the growth of Aspergillus parasiticus, Candida albicans, and Aspergillus fumigatus Extract was more effective as compared to the chips.	(Prasad and Sharma, 1981)
Garlic oil	Broilers affected with T2 toxin	0.3 g/Kg, 1.5 g/Kg	Mitigate the adverse effects of T2 toxin in broilers at a lower dose of about 0.3 g/Kg	(Ancsin et al., 2013)
Ginger	White Pekin ducklings affected with aflatoxin	250 mg/Kg Ginger capsules	Amelioration in the adverse effects of aflatoxicosis in ducks when ginger was supplemented in the diet	(Abu El-Ela et al., 2019)
Ginger	Broilers intoxicated with aflatoxin	0.75 g/Kg ration	Returned the physiological, biochemical values to normal, with improved effects on the histopathology of aflatoxin-infected broilers.	(H and A, 2015)
Ginger (Dried and powdered rhizome shade)	Broiler chicks (male) infected with ochratoxin or T2 toxin	0.5%	Plays a protective role against the oxidative stress caused by ochratoxin or T2	(Rani et al., 2009)
Ginger, Garlic, Turmeric	Broilers infected with dietary aflatoxins	2 g/kg	There was an improvement in biochemical parameters, digestibility of nutrients, hematology, and growth performance upon the diet supplementation with ginger, garlic, and turmeric. These parameters were negatively affected by the aflatoxins.	(Salako et al., 2022)
Cinnamaldehyde	Feed	0.4%, 0.8%, 1.0%	*Aspergillus parasiticus* and *Aspergillus flavus* multiplication and growth were inhibited within feedstuff.	(Yin et al., 2015)
Cinnamon powder	Japanese quails (laying) affected with aflatoxins	10 mg/Kg	Cinnamon powder in the diet ameliorated the adverse effects of aflatoxins in quails.	(Gadu, 2023)
Trans cinnamaldehyde	Chickens infected with aflatoxins	0.75%	Hepatoxicity and decreased performance of birds induced by aflatoxins were improved by cinnamaldehyde supplementation.	(Yin, 2017)
Trans cinnamaldehyde	Chicken embryos with aflatoxin-induced toxicity	0.1%	Its supplementation decreased the toxicity in chicken embryos induced by aflatoxins.	(Yin et al., 2017)
Aloe vera	Layers affected with aflatoxins	100 ppm, 300 ppm	Aloe vera supplementation ameliorated the adverse effects of aflatoxins in layers and improved egg weight, shell thickness, and egg production.	(Seifi et al., 2022)
Aloe vera powder	Laying hens fed with aflatoxin B1	100 ppm, 300 ppm	The remnants of B1 aflatoxin within eggs of the layers supplemented with B1-aflatoxin and aloe vera were diminished, indicating a positive role of aloe vera in inhibiting aflatoxin growth.	(Mohajer et al., 2021)
Aloe vera powder	Broilers fed on aflatoxin B1	100 ppm	Diet supplementation with aloe vera reduced the adverse effects of aflatoxins. Lower amounts of toxin residue were found in breast muscle compared to the control group.	(Sadighara et al., 2021)

Aloe vera dry powder	Ducklings	1% 2-4%	1%: it only relieved the negative impact of aflatoxin on the weight gain in ducklings. 2-4%: it eliminated the adverse effects on weight gain of ducklings induced by aflatoxin	(Hunan, 2011)
Turmeric	Broilers exposed to aflatoxins	5 mg per kg of diet 25 mg per kg of diet	Turmeric ameliorated the negative impact of aflatoxins over liver and kidney roles in broilers	(Gholami-Ahangaran et al., 2016)
Turmeric powder	Aflatoxin B1 exposed Broilers	400 mg/Kg in feed	Adverse effects of aflatoxin were diminished upon turmeric supplementation.	(Amminikutty et al., 2023)
Ethanolic Turmeric extract	Broiler chickens with aflatoxicosis	0.05%	The performance of aflatoxin-affected broilers improved upon turmeric supplementation	(Rangsaz and Ahangaran, 2011)
Turmeric powder	Broilers affected with aflatoxin B1	80 mg/Kg	The adverse effects of aflatoxin B1 were reversed by turmeric powder used in the diet	(Abd El-Ghany et al., 2013)
Turmeric ground roots powder	ducklings	1%	Turmeric protects ducklings against aflatoxicosis	(Ayoub et al., 2011)
Oregano essential oil	Japanese quails (growing) affected with aflatoxins	200 mg/Kg 400 mg/Kg	Especially at the dose rate of about 400 mg/Kg, the oregano essential oil ameliorated the adverse effects in quails caused by aflatoxin B1	(Abdelrazek, 2015)
Oregano	Breeder chickens	0.1% 1 liter of pure oregano dissolved in 1000 liters of water)	The growth of the fungi *Candida albicans* was decreased (95-99.5%) by oregano	(Sadri, 2008)
Oregano oil	Japanese quails affected with aflatoxins	400 mg/ Kg	The immunosuppression caused by aflatoxins in Japanese quails was ameliorated by oregano oil via its antioxidant effect	(Shalaby and El-Tawil, 2016)
Thyme oil	Broilers affected with candidiasis	200 ml/Kg	The symptoms of candidiasis in broilers were reduced upon thyme oil supplementation in the diet	(Abdel Fatah et al., 2020)
Thyme oil	Broiler chickens	200 mg/Kg	The adverse effects of aflatoxin on the weight gain parameters of broilers were ameliorated upon thyme oil supplementation	(Fawaz et al., 2022)
Thyme ethanolic extract	Broilers infected with aflatoxinB1	500 ppm	The adverse effects caused by aflatoxin in feed were alleviated upon thyme inclusion in the diet	(Manafi et al., 2014)
Moringa	White leghorn layers (Male) affected with Aflatoxin B1	1%	The adverse effects of aflatoxin B1 on the hematology and serum enzymes were reduced by adding Moringa to a contaminated diet	(Saleemi et al., 2023)
Moringa leaves	Broilers infected with aflatoxin B1	3 mg/kg	Lessened the aflatoxin-induced adverse effects on the broilers' antioxidative status and biochemical parameters.	(Suganthi Rajendran et al., 2012)

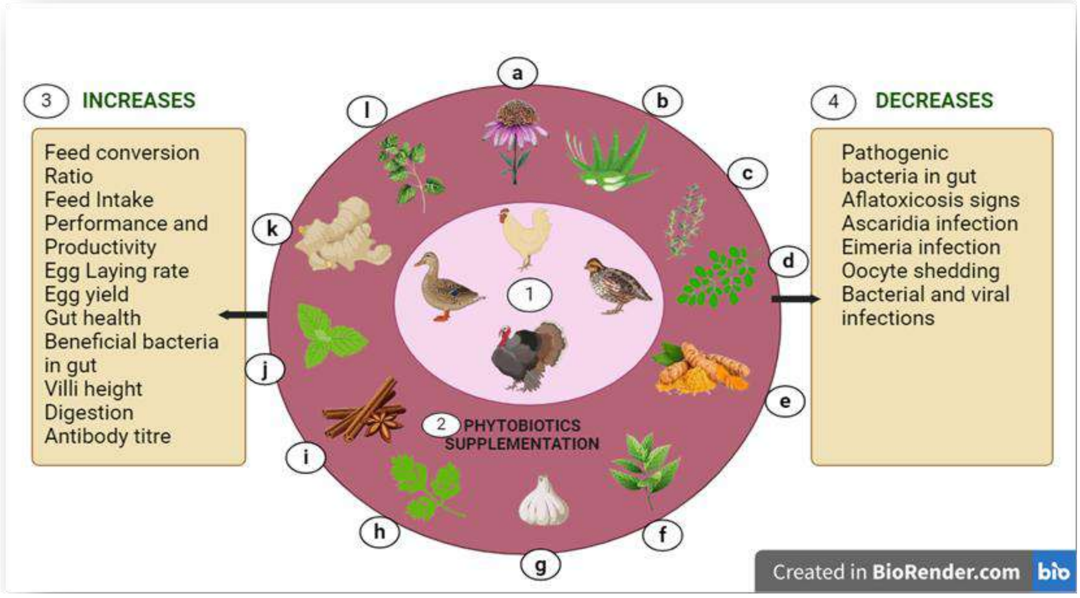

Fig. 1: Schematic diagram showing multiple effects of Phytobiotics used in poultry.
[1,2] In different species of poultry (chickens, ducks, quails, and turkeys), supplementation of various Phytobiotics ([a] coneflower, [b] aloe vera, [c] thyme, [d] moringa, [e] turmeric, [f] neem, [g] garlic, [h] coriander, [i] cinnamon, [j] peppermint, [k] ginger, [l] oregano) [3] increases feed conversion ratio, feed intake, overall performance and productivity, egg laying rate, egg yield, gut health, beneficial gut bacteria, villi height, digestion and antibody titers. [4] While it decreases gut pathogenic bacteria, aflatoxicosis, eimeria, and Ascaridia infections, bacterial and viral diseases, and oocyte shedding.

Conclusion

The beneficial effects of the different phytobiotics are described in the Fig. 1. In a nutshell, phytogenic feed additives usage, as substitutes for the antibiotic performance enhancers within poultry production represents significant progress. As described above, phytobiotics have demonstrated considerable potential in bolstering poultry gut health by increasing villi height and promoting beneficial bacterial populations like Lactobacillus while decreasing pathogenic E. coli and Salmonella. Their different forms and doses have also led to notable increases in growth performance without the residual effects of antibiotics. The bioactive compounds present within the phytobiotics demonstrate various properties such as antiviral, antibacterial, antifungal, and antiparasitic effects (Fig. 1), thereby significant contribution to poultry health maintenance and disease prevention. Future research endeavors should explore synergistic combinations of phytobiotics to modulate the poultry microbiome and further augment overall poultry health.

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Chapter 41

Nigella sativa: A Promising Alternative to Antimicrobials

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ABSTRACT

The *Nigella sativa*, also referred to as black seed, has long been utilized for medical purposes. *Nigella sativa* is a promising alternative to antibiotics due to the rising incidence of antibiotic-resistant illnesses. In exploring *Nigella sativa*'s nutritive and chemical profiles, this chapter highlights the plant's many medicinal uses, such as its antibacterial, antiviral, antifungal, and antiparasitic properties. Important active ingredients with strong antibacterial activity against a range of diseases include thymoquinone. The effects of *Nigella sativa* are discussed, including how it inhibits microbial development and interferes with microbial defense mechanisms. The study also examines the safety guidelines for using *Nigella sativa* and how it might develop as a complementary therapy, providing a viable natural defense against antibiotic resistance.

KEYWORDS		
Thymoquinone, Anti-inflammatory, Antimicrobial resistance, , Black seed, Therapy	Received: 25-Jun-2024 Revised: 12-Jul-2024 Accepted: 29-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

The kingdom of plants, apart from supplying oxygen necessary for life and preserving environmental equilibrium, is also vital to human and animal nutrition and an indispensable source of contemporary pharmaceuticals. Diets composed of plants fulfill the body's fundamental nutritional needs, maintain bodily health, and strengthen the immune system to fight off an array of diseases. Because there is a direct correlation between a healthy diet and an average life expectancy, the terms, nutraceuticals, and functional foods have gained popularity in recent decades among those who are health-conscious (Qadir and Raja, 2021). Spices and herbs, which are usually employed as flavoring additives and preservatives, are minor but essential components that include an extensive number of bio-functional molecules among the range of functional food elements. Due to their great potential for supporting health, most of these culinary herbs and spices are also widely recognized for their pharmaceutical properties. The increasing prevalence of bacterial infections and the growing threat of antibiotic resistance in most parts of the world have drawn the attention of physicians, dietitians, nutritionists, food scientists, and the food and pharmaceutical industries to these alternatives in recent times (Msomi and Simelane, 2019).

One of the top ten most dangerous diseases in the world is Infectious disease, and the threat of increasing antimicrobial resistance (AMR) has made most conventional medications less effective including most clinical antibiotics. Antibiotic overuse drives up the rate of antimicrobial resistance (AMR), which raises the number of AMR-related fatalities worldwide (Arbune et al., 2021). Patients with methicillin-resistant Staphylococcus aureus (MRSA) infection, for instance, have a 64% higher mortality rate than those with drug-sensitive forms of the infection (Carey et al., 2023). Furthermore, AMR has grown remarkably globally due to the reasons of changes in host vulnerability as well as genetic modifications in bacteria and other microbes with the advancement of science. Compounds and molecules derived from plant sources are naturally multi-targeting as they battle against various predators, including bacteria, fungi, viruses, insects, and herbivores, throughout their life cycle, from germination to maturity, and must withstand difficult defense mechanisms to survive (Dhandge and Deshmukh, 2023). Therefore, it is more practical and economical to investigate possible antibacterial compounds derived from plant sources as an alternative to creating new antibiotics. Furthermore, it is easy and secure to obtain plant sources because traditional medicine, particularly in the world's less industrialized and developing nations, provides healthcare for 75 to 80% of the worldwide population (Jamal, 2023).

Historically, medicinal plants have served as essential natural factories to produce phytochemicals with biological activity, including steroids, alkaloids, terpenoids, tannins, and flavonoids. The seeds of *Nigella sativa (N. sativa)*, commonly referred to as black seeds, are highly concentrated in phytoconstituents and have made the plant popular for a variety of therapeutic benefits (Abbas and Banno, 2020). Because of their chemical structure, *N. sativa* seeds have been shown to provide pharmacological qualities such as analgesic, appetizer, antidiabetic, antioxidant, anti-inflammatory, radical scavenger, and antibacterial activities. It has been evident that the extract and oil of black seed been widely used for the treatment and prevention of multiple disorders is both animal and human models. These disorders include asthma, oxidative stress, diabetes, ulcers, inflammatory disorders, hypertension, epilepsies, cancer, fatty liver and arthritis (Ara et al., 2020). Thymoquinone is the major component of black seed and had been extensively used for its pharmaceutical properties and applications. It promotes health due to its ability to cope with different ailments, here in Pakistan it has been extensively used in traditional and Unani medications for a long time (Shafodino et al., 2022). Besides all other activities the antimicrobial properties and potential of black seed is of great importance and it will be discussed in this chapter.

Overview of *N. sativa*

N. sativa is cultivated in different parts of the world, mainly in damp and moist areas. The general height of the plant to which it grows is 20-60 cm with aspects of leaves having the appearance of thread-like structures and very attractive flowers. The plant is an upright, branching herb with divided leaves, a tap root system, and attractive yellow-to-white blooms (M. T. Islam et al., 2017). Except for its many stamens, the plant is typically pentamerous. A wide area of the eastern Mediterranean, northern Africa, the Indian subcontinent, and Southwest Asia is home to the black cumin plant, which is grown in various nations such as Egypt, Iran, Greece, Syria, Albania, Turkey, Saudi Arabia, India, and Pakistan (Hannan et al., 2021).

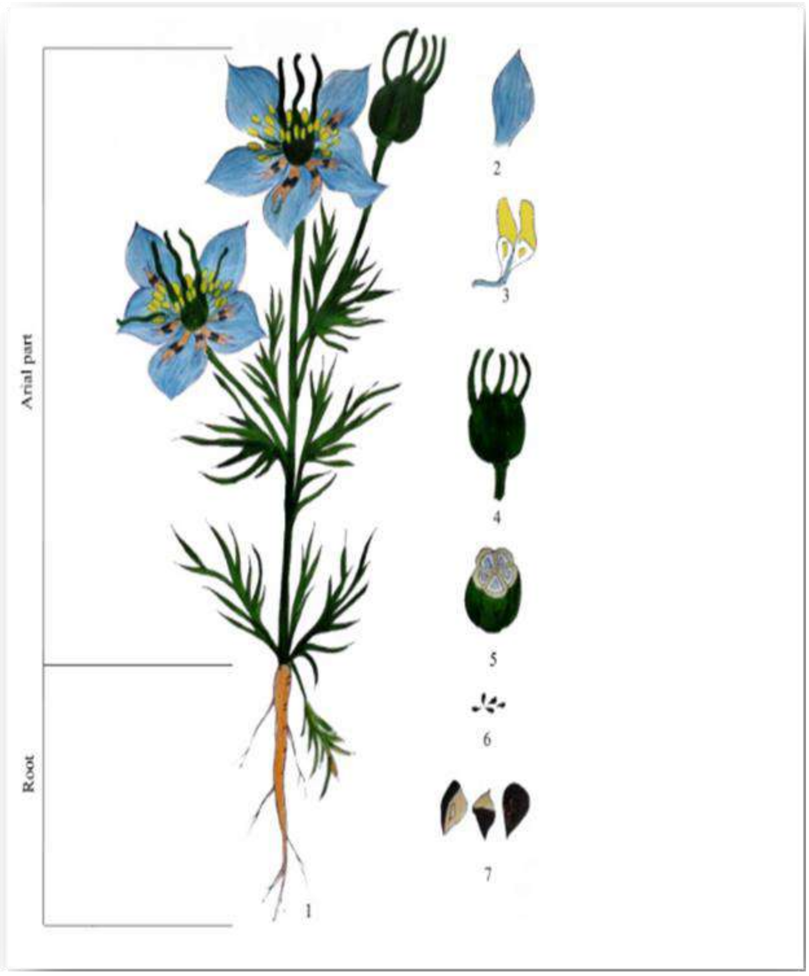

Fig. 1: Flower of *N. sativa* and its different Parts, 1; Habit, 2; Petal, 3; Stamen, 4; Fruit, 5; Transverse section of Fruit, 6; Seed, 7; Transverse section of seed. Source: (Hossain et al., 2021)

N. sativa is frequently referred to as *black seed* in English because, when exposed to air, the seeds typically turn black. In the Muslim community, it is also known by the names *Alhabahat Alsawda*, *Habbatus Sauda*, and *Alkamoun Alaswad*, depending on the color of the seeds (Thakur et al., 2021). The vernacular names of this significant black seed are shown in the figure below. Its seeds are a rich source of phytochemicals with a wide range of pharmacological potential, including steroids, alkaloids, terpenes, flavonoids, and polyphenols. Black cumin is a panacea used in traditional medicine to treat various illnesses and ailments and is also available as an essential oil, paste, powder, and extract. Some of these include eczema, hypertension, rheumatism, headaches, back pain, anorexia, amenorrhea, paralysis, inflammation, and asthma

(Dabeer et al., 2022).

English	Fennel Flower, Nutmeg Flower, Raman coriander, Blaxkseed, black caraway, black sesame
Hindi/Urdu	Kalaunji/Mangrail
Russian	Chernushka, Herbrew, Ketzakh
Turkish	Corek out
Arabic	Habbat ak-barkah
Indonesian	Jintan hitam
Bosnian	Curekor
French	Nigelle de Crete, toute epice
Germany	Schwarzkummel
Portuguese	Cominho-negro
Spanish	Ajenuz, aranuel
Swedish	svartkummin
Assamese	Kaljeera, kolajeera
Bengali	Kalo jeeray
Kannada	Krishna Jeeriage
Tamil	Karum, jeerakam

Fig. 2: Vernacular Names of *N. sativa*, Source: (Thakur et al., 2021)

Nutritional Profile of *N. sativa*

A small percentage of essential oils of 0.4 to 1.49%, fixed oils of 30 to 45%, and other chemicals are present in *N. sativa* seed. The other chemicals vary in concentration. Proteins, carbohydrates, amino acids, and bioactive compounds are all present in *N. sativa*. The protein percentage of 26.7%, fat at about 28.5%, carbs at 24.9%, crude fiber at 8.4%, total ash at 4.8%, volatile oil at 0.5 to 1.6%, fatty oil about 35.6 to 41.5%, cellulose at 6.8 to 7.4%, and moisture of 8.1 to 11.6% are all present in the black seeds of *N. sativa* (Albakry et al., 2022). Furthermore, the seeds are abundant in minerals including Ca, K, Se, Cu, P, Zn, Fe, and several vitamins particularly A, B1, B2, B3, and C. Its seeds, roots, and shoots have also been reported to contain beta-carotene and vanillic acid, respectively. The primary unsaturated fatty acids found in fat components are linolic acid at 50 to 60%, oleic acid at 20%, dihomo-γ-linoleic acid at 10%, and eicosadienoic acid at 3%. The two primary saturated fatty acids that palmitic acid and stearic acid are a part of are α-sitosterol at 44 to 54% and stigmasterol at 6.57 to 20.92%. It has also been claimed that *N. sativa* contains certain additional fatty acids, including myristic acid, palmitoleic acid, linoleic acid, linolenic acid, arachidonic acid, cholesterol, campesterol, β-sitosterol, 5-avenasterol, 7-stigmasterol, and 7-avenasterol (Mazaheri et al., 2019).

***N. sativa*'s Chemical Constituents**

The main chemical constituents of *N. sativa* and the main substances that make the chemical profile of Black seed include α-phellandrene, oleic acid, thymol, thymoquinone, carbohydrates, and proteins. As per the past literature, the main composition of *N. sativa* is comprised of linoleic acid, trans-anethole, palmitic acid, and oleic acid. Quinones (thymoquinone, thymol, di-thymoquinone, and thymohydroquinone) and phenolics were present in the plant. Monoterpene hydrocarbons dominated the chemicals that were extracted from *N. sativa* seeds. shown that *N. sativa* seeds contain proteins, oils, phenols, and alkaloids (Dalli, Bekkouch, et al., 2021). It has also been reported more recently that the plant contained a variety of biochemical compounds, primarily flavonoids, terpenes, and phenols. Alkaloids, fatty acids, polyphenols, phytosterol, terpenes, terpenoids, and other compounds are among the phytocompounds found in the plant (Imran et al., 2022).

Therapeutic Applications of *N. sativa*

The main ingredients that give black cumin seed its pharmacological and therapeutic actions are thymoquinone, thymohydroquinone, thymol, carvacrol, nigellidine, nigellicine, and α-hederin, especially in its essential oil. The Unani system lists *N. sativa* seeds as having stomachic, laxative, carminative, and galactagogue properties in addition to being used to treat paralysis, tertian fever, piles, inflammation, ascites, and eye disorders. It is also used to treat kidney stones and treat headaches, coughs, and asthma (Hosni et al., 2023). Moreover, *N. sativa* seeds have been utilized as an emmenagogue, stomachic, diaphoretic, diuretic, liver tonic, and parasite infection preventive. When mixed with other components, *N. sativa* can treat dyspepsia, reflux, obesity, and dyspnea, and improve breath. Relentless hiccups, anorexia, vomiting, edema, and puerperal illnesses are all treated with the seeds taken with buttermilk. They can be used to treat skin eruptions, amenorrhea, dysmenorrhea, leprosy, and polio in addition to being effective against mercury toxicity. It has been demonstrated that a tincture made from *N. sativa* seeds is beneficial. It has been employed as the anti-parasitic drench with its oils utilized as the oral dose, because of its immune-stimulant qualities (Ojueromi et al., 2022).

The oil is often used to treat skin ailments like boils, psoriasis, and eczema. Additionally, burns, joint pain alleviation, moisturizers, and anti-wrinkle agents can be treated using a mixture of beeswax and black seed oil. The oil can be used externally and possesses antibacterial qualities as well. Dried pods of *N. sativa* are sniffed to revive a sense of smell lost in time. By distributing them in between fabric folds, they prevent insects from damaging woolen textiles and act as insect repellents like mothballs (Abd-Rabou and Edris, 2021).

Antimicrobial Properties of *N. sativa*

Thymoquinone serve as the major and most important anti-microbial chemical constituent of the *N. sativa* that is responsible for the properties of anti-bacterial, anti-fungal and anti-parasitic aspects of this plant. Along with this substance, another chemical demonstrating anti-microbial properties for *N. sativa* involves the α-pinene, possessing both bactericidal and antimicrobial actions. Also, thymohydroquinone chemical of this plant also contains anti-bacterial and antifungal properties as per (Perera et al., 2021).

Thymoquinone's Role as an Active Chemical

A remarkable and significant anti-septic property is demonstrated by the active chemical, thymoquinone, at a specific dose rate. Along with this, the major active chemical fighting against the coronavirus and the virus of avian influenza in the *N. sativa* is the Thymoquinone as postulated by (Fatima Shad et al., 2021). Similarly, the research by (Al-Khalifa et al., 2021) evaluates that the consumption of *N. sativa* routinely has the capacity to block the multiplication and growth properties of coronavirus. Through this action, Nigella prevents the virus from entering the cell, thereby acting as the inhibiting agent against the corona infection. Besides, the analgesic, antioxidant, anti-inflammatory and anticancer properties are also manifested by Thymoquinone in the recent studies (Al-Khalifa et al., 2021).

Thymoquinone can inhibit the nuclear factor kappa beta (NF-κβ), mitogen-activated protein kinase (MAPK), Janus kinase/signal transduction, and activator of transcription (JAK-STAT) signaling pathways. Myeloperoxidase, cyclooxygenase (COX), lipo-oxygenase (LOX) enzymes, pro-inflammatory cytokines, reactive oxygen species (ROS), and elastase are all disrupted by thymoquinone (Khazdair et al., 2021).

Reported Anti-Bacterial Effects of *N. sativa*

It has been documented that *N. sativa* inhibits both Gram-negative (Pseudomonas aeruginosa and Escherichia coli) and Gram-positive (Staphylococcus aureus) microorganisms (Dalli, Azizi, et al., 2021). Along with beneficial effects when combined with spectinomycin, erythromycin, tobramycin, doxycycline, chloramphenicol, nalidixic acid, ampicillin, lincomycin, and co-trimoxazole, it demonstrated synergistic benefits with streptomycin and gentamycin (Al-Saedi, 2023). Additionally, it demonstrates actions like topical mupirocin. It has the potential to combat resistant pathogens, such as numerous multi-drug resistant gram-positive and gram-negative bacteria (Forouzanfar et al., 2014). In S. aureus, thymoquinone from *N. sativa* essential oils exhibited anti-methicillin-resistant action. The bactericidal potential of *N. sativa* was demonstrated by several studies (Dhahir Mansour Al Sultani et al., 2021). A study by (Arici et al., 2005) that used method of agar diffusion in the twenty four bacteria, including the spoilage, lactic acid and virulent bacteria, and then used *N. sativa* oil at doses of 0.5%, 1.0%, and 2.0%. 2.0% was the more effective concentration. 0.5% was the lowest active concentration of NS oil. When tested against Escherichia coli, E. Coli O157:H7, Pseudomonas aeruginosa, Yersinia enterocolitica, Lb. casei ssp. casei, Leu. pseudomesenteroides, or *Weissella paramesenteroides*, the concentration showed no activity. *Aeromonas hydrophila* was the most susceptible species of bacteria to all concentrations of *N. sativa* oils, whereas Y. enterocolitis was the most resistant. On average, fixed oils in *N. sativa* samples had more antibacterial activity than Lactic Acid Bacteria against pathogenic bacteria and spoiling. Another study by (A. R. Khan and Kour, 2016) used the agar-well diffusion method to examine the antibacterial activity of ethanol and hexane extracts of *N. sativa*. The extract's concentrations of 1.5, 3.0, 4.5, and 6.0 mg/ml were examined and compared with regular antibiotics (tetracycline, erythromycin, ciprofloxacin, and ampicillin). The ethanol extract demonstrated strong and notable action against *S. epidermidis* and *K. pneumonia*, followed by *Bacillus cereus*, *Bacillus subtilis*, *E. coli*, and *Salmonella typhimurium*. The extract had an antibacterial impact against both Gram-positive and Gram-negative bacteria. Methicillin-resistant Staphylococcus aureus (MRSA), the most frequent bacterium identified in clinics and laboratories, is also effectively prevented by *N. sativa*. MRSA has grown to be a significant global health issue (Badger-Emeka et al., 2021).

Mechanism of Action of *N. sativa* Against Bacteria

Multidrug efflux pumps are found in both Gram-positive and Gram-negative bacteria. These pumps play their role in the promotion of bacterial immunity and protection against the external antimicrobial substances. By origin, they act as the protein transporters playing their major role in the removal of the antimicrobial drugs and other molecules, harmful for the growth of bacteria and transport it outside the bacterial cell, thereby acting as the major root source of resistance of bacteria from anti-microbial and other multi-drugs (Randhawa et al., 2017). Listeria Monocytogenes has been examined to contain two to these major efflux pumps. These two pumps, recognized as the MdrL and Lde have been effective in removing several drug substances being MdrL in the removal of Ethidium Bromide, cefotaxime, macrolides and some heavy metals. The second efflux pump have been successful in the removal of acridine organe, flouroquinone and Ethidium Bromide as asserted by (Mosolygó et al., 2019). Such multi-drug antibiotic resistance can be effectively managed by the *N. sativa*. The active chemical of this plant, thymoquinone makes accumulation of these antibiotics possible through the blockage of the efflux pumps. This mechanism makes the antibiotics effective even at minimal dose rates. By generating reactive oxygen species (ROS), thymoquinone also interferes with its antibacterial action by inducing oxidative stress and cell death. P-cymene, on the other hand, has no antibacterial properties. However, it does so by making the membrane more permeable, which encourages the entry of antimicrobial compounds (Sicak and Eliuz, 2019).

Reported Anti-Viral Effects of *N. sativa*

As an herbal antiviral drug against novel coronavirus, *N. sativa* offers a great deal of potential, according to recent research (Shamim Molla et al., 2019). One significant phytochemical with potent antiviral properties that is present in *N. sativa* is DL-Arabinose. According to a study by (Basurra et al., 2021), *N. sativa* contains various bioactive ingredients, including Thymoquinone, dithymoquinone, thymohydroquinone, and nigellimine activity, which is enhanced by a zinc supplement, therefore, it may be regarded as a natural alternative to chloroquine. In another in-silico study using molecular docking (Bouchentouf and Missoum, 2020), the primary *N. sativa* compounds protecting the corona virus infection with the identical or higher potency as compared to the medications undergoing research experiments such as nigerlidine and α-hederin. Also, (Maiti et al., 2020) conducted an in-silico investigation and revealed that nigellidine had the strongest binding affinity of −7.61 to both nucleocapsid and N terminus protease, the primary protease required for viral maturation in terms of protein structures, RNA packaging, and other functions. Additionally, after viral infection, attaching to Interleulin-1 and Tumor Necrosis Factor-α receptors may lessen the surge of cytokines. The human system's ACE2 receptors, which are important for virus entry, have been found to bind well to α-hederin with a binding affinity of −6.265 kcal/mol) and thymohydroquinone with a binding affinity of −5.466 kcal/mol as asserted by (Jakhmola Mani et al., 2022). Dithymoquinone (DTQ), often described as nigellone, is one of the chemicals that exhibits a promising capacity to bind at the junction of ACES and SARS-CoV-2 and disturb contact of the virus and the host. It shows −8.6 kcal/mol after comparing to the chloroquine binding affinity as the positive control, with a binding affinity of −7.2 kcal/mol as postulated by (Ahmad et al., 2021).

When honey and *N. sativa* were taken orally, COVID-19 patients experienced a reduction in mortality, a rapid viral clearance, and a severity reduction in clinical symptoms. For COVID-19 treatment, Taibah University launched TaibUVID, a cutting-edge evidence-based treatment. Oil of *N. sativa* in one spoon and crushed anthemis hyaline of 1g along with the addition of honey makes up the dose of TaibUVID. For COVID-19 close contacts and patients, this mixture should be chewed in the mouth and eaten orally. This evidence-based strategy is encouraging for reducing deaths and quickly bringing the COVID-19 outbreak to a stop (El Sayed et al., 2020).

***N. sativa*'s Mode of Action Against Viruses**

Natural killer (NK) cells and the ratio of suppressor T cells (T4 and T8) are both increased by *N. sativa*. It has a suppressive effect against the human immune deficiency virus protease because it improves immunity. Moreover, it has been found to function against the murine cytomegalovirus and the protease of HIV. It was revealed that in the second scenario, the production of interferon-gamma (INF-γ) was associated with an increase in the number and effectiveness of CD4+ve T cells. Anti-influenza virus action is demonstrated by *N. sativa* (M. N. Islam et al., 2021). Through the induction of effective immunological responses, it has its effects in reducing the virulent actions of the virus. When *N. sativa* seed oil was used, patients with hepatitis C virus (HCV) infection showed a significant improvement in their HCV viral load. Patients with HIV can use *N. sativa* seeds to achieve sero-reversion and regain their health. It has been suggested that *N. sativa* oil interacts with murine cytomegalovirus, which in a rat model inhibited viral proliferation (Perera et al., 2021). The Newcastle disease virus was effectively inhibited by the ethanolic extracts of *N. sativa* in terms of both viral load and egg mortality in embryonic chicken embryos (Raheem et al., 2021).

Reported Anti-fungal Effects of *N. sativa*

Higher anti-dermatophytic action is present in *N. sativa* essential oil. In research conducted by b (Aljabre et al., 2005) some antifungal activity against dermatophytes, four species of Trichophyton rubrum and one each of *T. interdigitale*, *T. mentagrophytes*, *Microsporum cani*, and *Epidermophyton floccosum* was demonstrated by an ether extract of *N. sativa* seed and its active ingredient, Thymoquinone. Further, The *N. sativa* and Thymoquinone ether extracts had minimum inhibitory concentrations of 10 to 40 mg/ml and 0.125 to 0.25 mg/ml, respectively, which prevented 80 to 100% of the development of fungi. When applied at concentrations of 0.1% and 0.15%, *N. sativa* oil completely suppressed non-dermatophytic filamentous fungi including *F. moniliform*, *Alternaria alternative*, along with *Drechslera hawiinesis* as postulated by (Sitara et al., 2008).

Researchers found that *N. sativa* was able to inhibit *Macrophomina phaseolina*, one of the most harmful phytopathogenic fungi that cause charcoal rot disease, to the fullest extent possible at a concentration of 10% (Iqbal et al., 2014). Isolated from N. sativa seeds, Ns-D1 and Ns-D2, two new antifungal defensins, show strong, varying antifungal activity against a variety of phytopathogenic fungi (Rogozhin et al., 2011). Aflatoxin and mycelia formation in *Aspergillus parasiticus* are both inhibited by the essential oil of 67.4% of *N. sativa* @1.5 mg/ml. In Aspergillus flavus and Aspergillus fumigates, *N. sativa* oils @2 mg/ml caused the fibrillar layer of the cell wall to break down, as per the study by (Khosravi et al., 2011). It has been observed that the black seed hinders the growth of fungus causing aflatoxin, moreover it damages the cytoplasm of fungus causing less growth and disruption in cellular activity (Khosravi et al., 2011).

Anti-fungal activity of *N. sativa*

Black seed can decrease the activity of numerous disease-causing yeasts. It is believed that *N. sativa*'s antifungal effect stems from the presence of oleic acid and β-sitosterol in its oil composition. Furthermore, some constituents of natural spice oil, like stigmasterol and β-sitosterol, exhibit antifungal characteristics against certain pathogenic yeasts like *Geotrichum candidum*, *Candida tropicalis*, and *Candida albicans* (Shokri, 2016). A study conducted in vivo on mice demonstrated the antifungal efficacy of the aqueous extract from *N. sativa* seeds against candidiasis-causing *Candida albicans* (M. A. U. Khan et al., 2003). Nitric oxide (NO) is required for the candidacidal pathway in mouse neutrophils, according to another study. Potentially, the plant extract's active ingredient(s) could induce nitric oxide synthesis in monocytes and granulocytes, which would have strong antifungal effects and ultimately kill Candida albicans. At pH 7 and 30°C, *N. sativa* seed extract has its highest anti-yeast activity (Nadaf et al., 2015).

Anti-Parasitic Effects of *N. sativa*

N. sativa has been revealed to have strong anti-parasitic (anti-helminth, anti-cestodal, and anti-schistosomal) effects. *N. sativa* seeds demonstrate significant anti-cestodal actions. These locally available, inexpensive, and easily grown plant-based medications are suitable for use in treating roundworm and tapeworm infestations in children. With no severe side effects, the dose rate of 40 and 50mg/kg were the mostly effective and efficient doses (Akhtar and Riffat, 1991). While the major medication having synthetic origin, chloroquinone, had a suppression rate of 86 percent, the methanolic extract of *N. sativa* seeds at 1250 mg/kg had a 94% suppression rate against *Plasmodium yoelii* infection (Francis et al., 2023). To treat coccidiosis in rabbits, aqueous suspensions and oil emulsions containing 400 mg/kg of *N. sativa* seeds were utilized. The alkaloid nigellicine, which is lethal to parasites, is present in higher concentrations in the emulsion. The number of Schistosoma mansoni worms were also found to be reduced in the liver through the *N. sativa* oil action other than the decrease in the quantity of ova that were present in the liver and intestines. Besides this, the efficacy against the helminths were also examined such as, *Hymenolepis nana*. The potency of *N. sativa* was additionally tested against the adult worms of *Schistosoma mansoni*, miracidia and cercariae. It has shown significant biocidal action against every stage of the parasite and has an impact on the adult female worms' ability to produce eggs (Forouzanfar et al., 2014). The exact mechanism of action underlying *N. sativa*'s anti-parasitic properties, however, is yet unknown and needs more research.

Safety Standards of *N. sativa* Utilization

Thymoquinone is the primary ingredient in the volatile oil found in *N. sativa* seeds. There doesn't seem to be much toxicity in its seed extract or its components. The level of established toxicity following oral ingestion of Thymoquinone was insignificant (Hannan et al., 2021). Oral Thymoquinone is either bio-transformed in the gastrointestinal system into more modest toxic metabolites or converted into dihydro-thymoquinone in the liver. Because Thymoquinone is fully absorbed into the systemic circulation after injection, the toxicity increases. When male albino rats were given intraperitoneal injections of 200 mg/kg cyclophosphamide or phosphate-buffered saline (PBS) and then intragastric injections of *N. sativa* oil or Thymoquinone every other day for the period of twelve days, starting six hours prior and later to the injection of chemical cyclophosphamide, it was observed that the cyclophosphamide medication resulted in a substantial increase in overall pathogenicity, however the *N. sativa* oil or Thymoquinone treatment caused a significant decrease in overall toxicity as per (Alenzi et al., 2010). When administered sub-chronically in drinking water at levels around twelve times the cytoprotective dose, Thymoquinone has comparatively low acute toxicity and is often well tolerated. There were no alterations in the levels of liver enzymes or harmful effects on liver function after 28 days of *N. sativa* supplementation up to 1 g/kg (Burdock, 2022). In rodents, Thymoquinone can shield against and prevent cisplatin nephrotoxicity. Additionally, cisplatin-induced nephrotoxicity was significantly reduced by the intake of Thymoquinone orally @ 50 mg/L mixed in drinking water in the routine of 5 days before and 5 days with the follow up of a single cisplatin injection @ 5 mg/L in rats and 7 or 14 mg/l in mice (Zaoui et al., 2002).

Opportunities for advancement as an Alternative medicine

Modern medications, also often known as chemical medicines, pharmaceuticals, pharmaceutical products, and conventional medicines, more especially, antimicrobial drugs have been utilized extensively to effectively treat a variety of illnesses. However, the side effects of using these medications have drawn millions of individuals worldwide to turn to herbal and natural therapies as alternatives for pharmaceuticals in medical treatment. Most patients prefer to prevent the negative consequences of long-term use of modern medicine for chronic illnesses, which is why they turn to herbal medicine. Given the established benefits of various herbal medicines, the modern medical system must fully utilize this valuable plant as an efficient replacement for antimicrobials on a large scale, thereby directing the aspirational role of *N. sativa* in a variety of medical conditions within the anti-microbial universe (Bhat et al., 2019). Synthetic medicine formulations go through numerous stages, from the first assessment of the drug's effectiveness in model organisms to the assessment of toxicity and tolerance, human trials, and ultimately, production. Modern medical systems may use the same stages for *N. sativa*, considering the affectivity trials and toxicity assessment. The current pharmaceutical system has the ability to produce *N. sativa* seed extract, pills, and capsules, which could be used as alternative medicines (Bhikha and Glynn, 2019).

Conclusion

In a nutshell, an insightful understanding and in-depth discussion on the overall description of *N. sativa* and its role in the therapeutic world, along with the brief understanding of the anti-microbial effects of *N. sativa* thereby, demanding the critical and clinical experimentation in the contemporary medicine. Through this discussion, it was evaluated that the antifungal, anti-bacterial, anti-parasitic and anti-viral effects were reported by the various active chemical substances of this plant. This plant, *N. sativa* belonging to the family of Ranunculaceae, has been found effective and proficient against various antimicrobial infections and restoration of health from these infections through the therapeutic action against various microbes. Various forms of this plant have been utilized for therapeutic effects including the oils, seeds along with the extracts of seeds and oils. The major active chemical in this plant, known as thymoquinone has been evaluated to possess the anti-cancer, anti-microbial, anti-diabetic and hepatoprotective function. Many other active chemicals are also present in *N. sativa* manifesting the therapeutic properties. Major active chemical substances against the antimicrobial resistant bacteria are found to be thymoquinone, carvacoal, and many others as apparent by the discussion from this chapter. The mechanism by which these active chemical acts involved the accumulation of anti-bacterial molecules by the inhibition of the efflux pumps. Bacteria eventually develop sensitivities and die. Even at smaller dosages, this activity may be effective. Thymoquinone stimulates oxidative stress and the generation of reactive oxygen species (ROS), which leads to cell death. P-cymene, a more powerful *N. sativa* compound, enhances the permeability of bacterial membranes, which facilitates the entry of antimicrobial agents. Potential antibacterial agents include *N. sativa* oil, carvacrol, p-cymene, and thymoquinone. When processed and utilized appropriately, phytochemicals, nutritionally essential components, polyunsaturated fatty acids, and highly active volatile compounds like p-cymene, Thymoquinone, α-thujene, carvacrol, β-pinene, limonene, methyl linoleate, sabinene, d-limonene, 4,5-epoxy-1-isopropyl-4-methyl-1-cyclohexene, and 4-terpineol found in *N. sativa* may have medicinal value. It is recommended that *N. sativa* be widely used in both conventional and modern medication systems due to its broad range of therapeutic potential as an antimicrobial.

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Chapter 42

Modulating the Inflammatory Signals with Phytomedicines: An Approach to Manage Inflammatory Diseases

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ABSTRACT

Inflammation is the first multifaceted innate immune response against infectious agents, leading to clearance of invaded microbes and repair of the damaged tissue. Binding of the pathogen receptors, such as PAMPs, with the immune cells causes the release of proinflammatory mediators that cause the migration of leukocytes at the infection site. However, excessive release of these cytokines and ROS leads to irreversible tissue damage and other life-threatening diseases, including metabolic disorders, cancer, and cardiovascular diseases. The classical therapeutic approach for treating inflammatory diseases includes COX inhibitors and glucocorticoids. However, these conventionally available drugs cause severe toxicity and complications. Thus, there is a need to explore effective and affordable alternatives that actively module the inflammatory signals. Phytomedicines are promising therapeutic options to treat inflammatory diseases, and several new medicines have been discovered from plant-derived secondary metabolites. Studies have shown that plants such as *Sorghum bicolor* and *Alepidea amatymbica* prevent the eicosanoid release and lower the symptoms of inflammatory disorders. Similarly, researchers have also successfully targeted the NF-κB, JAK-STAT, and PI3K/AKT/mTOR pathways using plant-derived polyphenols, alkaloids, and peptides to treat life-threatening inflammatory disorders. Most phytomedicines have low solubility and poor bioavailability, which can lower their effectiveness. Thus, other technologies should be considered to enhance the bioavailability of phytomedicines.

KEYWORDS		
Inflammation, Cytokines, Drug Resistance, Phytomedicines, Efficacy	Received: 25-Jun-2024 Revised: 12-Jul-2024 Accepted: 15-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Inflammation is considered a highly dynamic process, activated as the first multifaceted innate response against microbial invasion or damage to the cell due to any external stimuli, leading to the repair of the damaged tissues and clearance of microbes or microbial products from the body. Inflammation is mediated by the activation of different immune cells that regulate the release of the chemokines responsible for cell chemotaxis, migration, and proliferation in a highly uniformed manner. Cytokines are the essential signalling proteins released by immune cells in response to inflammation and immune response. They can be further divided into two categories: pro-inflammatory (IL-1, IL-6, IL-15, IL-17, IL-23, and TNFα) and Anti-inflammatory cytokines (TGFβ, IL-4, IL-13, IL-10, and IFNγ). Exposure to pathogen-associated molecular patterns (PAMPs) or other pathogen-associated signals results in the release of proinflammatory mediators, leading to the activation of a complex cascade that ends with migration and penetration of leukocytes into the site of infection (Rauch et al., 2013). Uncontrollable or unregulated release of inflammatory markers such as cytokines and Reactive Oxygen Species (ROS) constitutes the primary cause of immune pathology, responsible for irreversible damage to multiple organs and other life-threatening diseases, including cancer, cardiovascular dysfunctions, and metabolic disorders (Bagad et al., 2013; Li et al., 2022). According to a report published by Global Health Metrics to understand the causes of mortality from 1980 to 2017, inflammation-associated disorders are responsible for 50% of all mortalities. Among these disorders, cancer, ischemic heart diseases, diabetes mellitus, chronic kidney diseases, and non-alcoholic fatty liver, are the most common inflammatory diseases (Roth et al., 2018). The classical therapeutic approach for treating inflammatory diseases includes COX inhibitors and glucocorticoids. However, these drugs, such as valdecoxib and rofecoxib, are associated with severe toxicity and complications, such as stroke, raised blood pressure, blurred vision, angioedema, and rashes (Arora et al., 2020; McEvoy et al 2021; Stone et al., 2022).

To overcome the complications and toxicity associated with glucocorticoids and COX inhibitors, effective and affordable, alternatives should be explored. Phytomedicines are promising therapeutic option to treat inflammatory diseases and several new medicines also possess unique bioactive molecules, including phenol, flavonoids, alkaloids, carotenoids, and organosulfur compounds. Due to their anti-inflammatory properties, these compounds can treat different inflammatory diseases (Akhtar 2022). The harmonious blend of age-old botanical wisdom and meticulous scientific evidence has unveiled an exquisite tapestry of therapeutic possibilities, showcasing the profound potential of plants to yield a myriad of healing remedies.

Inflammation Associated Pathways and Modulation with Phytomedicines

The inflammatory response is managed by a wide variety of mediators that create intricate regulatory networks. These coordinated pathways are controlled by releasing different cell-signaling mediators, including Eicosanoids, Cyclooxygenases, and Lipoxygenases. Other important inflammation-associated signals include NF-kB signal transduction, JAK-STAT, MAPK pathway, P13K/AKT/mTOR pathway, and TNF-B/Smad pathways. Many studies have shown that chemotherapy and radiation can trigger this tumor-associated inflammatory response (Vyas et al., 2014; Brown et al., 2021). Thus, researchers should focus on phytomedicines and other natural products to treat inflammatory diseases. The below section explains the general mechanism of inflammatory pathways and their modulation with phytomedicines.

Eicosanoids: Their Role and Modulation

Eicosanoids are a group of enzymatically generated metabolites of 20-carbon polyunsaturated fatty acids (PUFAs). The biosynthesis of eicosanoids is usually initiated by the release of Arachidonic acid and phospholipaseA2 membrane from phospholipids. Arachidonic acid is then converted into different metabolites, including pro-inflammatory eicosanoids, such as prostaglandins, thromboxane, and leukotrienes. Maintaining a balance between anti-inflammatory and pro-inflammatory eicosanoids is crucial in the hallmark of inflammatory diseases. Severs studies have shown that plant extract of ginger root, Rhodiola rosea, and *Eleutherococcus lenticonus* causes the release of anti-inflammatory eicosanoids and is used to treat several inflammatory diseases, including arthritis, cancer, asthma, and cardiovascular diseases (Zick et al., 2011; Panossian Efferth et al., 2019; Jasemi et al., 2023). These plants downregulate the expression of genes, such as DPEP2, LTC4S, ALOX5AO, ALOX12, and receptor 3 gene (PTGER3) which are involved in the biosynthesis of the pro-inflammatory cytokines, leading to the inhibition of leukotriene, lipoxins, and prostaglandins signaling pathways, indicating their potential against inflammatory diseases (Jasemi et al., 2023).

Inhibition of COX and LOX pathways by phytomedicine is mediated by the active compounds present in plants. The most important active compounds that inhibit the release of eicosanoids include phenol, polyketides triterpenes, flavonoids, and cinnamic acid. Another study published by Pongprayoon et al. (1991) showed the inhibition of prostaglandins by Ipomoea, pes-caprae due to the presence of 2-hydroxy-4,4,7-trimethyl-1(4H)-naphthalene, mullein, eugenol, and 4-vinyl-guaiacol, indicating the potential application of plants against inflammatory diseases (Pongprayoon et al., 1991).

Cyclooxygenase Inhibition with Phytomedicine

The Cyclooxygenase (COX) enzyme system is an important signaling pathway that involves the conversion of Arachidonic acid into prostaglandins, which causes the activation of different pro-inflammatory metabolites. Prostaglandins are an important group of eicosanoids that are involved in pain sensation and induction of inflammation. These are two iso-enzymes of COX, i.e., COX-1 and Cox-2. COX-1 enzyme pathways cause the release of PGE2 and PGI-2, whereas COX-2 causes the release of thromboxane. Thromboxane causes vasoconstriction and stimulus for platelets aggregation at the site of inflammation. Many NSAIDs perform their function by inhibiting the release of prostaglandins by blockade of COX-1 and COX-2 Pathways (Norregaard et al., 2015). Several studies have shown that several plants contain active compounds that inhibit the cyclooxygenases and can be used to treat pain and relief from inflammatory diseases (Jager and Staden 2005; Akinloye at al., 2019; Termer et al 2021). According to research published by Akinloye et al. (2019), the flavanone from *Sorghum bicolor* can inhibit the activity of COX-2 and can be used to protect liver from damage due to inflammation.

Lipoxygenase Inhibition

Lipoxygenases are an important group of enzymes that catalyze the catalysis of Arachidonic acid into hydroperoxides, which are then converted into leukotrienes, eicosanoids responsible for the activation of other cells at the inflammation site. Leukotrienes also cause contraction of airway bronchial muscles, mucus production, and increase vascular permeability. Several plant extracts have been studied to prevent the conversion of Arachidonic acid into hydroperoxides by LOXs (Loncaric et al., 2021). Apiaceae (*Umbelliferae*), *Alepidea amatymbica*, and *Petroselinum crispum* are important plants that prevent the activation of LOXs and are used to treat several inflammatory diseases, including arthritis, CVDs, and cancer (Amiri and Joharch, 2016; Muleya et al., 2017; Danciu et al., 2018).

Several studies showed that green nanosynthesis with plant extracts inhibit the LOX pathway and reduces inflammatory diseases (Bakir et al., 2022; Ongtanasup et al., 2024). The LOX pathway inhibition by the plant extract can also be used to treat asthma. Activation of leukotrienes by the LOX pathway results in an increase in mucus production associated with the symptoms of asthma, bronchoconstriction, and formation of edema (Amaral-Machado et al., 2020). A review published by

Isabella Schneider and Franz Bucar (2005) demonstrates the application of different plan species to inhibit leukotriene release and treat asthma.

The below figure shows different pathways involved in the synthesis of eicosanoids and the possible mechanisms of action of plant extract against these eicosanoids.

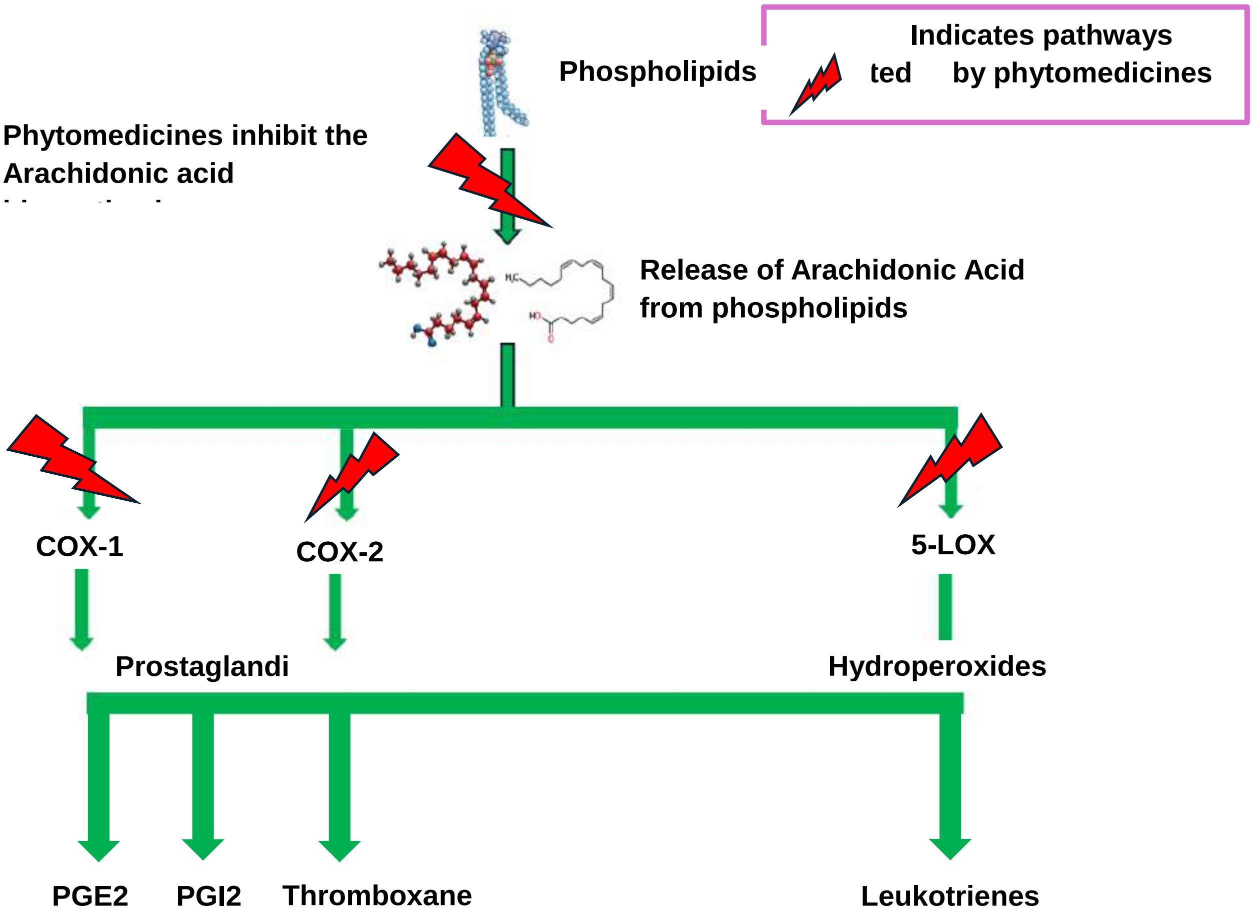

Fig. 2.1: Eicosanoids release in inflammation and possible pathways inhibited by phytomedicines

NF-κB Signal Transduction

The NF-κB is a crucial transcription factor that play a key role in inflammation and innate immunity. This transcription family comprises five major members, including NF-κB1, NF-κB2, RelA, RelB, and c-Re, and binds with the specific DNA element (as κB enhancer), increasing the transcription of target genes. Two important pathways mediate the activation of NF-κB: the canonical and alternate pathways. Canonical pathway of NF-κB signal transduction starts by the binding to the ligands of specific cytokine receptors, pattern recognition receptors (PRRs), TNF receptor (TNFR) superfamily members, as well as T-cell receptor (TCR) and B-cell receptor. On the other hand, non-canonical pathways respond to various stimuli, including TNFR.

Along with the mediating induction of various proinflammatory genes in innate immune cells, NF-κB also activates and differentiates inflammatory T cells (Liu et al., 2017). Several studies have also demonstrated the activation of inflammasomes by NF-κB. Activation of NF-κB signaling pathways is usually controlled by IKK, which contains two kinase subunits, IKKα (IKK1) and IKKβ (IKK2), and a regulatory subunit, IKKγ, also known as NEMO. IKKβ causes the activation of the canonical pathway by phosphorylation of IκBs. On the other hand, IKKα causes the phosphorylation of p-100, activating the non-canonical pathway (Lawrence, 2009). Lipopolysaccharide (LPS) induced inflammation is mediated by microbial invasion. Bacteria, especially gram-negative ones, release specific endotoxins, known as Lipopolysaccharides (LPS) which bind with Toll-like receptor 4 (TLR4) which in turn causes the release of cytokines from the immune cell. These cytokines activate the NF-κB, leading to the release of inducible nitric oxide synthase (iNOS), activation of the COX-2 pathway, and release of more cytokines. Thus, microbial invasion causes the activation of multiple inflammatory pathways and severe symptoms of disease (Gil et al., 2020). Figure 1.2 Illustrates the mechanism involved in the NF-κB pathway due to activation of receptors with different inflammatory ligands. Dysregulation of NF-κB has also been reported in different inflammatory diseases, especially autoinflammatory diseases, such as Alzheimer's disease (Snow and Albensi, 2016). NF-κB is a promising therapeutic target the neurodegenerative and chronic inflammatory disease. Several studies have provided convincing evidence that several phytomedicines with anti-inflammatory potential modulate the NF-κB to treat chronic inflammatory diseases, especially cancer and CVD. A study published by Paur et al. demonstrates the modulation of NF-κB with 34 different plant extracts (Paur et al.,2008). Another study showed the anti-inflammatory potential of *Populus deltoides* by inhibiting the phosphorylation of NF-κB and inhibitor of Kappa Bα (IκBα). This plant extract also has potential to modulate other inflammatory pathways as well (Jeong and Lee, 2018). Similarly, Kim et al., (2020) successfully demonstrated the application of *Smilax guianensis* against LPS-induced inflammatory response.

Below table highlights the most important plants that modulate the NF-κB along with the active compound responsible for this mechanism.

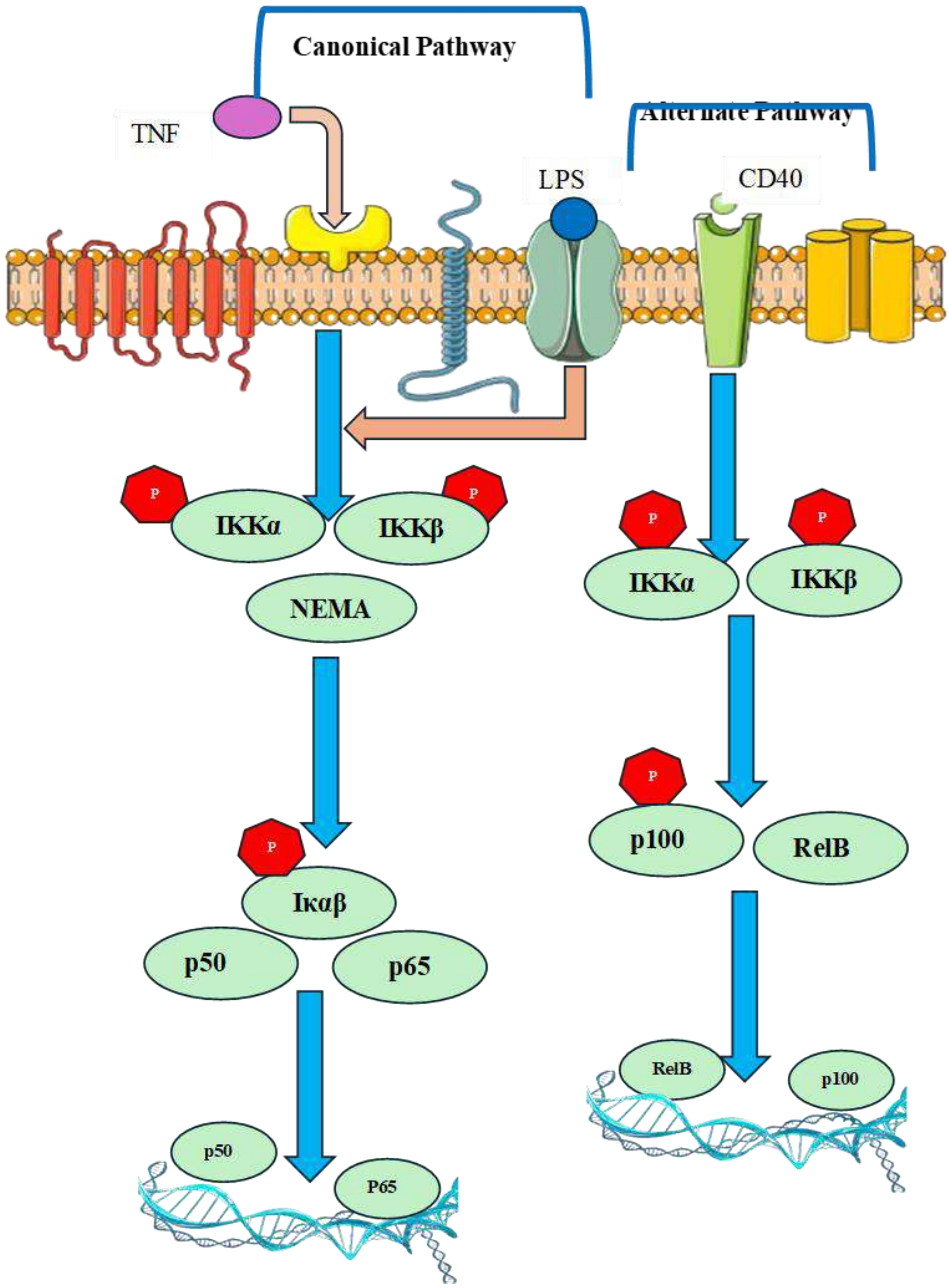

Fig. 2.2: NF-κB signal transduction pathway involve in inflammation

Table 1: Plants that modulate the NF-κB along with the active compound responsible for this mechanism.

Plant	Active Compound	Class of compound
Helminthostachys zeylanica	Neougonin A	Flavonoid
Patrinia scabra	Patriscabrin F	Iridoid
Forsythia koreana	Koreanaside A	Lignin
Tetrastigma hemsleyanum	S-(−)-trolline	Alkaloid
Psacalium decompositum	Cacalol acetate	Sesquiterpene

Targeting JAK-STAT with Phytomedicines

The Janus kinase/signal transduction and activator of transcription (JAK-STAT) is an important signaling pathway that plays a pivotal role in the pathogenesis of inflammatory diseases. Composed of five important members JAK1, JAK2, JAK3, and TYK2, the JAK family is expressed by different cross various cell types and plays a crucial role in cytokine signaling and other cellular processes. The binding of type I/II cytokines to their cognate receptors leads to oligomerization of the receptors, which in turn causes separation of the intracellular portion of receptors, resulting in the activation of receptor-associated JAKs and initiation of the JAK-STAT pathway. Phosphorylation of JAK takes place, serving as docking sites for STAT transcription factors. Phosphorylation of STAT causes conformational changes in inactive cytosolic STAT, resulting in the formation of active homodimers, heterodimers, or tetramers. These active sites then translocate in the nucleus, serving as a transcription factor for gene expression (Banerjee et al.,2017; Sarapultsev et al., 2023). Aberration in the JAK-STAT pathway can lead to oncogenic transformations and other life-threatening conditions. Several studies have proved the distinct roles in different inflammatory diseases (Coskun et al., 2013; Malemud, 2018).

Targeting the JAK-STAT pathway is one of the most important therapeutic options to treat inflammatory diseases. Studies have shown that the presence of unique compounds in plants can actively target the JAK-STAT pathway, providing an opportunity to treat life threatening inflammatory diseases. Fu et al., (2022), have successfully targeted the JAK/STAT signaling pathway to treat atherosclerotic inflammation by using Glycosides from *Buyang Huanwu Decoction*. Another study showed that the extract of *Paederia scandens* inhibits the phosphorylation of JAK 2 and STAT 3, regulating cell proliferation and reduce the mRNA LEVEL OF-IL-6, IL-b and IL-17 (Chen et al., 2022).

Neuroinflammation is one of the most common causes of neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease (PD), multiple sclerosis (MS) amyotrophic lateral sclerosis (ALS), and other neurological disorders Studies have shown that the phenolic and alkaloid compounds from natural herbal products, including curcumin can be used to target JAK/STAT and other pathways to treat neurodegenerative disorders (Kooshki et al., 2023). Phytomedicines have also been used to manage skin inflammatory diseases, such as Atopic Dermatitis. Biomolecules, such as *Leonurine, Astragalin,* and *Diosmetin* prevent the release of cytokines and target the JAK/STAT pathway. Furthermore, these biomolecules also actively target the SOCS family of proteins, modulating the JAK/STAT mediated pathway in the pathogenesis of atopic dermatitis (Kopalli et al., 2022).

P13K/AKT/mTOR Pathway Modulation

The P13K-AKT-mTOR signaling pathway plays a pivotal role in various physiological conditions and the pathogenesis of inflammatory diseases. Several researchers have shown that the P-13-AKT-mTOR pathway is a major hub in external stimuli, including TLRs, IL-6, insulin, and EGF. P13K, a family of five lipid kinase members, has been reported in the transformation activity of the vital oncogenes and activation of protein-tyrosine kinase. AKT is another essential member of the P13K-AKT-mTOR signaling pathway that plays a vital role in protein synthesis, metabolism, cell cycle progression, and survival. AKT is involved in the immune cell activation and the release of pro-inflammatory cytokines by inhibiting the transcription factor NF-kB. The mammalian target of Rapamycin, also known as mTOR is an important component of mammalian cells that plays a key role in cell survival, growth, and the synthesis of essential nucleotides, and lipids. mTOR also causes the activation of neutrophils and enhances the release of proinflammatory cytokines (Roy et al., 2023).

Modulating the P13-AKT-mTOR signaling pathway is one the most important strategies for treating inflammatory diseases. Rapamycin, an inhibitor of mTOR, is most commonly used to treat atopic dermatitis (Yang et al., 2014). Similarly, several plant-based medicines have also been used to target the P13K-mTOR pathway for the treatment of inflammatory diseases associated with skin, nervous system, and cancers. For example, bioactive compounds from *Actinidia arguta* have been successfully targeting the P13K-AKT-mTOR pathway to treat glioblastoma and skin diseases (Bae at al., 2016; Macedo et al., 2023). The P13K/AKT/mTOR signaling pathway also plays an essential role in the pathogenesis of neurodegenerative disorders such as, Alzheimer's disease, Parkinson's disease and other inflammatory diseases associated with the nervous system. Natural plant-based products such as curcumin and Pueraria lobata can be used to treat different neurodegenerative disorders by directly targeting the P13K/AKT/mTOR signaling pathways. Similarly, active compounds, such as alkaloids, phytosteroid secondary metabolites, and ursolic acid, from phytomedicines can be used to inhibit the release of pro-inflammatory cytokines and modulating the pathway (Fakhri et al., 2021).

Atherosclerosis is one of the common chronic inflammatory diseases that affects large and medium-sized arteries, leading to ischemia, stroke, and other life-threatening diseases. Studies have shown the direct role of the mTOR signaling pathway in the pathogenesis of arthrosclerosis. Many natural compounds extracted from plants have shown their action against occurrence and development of atherosclerosis. For example, different polyphenols, alkaloids, and glycosides can be used to regulate blood lipids concentration, reduce inflammatory factors, and alleviate cellular senescence to lower the chances of arthrosclerosis occurrence (Wu et al., 2023).

Anti-inflammatory Compounds of Plant Origin

Plants have played a key role in treating inflammation for centuries. Application of the novel active compounds from plants and other natural sources for pharmaceutical purposes has been gradually increasing in recent years. Studies have shown the potential of unique active compounds against the release of cytokines and inhibition or modulation of the pro-inflammatory signaling pathways. Plant-derived medicines also interact with gut microbiota, leading to the release of the release of low-molecular-mass products of secondary metabolisms. These metabolites are small in size with more bioavailability. Due to the production of secondary metabolites, phytomedicines are potential source of therapeutic agents to treat different life-threatening inflammatory diseases. The most common biomolecules present in phytomedicines include polyphenols, alkaloids, peptides, and several other novel compounds.

Polyphenols

Phenolic compounds are present in most of the phytomedicines and have anti-inflammatory, antioxidant, antibacterial, and anti-proliferation activities. Studies have shown that the application of phenol-rich plants can be used to treat chronic hepatitis, neurodegenerative diseases, arthritis, etc. Phenolic compounds interact with pro-inflammatory cytokines and module the inflammatory pathways. For instance, flavonoids, a class of phenolic compounds, inhibit the release of TNF-α and IL-6 from macrophages. Phenolic compounds, such as Hesperidin, luteolin, chrysin, naringin, and kaempferol, interact with the MAPK pathway to treat inflammation. Quercetin, a flavonoid, inhibits the PI3K/Akt signaling pathway and is used to treat malignancies. Curcumin is another important class of phenolic compounds that modulate the NF-κB. Fisetin, naringenin, and butene inhibit the MAPK signaling pathway, leading to dysregulation in LPS-induced inflammatory protein expression and cytokine production. The below table explains the major classes of phenolic compounds along with their mechanism of action against inflammation and the sources of their origin (Calixto et al., 2004; W. Liu et al., 2023).

Table 2: Phenolic compounds with anti-inflammatory properties, their targeted pathways, and plant sources.

Phenol Compound	Pathway Targeted	Plant source
Curcumin	Modulation of NF-κB	Turmeric (Curcuma longa)
Hesperidin	Alteration of MAPK signaling pathway	Citrus fruits
Kaempferol	COX inhibition and prevent release of iNOS	Broccoli, apples, and strawberries
Quercetin	Modulation of the PI3K/Akt signaling pathway	Onions, grapes, berries, cherries
Fisetin	Inhibit the MAPK signaling pathway	Euroasiansmoketree, Acacia berlandieri, and Acacia greggii
Naringenin	Inhibit the MAPK signaling pathway	Citrus fruits, bergamot, and tomatoes

Alkaloids

Alkaloids are unique nitrogen-containing organic compounds that can be commonly extracted from plants and fungi. Studies showed that there are almost 12,000 different classes of alkaloids. These alkaloids can be divided into organic amines, quinolines, isoquinolines, indoles, pyrrolidines, and piperidines. These secondary metabolites of medicinal plants possess unique anti-inflammatory properties, such as antioxidant, anti-inflammatory, and antimicrobial effects. Alkaloids modulate the release of cytokines and inhibit the activation of pro-inflammatory pathways to reduce inflammation. Caulerpin, indole alkaloids, can be extracted from Caulerpa racemose and possess anti-inflammatory properties by reducing the production of TNF-α, IFN-γ, IL-6, and IL-17. Furthermore, it also alters the NF-kB p65 and increases the production of IL-10. Other indole alkaloids include Cassiaindoline from *Cassia alata*, Strictosidine from *Uncaria rhynchophylla*, and Alstoyunines E from *Alstonia yunnanensis*. There are several other alkaloids with anti-inflammatory activities (Bai et al., 2021).

Carbazole alkaloids are another important class of alkaloids with anti-inflammatory potential.

O-Demethylmurrayanine from *Clausena lansium* attenuates the production of superoxide anions. Other Carbazole alkaloids alter the production of cytokines, suppress COX-2 enzyme, and modulate pro-inflammatory pathways (Bai et al., 2021).

7-Methoxy-1-propenoic is a novel β**-** β -carboline alkaloid isolated from the hairy root culture of *Eurycoma longifolia* and its anti-inflammatory mechanism was investigated. Studies have shown that this unique β**-**carboline reduces the NO, PGE2, and IL-6. Other sources of β-carboline include *Ailanthus altissima, Peganum harmala,* and *Houttuynia cordata*. Quinolone alkaloids are important anti-inflammatory alkaloids that inhibit NF-κB levels, alter COX-2 and 5-LOX activities, and reduce level of TNF-a, IL-6, PGE2, and NO (Souto et al., 2011; Bai et al., 2021).

Peptides

Plant-derived bioactive anti-inflammatory peptides are the most unique class of biomolecules that have been used to treat different inflammatory and neurodegenerative disorders, such as Rheumatoid arthritis, Alzheimer’s disease, hepatitis, cardiovascular disease, and cancer. Millet bran peptides can be used to alter the JNK and p38 pathways. Similarly, rapeseed crude hydrolysate from rapeseeds has anti-oxidant potential and is used to treat inflammation by reducing the oxidant enzymes. Studies have shown that wheat peptides blocked the MAPK pathway downregulating the protein phosphorylation levels of ERK and p3. Several plant-derived peptides, such as rice bran, alter the s inhibited NF-κB signalling pathway by decreasing IκB protein phosphorylation. Several peptides also modulate the MAPK pathway by inhibiting the release of IL-1, IL-6, and TNF cytokines (Wanlu Liu et al., 2022).

Challenges and Opportunities Associated with Phytomedicines

Although phytomedicines are obtained from a "natural" source it is believed that these are safer than conventional drugs, the low solubility and poor bioavailability of the phytomedicines can lower the effectiveness of phytomedicines. Furthermore, a higher dose of some herbal medication can also cause nephropathies and urothelial malignancy as in the case of *Aristolochia* spp. Studies have also shown that herbal medication can alter the pharmacokinetic profile of prescribed conventional pharmaceuticals and lead to complications such as allergies (Khan and Rauf, 2014). Another important issue in the application of phytomedicine is low purity control regulations, leading to adulteration and pollution of the available phytomedicines. Herbal medications rarely meet the requirement of standardization, which is partly due to a lack of scientific information about the operating pharmacological principles of the extracted phytocompounds, as well as the fact that the plants are not grown under controlled conditions.

To overcome the issues associated with the solubility and bioavailability of phytomedicines, drug-delivery technologies have attracted enormous attention in the recent era. Encapsulation of plant-derived biomolecules into nanoparticles provides an opportunity to enhance the drug bioavailability and sustained release of drug at active sites. A novel drug-delivery system can actively target the inflammation site and increase the therapeutic index of the drug. Furthermore, herbal medication is also an alternative to chemotherapeutic agents, providing an opportunity to overcome the drug resistance (Sajid et al., 2019).

Conclusion

Phytomedicines have been one of the most pivotal components of complementary medicines from centuries. Plants contain several unique biomolecules, such as polyphenols, peptides, and alkaloids, which modulate the inflammatory signal pathways and inhibit the release of cytokines from immune cells. Numerous studies, including in-vivo and in-vitro have been performed to uncover the potential of phytomedicines against inflammatory diseases. efficacy of herbal medicines. Thus, there is a need to focus on "green nano synthesis" to improve the bioavailability and sustained release of the drug. Furthermore, considering the side effects, contraindications, and pregnancy properties of plants is another major challenge that requires great caution before the application of phytomedicines. However, there is limited reliable evidence available on these matters. More evidence-based studies and meta-analyses could provide clearer guidance and approaches for healthcare professionals.

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Chapter 43

Nigella Sativa: A Natural Remedy for Sepsis Amelioration

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ABSTRACT

Current medicine always faces sepsis as one of the most threatening issues that requires unparalleled and unique treatment to enhance the chances of adequate patients' recovery. Originally known as Blacks seeds other name is *Nigella sativa* being used over a long time as medicinal plant due to the positive results in the treatment of many diseases including sepsis. In this chapter, the *Nigella sativa* has been described with regards to its biochemical and pharmacological Profile, its significance and the constituents participating in the alleviation of sepsis. Additionally, it also reviews the rising research publications in preclinical and clinical research outlining the anti-inflammatory, antioxidant and organ protective effects of *Nigella sativa* in sepsis. The other things discussed in the chapter include antibacterial properties, immunomodulating effects and what may be the additive action of *Nigella sativa* with conventional treatment. More studies should be done to determine black seed's benefits on sepsis where more intense research is required to prove its use as an adjuvant therapy.

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INTRODUCTION

Popularly referred to as ''black cumin'' or ''black seed'.' *Nigella sativa* belongs to the Ranunculaceae family, is an annual herb that is found in Asia, North Africa, Europe and the Middle East among other regions (Dalli et al., 2022). It has been applied for centuries to cure different human and animal diseases in the numerous civilizations of the globe. Thus far, a multitude of studies have shown that *Nigella sativa* seeds and thymoquinone, the primary active ingredient, are highly effective medicinally against a wide range of illnesses, including but not limited to a variety of chronic conditions, inflammatory illnesses, cancer, diabetes, neurological and mental disorders, cardiovascular disorders, and infections caused by bacteria, fungi, parasites, and viruses (Yimer et al., 2019). It has proven efficacy in ameliorating sepsis. It is the saying of Holy Prophet Mohammed (peace be upon him), "*Nigella sativa* seeds treats all diseases and ailments excluding death" (Al-Bhukhaari, 5688). The scientist Ibn Sina, who wrote "The Canon of Medicine" and is better known in the West as Avicenna, gave advice on the use of *Nigella sativa*. It increases the body's energy and aids in the body's recovery from exhaustion and depression. More times than any other plant, NS is referenced in the Bible. It is used for both birth control and cancer cure. Pliny refers to it as Gith while Hippocrates and Dioscorides refer to it as Melanthion. According to Pedanius Dioscorides, NS seeds can be consumed and used medicinally to heal leprosy, eye disorders, toothaches, and for diuresis and repel snakes. The NS plant was used both internally to cure stomach issues and externally to alleviate bruising and swelling in Babylonia. It also functioned as a medicinal ingredient that protected against the venomous species' poisons and stings (Hossain et al., 2021). This chapter is focused to explore how *Nigella sativa* helps alleviating sepsis. So firstly, we are going to have a look at what sepsis is, and what is its pathophysiology.

Sepsis can be defined as a life-threatening condition which results when our immune system shows a dysregulated response against various infections. This dysregulation in response may lead to tissue and organ injuries and death. Though a considerable set of advances are evident in how to manage this condition but it is still a major healthcare problem globally (Esposito et al., 2017). We can also define sepsis as a severe systemic condition as a result of an increased inflammatory response to infections caused by microbes which usually results in high death rate (Alkharfy et al. 2018).

Sepsis is usually dealt in Intensive Care Units (ICUs), and the database of National Hospital Discharge Survey analyzed by Martin et al. shows that there was an annual increase in the incidence of sepsis of 8.7% between 1979 to 2000 in USA, which means every 83 to 240 people per 100,000 population gets sepsis. A recent review that attempted to quantify the global incidence of sepsis concluded that the total incidence rate is 288 for sepsis and 148 for severe sepsis per 100,000 person/years, even though epidemiological data are still lacking, particularly for low- and middle-income countries. In summary, throughout the past few decades, there has been a noticeable increase in the occurrence of sepsis syndromes (Esposito et al., 2017). Sepsis is thought to be the cause of about 5 million fatalities worldwide each year, accounting for over half of all hospital deaths in the United States (Alkharfy et al., 2018). Sepsis still claims the lives of up to 25% of people worldwide, despite the fact that general mortality rates seem to be declining (Jarczak et al., 2021). Keeping in view the statistics mentioned above, sepsis is a foremost challenge to deal with. Given how quickly sepsis can cause septic shock or a serious infection, prompt medical attention is necessary. Many of the components of plants have received less recognition and appreciation despite having been shown to have significant advantages. *Nigella sativa* seeds and their contents are not a fresh discovery, given the nature and significance of the seeds; rather, they have long been used in traditional nutritional and therapeutic purposes. Results show that these seeds have a wide range of uses, especially in the food and pharmaceutical sectors. Researchers have been attempting to offer a thorough comprehension of the historical and contemporary experimental many applications of *Nigella sativa* seeds (Msibi, 2023). The purpose of this chapter is to look over how *Nigella sativa* seeds have been used evolutionarily to treat sepsis.

Pathophysiology of Sepsis

Before going through the role of *Nigella sativa* in amelioration of sepsis, let us discuss its pathophysiology first. Despite all the experimental and clinical research conducted over the past three decades, there is still little that can be done to positively affect the course and outcome of sepsis. Prompt fluid resuscitation and early administration of broad-spectrum antibiotics are the only proven strategies to reduce death rates. A crucial factor is the time of the correct diagnosis and the initiation of the supportive, adjunctive, and causal therapy (Jarczak et al., 2021).

Depending on the strength of the host reaction, the pathophysiological mechanisms underlying sepsis may begin as protective and adaptive but eventually turn maladaptive and destructive (Arina & Singer 2021). However, a significant body of research on the molecular mechanisms of sepsis has demonstrated that the host and the infectious agent interact in a much more complex and nuanced way, which ultimately results in the numerous symptoms of sepsis (Gyawali et al., 2019).

Innate Immunity and Inflammatory Mediators

Sepsis is not a simple infectious process involving the immune defense systems as an inflammation-on/anti-inflammation off switch but is a complex dysregulation of the human immune response to infection. Both pro-inflammatory and anti-inflammatory messages are produced systematically in terms of cytokines and other mediators and pathogen-related collections that activate the complement and coagulant sequences. The first alarm is an identification of the pathogen-associated molecular patterns (PAMPs including endo- and exotoxins, lipids, or DNA fragments) or endogenous host-derived danger signals (damage-associated molecular patterns, DAMPs). It becomes apparent that these substances bind to certain receptors on the surface of such immune cells as APC's and monocytes, triggering the clinical picture of sepsis via the genes' transcription, which are implicated in inflammation, cell metabolism, and immune adaptation (Jarczak et al., 2021).

Even while pro- and anti-inflammatory pathways are both upregulated, the ensuing inflammation eventually results in gradual tissue damage that compromises multiple organs. In many patients, concurrent immunosuppression might result in "immunoparalysis" later in the illness course because of increased immune cell death, T cell fatigue, and downregulation of activating cell surface chemicals. This makes people more vulnerable to opportunistic infections, viral reactivation, and nosocomial infections. The process of signal transduction occurs when PAMPs and DAMPs bind to TLRs on APCs and monocytes. This results in the translocation of NF-κB, also referred to as nuclear factor-kappa light chain enhancer of activated B cells, into the cell nucleus. Among the "early activation genes" that are expressed as a result are tumor necrosis factor alpha (TNF-α), interferons (IFNs), and pro-inflammatory interleukins (IL) such IL-1, IL-12, IL-18, and others. These subsequently cause the downregulation of elements of the adaptive immune system because of negative feedback, as well as the activation of complement, coagulation, and other cytokines (including IFN-γ, IL-6, and IL-8). The presence of these pathways is indicated by the upregulation of pro- and anti-inflammatory cytokines in the early stages of septic disease. The immunological phenotype (hypo- vs. hyper-responsiveness) is still highly individualized overall, which greatly complicates diagnosis (Jarczak et al., 2021).

Furthermore, some PRRs like the NOD-like receptor group can assemble into big protein structures called inflammasomes and they are involved in synthesis of caspases involved in apoptosis and cytokines like IL-1β and IL-18. The effects of proinflammatory cytokines include chemokine synthesis and endothelial adhesion protein expression, leukocyte activation, complement activation, tissue factor production, and stimulation of hepatic acute phase proteins. Sepsis increases the hitherto described immunological effect which comes with a 'collateral damage', accompanied by host cell/tissue demise (Gyawali et al., 2019).

Dysregulation of Hemostasis

Hemostasis and inflammatory pathways interact intricately in sepsis, with both cascades being active at the same time. Mild thrombocytopenia to severe disseminated intravascular coagulation (DIC) are examples of this interaction. Sepsis-related dysregulation of coagulation is caused by several causes. Hypercoagulability is brought on by the release of tissue factor, which is mostly produced by damaged endothelium cells. Tissue factor blocking reduces the amount of thrombin produced in response to inflammation, according to experimental models. Tissue hypoxia and organ dysfunction result from tissue factor's stimulation of the coagulation cascade, which in turn triggers the synthesis of thrombin, platelet activation, and microthrombi (Gyawali et al., 2019).

Moreover, sepsis inhibits the coagulation cascade's normal regulation by proteins C and antithrombin, which have anticoagulant properties. Low levels of protein S, downregulated thrombomodulin, and lowered plasma levels of protein C are all indicators of severe inflammation, including sepsis, and they all contribute to the uncontrollably proliferating coagulation cascade. Fibrinolysis is also inhibited by sepsis. Tissue plasminogen activators are released more often in response to elevated levels of TNFα and IL-1β. Persistently high levels of plasminogen activator inhibitor type 1 (PAI-1) mitigate this by reducing fibrinolysis and extending the duration of microvascular thrombosis (Gyawali et al., 2019).

Immunosuppression

At the commencement of sepsis, a proinflammatory state eases the way for a longer period of immunosuppression. This shift is characterized by a decrease in T cells due to apoptosis and a decreased sensitivity to inflammatory cytokines. When sepsis-related ICU patients are examined after they die, a significant loss of CD4+ and CD8+ T cells is seen, particularly in lymphoid organs like the spleen. Moreover, neutrophils in severe patients react to IL-8 by showing reduced chemokine receptor expression and chemotaxis (Gyawali et al., 2019).

These findings imply that sepsis patients' immunological responses to ensuing bacterial, viral, or fungal infections are impaired. Low lymphocyte counts, a sign of early lymphopenia around the fourth day following the diagnosis of sepsis, have been found to be a predictive biomarker for both short-term (28 days) and long-term (one year) mortality. This highlights how crucial it is to identify immunosuppression in order to improve patient outcomes when treating sepsis (Gyawali et al., 2019).

Function Impairment at Cellular, Tissue and Organ Level

Sepsis primarily results in tissue and organ failure due to hypoperfusion brought on by impaired circulatory function. Septic cardiomyopathy, which is brought on by mitochondrial malfunction and cytokine-mediated ventricular depression, affects between 18% and 60% of patients. Due to venous and arterial dilatation, this disease results in distributive shock, altered hemodynamics, and systolic and diastolic dysfunction. It is distinguished by reversible left ventricular dysfunction and an abrupt onset (Gyawali et al., 2019).

Endothelial dysfunction, which is defined by reduced barrier function, vasodilation, and a procoagulant state, has a significant impact on the pathophysiology of sepsis. Interstitial edema, acute renal damage, hepatic cholestasis, gastrointestinal mucosal permeability, and central nervous system dysfunction are the outcomes of this. In addition, muscle breakdown for amino acids to sustain immunological function and insulin resistance, which results in hyperglycemia, are signs of a catabolic condition brought on by sepsis. All of these complex changes add up to the morbidity and mortality that come with sepsis (Gyawali et al., 2019).

Bioactive Compounds in *Nigella sativa*

Every illness has a cure in the domain of plants. There were either very few or no synthetic medications available 250 years ago. Most of the world's population used to get their medications from these plants. The impoverished three-fourths of the world's population, or 75% of the total, still use these herbs and other traditional medical instruments. Novel medicinal molecules have been inspired by plants, as the health and well-being of people have benefited from plant-derived medicines. The World Health Organization (WHO) has proposed that the greatest source for a wide range of medications would be medicinal plants. The health of individuals and communities is deemed to be impacted by the usage of therapeutic plant-based medications, as they have few or no adverse effects. Based on estimates from the World Health Organization, traditional medicine provides primary medical treatment to 80% of people in developing countries. About 85% of these cases involve the use of plant extracts. This indicates that between 3.5 and 4 billion people worldwide get their medication from plants (Yessuf, 2015).

It is proven from studies that Black Cumin (*Nigella sativa*) has over 100 components, and the synergistic interaction between them promotes the immune system and are supportive to the body, better than any other single substance. It is a critical source of proteins, carbs, and other vitamins and minerals in addition to crucial fatty acids. The seeds are rich in sterols, particularly beta sitosterol, which is well-known for its anti-carcinogenic properties (Tabassum et al., 2018). *N. sativa* seeds have saponins, essential oils, alkaloids, fixed oils and proteins. As far as the unsaturated fatty acids portion is concerned, it has myristic acid, linoleic acid, arachidonic acid, palmitic acid, palmitoleic acid, eicosadienoic acid and stearic acid. It also has relatively a good amounts of Copper (Cu), Iron (Fe), Potassium (K), Phosphorus (P), Calcium (Ca), and Zinc (Zn) (Qayyum et al., 2020). Most of the black cumin is composed of non-volatile components such as flavonoids, phenolic acids, tannins, and a volatile fraction of terpene compounds. Many biological activities, particularly those connected to antioxidants, anti-inflammatory, antihepatotoxic, analgesics, anti-tumor necrosis, immunostimulants, anti-ulcer, antimicrobial, and antiparasitic properties, are attributed to a number of bioactive compounds and extracts from the seeds, particularly the essential oil and its primary constituent thymoquinone (Dalli et al., 2022).

Volatile Compounds of *N. sativa*

Research analyzing the essential oil of *Nigella sativa* has identified several different molecules with different characteristics. They consist of ketone, sesquiterpenes, monoterpenoid alcohols, diterpenes, and monoterpenes. We list carvacrol, α-pinene, β-pinene, thymol, thymoquinone, thymohydroquinone, and thymol among them (Dalli et al., 2022). Many of these compounds possess pharmacological effects and have therapeutic potential in humans. A primary component of *N. sativa*, thymoquinone, has been shown by researchers to possess anti-inflammatory, antibacterial, and anticancer as well as asthma relieving properties (Kabir et al., 2020). Thymoquinone is the main active ingredient in the *N. sativa* seeds (Cheikh-Rouhou et al. 2007). It is the main ingredient of *Nigella sativa*'s volatile oil (Kabir et al., 2020). Among other tautomeric forms, this chemical is present in mixtures, the enol form, and the keto form. Thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC) assays reveal that the pharmacological activities of thymoquinone are attributed to its keto form, which constitutes approximately 90% of the compound. Its effects on the heart, lungs, immune system, cytotoxicity, and inflammation have all been researched. In a research experiment, sepsis was induced in mice via lipopolysaccharide (LPS) and live E. Coli challenge. Then, they were given thymoquinone at the dose of 0.75-2mg/kg intra-peritoneally, which resulted in the reduced mortality up to 80-90%. By measuring the level of creatinine and ALT, it was also evident that thymoquinone resulted in protection of kidney and liver function, respectively. Serum creatinine, BUN, ALT, LDH, albumin, and CK elevations are indicative of induced sepsis, which damages and impairs the liver and kidney, among other organs. Thymoquinone therapy was shown to improve these indicators, supporting previous research that used animal models. Oxidative cellular damage can result from the prolonged generation of reactive oxygen species, such as superoxide anion and nitric oxide, during sepsis. At least in part, thymoquinone's protective benefits in sepsis can be ascribed to its antioxidant properties during the redox cycle between quinine (the keto form) and hydroquinone (the enol form) in biology. (Alkharfy et al., 2011). Thymohydroquinone isolated from the volatile oil of *Nigella sativa* was proved to have a high activity against gram positive organisms (Randhawa & Al-Ghamidi, 2002) .

Phenolic Acids and Flavonoids in *N. sativa*

Among the extracted phenolic compounds, gallic acid, ferulic acid, vanillic acid, p-coumaric acid, chlorogenic acid, catechin, quercetin, apigenin, flavone, nigelflavonoside B and rutin are worth mentioning. All these compounds inherit antioxidant properties which protect an organism against free radicals (Dalli et al., 2022). According to a phytochemical investigation, N. sativa has polyphenols in various sections of the plant. Vanillic acid was the main component in the mixture of phenolic acids, and phenolic acids were identified in the highest concentration (Cheikh-Rouhou et al., 2007; Topcagic et al. 2017). Topcagic et al. (2017) was the first to report the antibacterial effect of phenolic portion of *N. sativa* oil. There have been reports of a wide range of action against various bacteria by both the oil and the extract. Even at 1:1000 dilutions, the essential oil's in vitro antibacterial activities shown strong effectiveness against several species, including Vibrio cholera, Salmonella typhi, E. coli, and Staphylococcus albus. It was discovered that the oil exhibited outstanding antifungal action, especially against Aspergillus species (Tembhurne et al., 2014). Flavonoids mostly show antidiabetic activity (Parveen et al., 2020).

Alkaloids

Different *Nigella sativa* alkaloids were extracted and identified between 1985 and 1995. Examples are nigellimine, an isoquinoline molecule, nigellimine N-oxide, and nigellidine, an indazole molecule. nigellicine is made up of an indazole nucleus. Recently, a chemical known as magnoflorine has been discovered (Dalli et al., 2022). *N. sativa* and honey have synergistic antibacterial properties when treating P. aeruginosa infections. For bacterial infections, mouthwash containing chlorhexidine gluconate is used as a germicidal agent. Research has demonstrated that *N. sativa* oil extract is more effective than chlorhexidine gluconate in treating S. mutans infections and other common dental diseases (Ahmad et al. 2021). In one trial reported by Barakat et al. (2013), patients with hepatitis C virus were given 450 mg capsules of *N. sativa* oil three times a day for three months. Overall, there was a notable decrease in viral load, a notable improvement in oxidative stress, and notable increases in albumin, total protein, platelet, and red blood cell levels. The reduction in membrane lipid peroxidation and the likelihood of hemolysis are aided by the increase in RBC count (Ahmad et al. 2021). Nigellidine suppresses the development of viruses by binding to nucleocapsid and N-terminus protease (Hossain et al., 2021).

Saponins

The secondary metabolites of black cumin include saponins. Numerous saponins were found in NS in a study, however nigelloside, kaempferol 3-O-rutinoside, and flaccidoside are the most prevalent ones (Dalli et al., 2022). Thanks to medicinal plants and the compounds they produce, significant drugs like quinine, morphine, digoxin, and vincristine that treat life-threatening conditions like diabetes, cancer, coronary heart disease, HIV/AIDS, and neurological disorders have been developed for modern medicine (Parveen et al., 2020).

Fatty Acids

Through the GC MS analysis of the Qualitative Analysis of active constituents of *Nigella sativa*, it was realized that it contains several fatty acids. Thus, the analysis of the fatty acid composition of *NS* seeds showed that linoleic acid amounted to 55. 6% of the total fatty acids; oleic acid was 23. 4%; and palmitic acid comprised 12. 5%. Concentration of stearic acid, lauric acid (myristic acid), linolenic acids and eicosadienoic acids are labelled in trace quantities as they are between 0. 5% to 3. 4% (Dalli et al., 2022). Any disruption of this finely tuned concept of homeostasis whether through sepsis following an infection/trauma, or through more extreme inflammatory responses, often results in very dangerous consequences including organ failure, shock or death (Körner et al., 2018). The supplement value of *N. sativa* is attributed to the presence of several phytochemicals, nutritionally essential components, and polyunsaturated fatty acids (PUFA) which makes it possible to reverse sepsis (Hossain et al., 2021).

Biological Activities of *N. sativa*

The Immunomodulatory Effect

The properties like the splenocyte proliferation, macrophage function and NK anti-tumor activity make it clear that nigella seeds comprise of strong immunomodulatory compounds. Moreover, nigella oil has hepatoprotective activity against humoral immune responses, non-cellular immune responses and hypervitaminosis A. Immunomodulatory effect of *Nigella sativa* is mainly through head-on stimulation of phagocytic activity of macrophages, or via lymphocyte activation (Khan and Afzal, 2016).

Nigella sativa is a well know immune stimulant having a protective role against various pathological conditions. Nigella compounds like Thymoquinone and other terpenoid compounds like carvacrol, trans-anethole and 4-terpeneol have antioxidant properties. Carvacol inhibits neutrophil elastase enzyme and thus may prove a useful agent for phytotherapy of injuries like chronic obstructive pulmonary disease and emphysema (Khan and Afzal, 2016). In a study conducted to investigate the effects of *N. sativa* on immune system, it was proved that use of its seeds or oil improved helper T cell (T4) to suppressor ratio and also enhanced the activity of Natural Killer cell (Randhawa & Al-Ghamidi, 2002).

Anti-Microbial and Anti-Parasitic Actions

Since the latter part of the 20th century, antimicrobials have formed the cornerstone of clinical medicine and have prevented several cases of deadly microbial infections. However, it has been observed that antibiotic resistance in pathogenic bacteria has emerged and expanded globally in the late 20th and early 21st centuries. An international effort is required to find creative answers to the growing threat of microbial diseases and antibiotic-resistant bacteria. One potential source of these remedies could be natural goods like plants, which are chosen for their well-established ethnomedicinal uses. Black cumin (*N. sativa*) is one of the most inspiring medicinal plants; it exhibited potent antiviral, antibacterial, antifungal, and antiparasitic properties (Yimer et al., 2019).

In the study conducted by Hanafi and Hatem the anti-microbial effect of *N. sativa* Di-ethyl Ether Extract was looked into. It was also found out that the extract of the plant affected growth of both gram positive bacteria Staphylococcus aureus and gram-negative bacteria Pseudomonas aerogenosa and Escherichia coli through concentration. When used together with Gentamycin and Streptomycin, probability of synergism was found out; while in using it together with Spectinomycin, Erythromycin, Tobramycin, Doxycycline, Chloramphenicol, Nalidixic acid, Ampicillin, Lincomycin, and Co-Trimoxazole the chance of an additive was found out. In the same study, it was also identified that it had an inhibitory effect against Candida albicans, which is a pathogenic yeast and this effect was dose dependent. In prospective research, it has been shown that the extract of *N. sativa* has a favorable impact on multi-antibiotic resistance on organisms including both gram-positive and gram-negative bacteria (Randhawa & Al-Ghamidi, 2002).

In another study, mice with murine cytomegalovirus received intraperitoneal injection with *N. sativa* oil and the level of virus titer in the organs liver and spleen were found significantly lowered. This activity may have transpired due to higher recruitment of M and Phi numbers and functions, and also due to augmentation of IFN-γ production (Randhawa & Al-Ghamidi, 2002). The aqueous extract of *N. sativa* which was prepared by boiling of it seeds when used at the concentration of 100ug/L showed anti-microbial activity against both the gram-positive bacterial isolates such as Bacillus subtilis, S. aureus, Micrococcus luteus and the gram-negative bacterial isolates like Salmonella Setubal, Enterobacter aerogenes and Agrobacteria tumefaciens. A study that contrasted thymoquinone to the escorted counselling of microorganisms proved that the compound is oriented towards the inhibition of the escalation of distinguishable categories of bacteria. Experimenting with the formation of biofilm using different concentration of the same substance helped to know that the formation of the biofilm decreases. Besides, the compound studies shown here provided evidences that the chemical indeed compounded with the antibiotics and enhanced the effect in case of both gram-positive and gram-negative bacterial species. Thus, the n-butanol extract from the NS seeds LH demonstrated a very high antibacterial effectiveness against P. aeruginosa, K. pneumoniae, and A. baumannii, with the least inhibitory zones at 0. 25 to 1 μL/mL (Dalli et al., 2022).

The activities of thymoquinone isolated from seeds of *N. sativa* were found to be broader with most gram-negative and positive bacterial strains including Salmonella Serovar, Bacillus, Listeria, Enterococcus, Micrococcus, Staphylococcus, Pseudomonas and Vibrio parahaemolyticus. It not only inhibited bacterial biofilms, but also inhibited their growth a part from having potent anti-bacterial effect (Yimer et al., 2019).

El-Sayed et al., in their research work published in 2019 mentioned that out of all the parasites i.e., *Theileria equi*, *Babesia caballi*, *Babesia bigemina*, *Babesia divergens* and *Babesia bovis* are some of the parasites that are effectively inhibited by Thymoquinone in vitro. Interaction between Thymoquinone and the diminazen aceturate on the parasites Babesia and Theileria was very satisfactory. *Babesia microti* growth suppression was induced in mice by intraperitoneal injection of Thymoquinone at a dose of 50 and 70 mg/kg and by oral treatment (Dalli et al., 2022)

Antiviral Activity

Using female rats immunized against Candida albicans-thought to be the main cause of vulvovaginal candidiasis—the therapeutic potential of black cumin was validated in vivo. The results showed that after giving *NS* extract at a dose of 6.6 mL/kg, the number of fungal colonies dramatically dropped (Dalli et al., 2022).

Antioxidant Activity

Oxidative stress and elevated amounts of free radicals are two of the most significant critical markers associated with numerous progressive pathological conditions, including cancer, aging, neurological disorders, and endocrine disorders. The utilization of therapeutic plants as natural antioxidants is growing in importance now. Among the many naturally occurring medicinal plants, *N. sativa* has been demonstrated to have strong antioxidant qualities in both in vitro as well as in vivo studies. Antioxidant measures improved dramatically in a study where Wistar rats received *N. sativa* and nanosized clinoptilolite separately (Yimer et al., 2019).

Anti-Inflammatory Properties

Thymoquinone, an important component of *N. sativa* oil, and its extracted form demonstrate their mode of action through a variety of mechanisms, including cytoprotective, immunomodulatory, antioxidant, and inflammatory mediator inhibitory actions. Thymoquinone activates lymphocytes, macrophages, mast cells, neutrophils, and eosinophils in cases of auto-immune and infectious disorders due to antigen exposure or host cell damage. The most crucial components of an immune response are an increase in T cell and Natural Killer Cell-mediated immunity, regulation of the CD4(+) and CD8(+) ratios, and improvement of the oxidant scavenger system (Alkharfy et al., 2011).

Conclusions and Future Perspectives

Given the overwhelming scientific information we got, it is evident that the claim by Prophet Muhammad (PBUH) over 1400 years ago that "*Nigella sativa* (Black seed) can cure all illnesses except death" is true and acceptable. Numerous studies conducted to date have demonstrated the remarkable natural therapy properties of black seed and its component thymoquinone for the treatment of a wide range of illnesses, including both infectious (bacterial, fungal, viral, and parasitic infections) as well as chronic noninfectious diseases (neurological disorders, diabetes, hypertension, dyslipidemia, inflammatory disorders, cancer, and so forth). This review chapter was meant for exploring the use of *Nigella sativa* for amelioration of sepsis. As mentioned above, it is evident that *Nigella sativa* seeds and oil have plenty of useful compounds including sterols, essential oils, phenolic acids, flavonoids, alkaloids, saponins and fatty acids. Keeping in view the chemical composition of *N. sativa* and its biological activity, we have seen that these compounds have immunomodulatory, antimicrobial, antiparasitic and antiviral effects. Immunomodulatory activity enhances the immune system's ability to tackle sepsis, while antimicrobial activity adds another layer of power for this purpose i.e. to fight sepsis. It is also clear that when used in combination with antibiotics, *N. sativa* either has synergistic or additive effect which is also a plus point for amelioration of sepsis. Keeping in view the above discussion, it is evident that *N. sativa* has a promising potential in ameliorating the sepsis given its ability to inhibit various gram positive and gram-negative bacteria as well as making positive changes for enhanced immune activity.

A limited literature is available on the use of *N. sativa* for amelioration of sepsis and more research needs to be conducted to have a clear understanding of its role in controlling the sepsis so that it may be used as a complementary medicine to tackle this condition. Moreover, it may also prove a great support in decreasing the dose of antibiotics and help control the antibiotic resistance development.

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Chapter 44

Effective Role of Herbal Medicines in Sepsis Treatment

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ABSTRACT

Throughout the world, herbal medicines are considered as a significant part of healthcare. Plant based medicines have been used extensively for many years. Plants have been used for the treatment of various health conditions including allergy, arthritis, skin infections, respiratory problems, gastrointestinal problems and others. Different herbal medicines possess anti-oxidative, anti-inflammatory, antibacterial, antiviral as well as antifungal characteristics. In sepsis, there is uncontrollable and excessive innate immune system response as a result of the invading infectious microorganisms. Despite the presence of modern antibiotics and technologies, the treatment of sepsis is a challenge as it is life threatening. Different Chinese Herbal Medicines can be helpful in sepsis treatment. However, in several countries, herbal products are not regulated as widely as compared to conventional drug treatment. In recent times, there is a need of conducting more research that evaluates the utilization of herbal drugs. Apart from the benefits of using herbal medicines, there are some concerns such as possibility of contamination of product, or adulterations, toxicity associated with the herb, and possibility of unknown and known drug and herb interactions. Herbal experts or clinicians should be aware of the potential interactions and potential toxicity.

KEYWORDS
Herbal medicine, Sepsis, Treatment, Herbs, Inflammatory

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INTRODUCTION

Herbal medicines are of natural origin and derived from plants that can be used for the treatment of different illnesses. These products are considered as complex mixtures of organic chemicals. These products may be obtained from any processed or raw part of a plant. Herbal medicine, also termed as herbalism is a medical system which depends on the utilization of plant extracts or plants that can be either applied to the skin or eaten (Sam, 2019). Herbal medicines are thought to be the most commonly used and oldest medical system throughout the world. In present years, plant derived products are used either alone or in combination with other drugs by several people for healing purpose and to promote health care. In the developing and developed countries, many people depend on the utilization of herbal medicines for their health maintenance. The World Health Organization (WHO) reported that herbal medicines meet the medical needs of 80% of people living in advanced countries (Mirzaeian et al., 2021).

Sepsis can be defined as a systemic infectious inflammatory response syndrome which can result in tissue hypo-perfusion, dysfunctioning of the organ and even irreversible persistent hypotension (termed as septic shock) and mortality rate to the extent of 80%. Sepsis is usually seen in ICU (intensive care unit). It is a frequent complication of severe infection, trauma, surgery and severe burn. The body is occupied by pathogens and endotoxins resulting in the release of large amount of inflammatory mediators, increasing the expression of inflammatory factors of serum [interleukin-6 (IL-6), interleukin-2 (IL-2), tumor necrosis factors- α (TNF- α) and C-reactive protein (CRP)]. The immune system as well as the anti-inflammatory system will be disturbed with deregulation of the intestinal flora. Coagulation disorders will occur and there will be damage to the organ function. The typical causes of sepsis include decrease in the autoimmunity, surgery, use of cytotoxic drugs, chronic disease and invasive examination. For the treatment of the disease, infection control and mechanical ventilation adjuvant therapy are considered. However, the conventional therapy doesn't have the ability to instantly control the serum inflammatory response and regulate the immune system of the body. Therefore, Traditional Chinese Medicine (TCM) has been helpful for the treatment of sepsis. The components of Traditional Chinese Herbal Medicine possess the characteristics to clear away toxic substances and heat as well as to destroy bacteria, regulate immunity, and promote the restoration of the neuro-endocrine network system (Wen et al., 2021).

Significance of Herbs

It has been estimated that almost 25% of the drugs which have been prescribed throughout the world are driven from plant sources. Out of the 252 drugs, according to the list of essential medicines provided by the World Health Organization (WHO), 11% of the drugs are from plant source. As a matter of fact, the first pharmacological compound, morphine, was processed almost about 200 years ago from opium which was extracted from the poppy flower's seed pods. From that times, different scientists have been investigating plants to form different pharmaceutical drugs that are known to us at present. Nowadays, plants are being utilized to treat many health conditions including arthritis, allergies, skin infection, migraines, fatigue, burns, wound, gastrointestinal problems, and even though for the treatment of cancer. This has truly proven that food is medicine. These herbal medicines seem to be safer for treatment purposes and less costly than the conventional treatment drugs. This is the reason that many people are now choosing the idea of using traditional medicines (Sam, 2019).

Herbal Medicine in the Treatment of Different Diseases

Herbal medicines which are derived from plant extracts have been increasingly used to treat different clinical diseases (Ghosh et al., 2011). Since the origination of human civilization, herbs have been a fundamental part of the society. Their medicinal as well as culinary properties are responsible for their utilization. In the manufacturing of commercial drug products known today, herbal medicine has contributed largely. This includes salicin (source of aspirin) from *Salix alba*, reserpine from *Rauwolfia serpentina*, digitoxin from *Digitalis purpurea* and ephedrine from *Ephedra sinica*. Plants based medicines have been used for different cardiovascular conditions such as in systolic hypertension, congestive heart failure, atherosclerosis, arrhythmia, venous insufficiency, and angina pectoris (Rastogi et al., 2016).

Plants based medicines have been commonly used since centuries for the treatment of liver diseases due to the lower toxicity factor. Through clinical evaluations, the hepato-protective ability of different herbs has been assessed (Ghosh et al., 2011). Herbal products seem to be a favorable alternative medicine for the treatment of Alzheimer's patients. Experiments have been carried out to test herbal medicines in animal models as well as in cell models of Alzheimer disease. Also herbal drugs have been tested to a less extent in clinical trials (Anekonda and Reddy, 2005). Phenolic compounds from natural sources have an important role to prevent and treat cancer. Phenolic compounds (from dietary plants and medicinal herbs) involve flavonoids, phenolic acids, tannins, curcuminoids, lignans, coumarins, quinones and some others (Huang et al., 2009). In many Asian countries including China, Traditional Chinese Herbal Medicines (TCHMs) and western pharmacotherapy are often used in combination to treat chronic kidney diseases (CKD) (Zhong et al., 2013). Various herbs have been traditionally recommended to treat diabetes. In addition to this, many researchers have outlined the anti-diabetic effects of a number of plants (Ghorbani, 2013). A while ago, publications have reported the antiviral properties of *Chaihu*, *Prunella vulgaris* and *Herba patriniae* against Coxsackie B virus, Herpes simplex virus, and Respiratory syncytial virus, respectively (Wang et al., 2009).

SEPSIS

Sepsis can be defined as an organ dysfunction which is life threatening and caused by dysregulated host response to infection. A latest report of Global Burden of Diseases highlighted that sepsis is prevalent with almost 50 million cases of sepsis globally on annual basis. This can affect people of all ages (van der Poll et al., 2021). The pathophysiology of sepsis is complex. The occurrence of sepsis is gradually rising. The mortality rate ranges between 30% and 50% throughout the world (Cheng and Yu, 2021). Sepsis may be caused by bacteria, viruses or fungi. Among hospitalized patients in the intensive care unit (ICU), it is of the most frequent cause of death. Due to its high mortality and morbidity rate, sepsis stands as a considerable health problem. To enhance the probability of survival, identification and early treatment are very important (Rello et al., 2017).

Pathophysiology

In sepsis, there is uncontrollable and excessive innate immune system response as a result of the invading infectious microorganisms. It is characterized by excessive production of pro-inflammatory mediators, for examples, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), interleukin-1β, and high mobility group box 1 (HMGB1). In case of severe sepsis, the massive formation of pro-inflammatory cytokines together with reactive oxygen species may affect the function of organ and contribute to the initiation of abnormal apoptosis in various organs, following multiple organ dysfunction syndrome and death. Therefore, drugs which have the potential to weaken the inflammatory response may be helpful as therapeutic agents for sepsis (Alikiaii et al., 2021).

Causes of Sepsis

The causes for sepsis can be divided in to infectious and non-infectious. Systemic inflammatory response syndrome (SIRS) occurs as a result of non-infectious agents. Sepsis features can be seen without any identifiable infection. Surgical injuries, trauma, drug reactions, tissue ischemia, pancreatitis, autoimmune diseases and neoplastic diseases can be the examples and can be progressed to shock and different organ failure. Infectious sepsis can be caused by gram positive bacteria, gram negative bacteria, parasites and fungi. These infectious agents include vancomycin resistant enterococcus (VRE), methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin sensitive enterococcus (VSE), *Streptococcus pneumoniae*, *Staphylococcus epidermis*, Klebsiella spp., *Escherichia coli*, Acinetobacter spp., Pseudomonas spp., Candida spp., and Aspergillus spp. (Alikiaii et al., 2021).

Role of Herbs in the Treatment of Sepsis

Despite the presence of numerous modern antibiotics together with the intensive care technologies, the treatment for septic shock persists to be challenging. Dependence on antibiotics along with other methods which target the modulation of the systemic inflammatory response including cytokine antagonists, steroids and hemofiltration have not resulted in reliable successful therapy for inflammation and infection related septic shock. Resistance of bacteria to different drugs is one factor leading to the lack of success to the therapy (Wang et al., 2009).

The diagnosis and treatment of sepsis have been a focal point for infectious disease studies, emergency medicine and critical medicine. This is because of the massive incidence and mortality rate of sepsis. From the time of 1992, experts have suggested diagnoses and several plans for the treatment. Considering the treatment of sepsis, Chinese Herbal Medicines appear to have therapeutic properties. Basic scientific experimentation on these herbal medicines is expanding. Chinese Herbal Medicines (CHMs) have the potential to restrain aggregation of platelet, regulate inflammation as well as immune response, and also refine microcirculation, thus preventing sepsis progression and improving sepsis prognosis in patients. Such medicines are single Chinese herbs, Chinese herbal prescriptions and Chinese patent medicines (Cheng and Yu, 2021).

For thousands of years, herbal medicines have been used as therapeutics for shock and infections globally. The active compounds of these natural products generally possess one or more of the below mentioned properties:

1) Directly attack or suppress the bacterial pathogen
2) Modulate the immune system of host which results in inflammation suppression and repression of excessive production of inflammatory mediators
3) Neutralization of toxic free-radicals (Wang et al., 2009).

Immunomodulators are well known for modulation of the immune response and improve diseased conditions thus playing an important role in inflammatory conditions. These can either exist naturally from plant sources or can be synthetically produced from parent compound. Natural modulators acquired from raw vegetables and fruits involve plant sterols and sterolins. Various plants parts and their extracts have been acknowledged as effective natural immuno-modulators. For example, juice of Aloe vera leaf, oil of *Nigella sativa*, ginseng root, root of Ashwagandha, *Syzygium jambolanum* extract, extract of mushroom, Rhubarb extract, chamomile tea, *Isodon serra* extract, juice and extract of leaves of *Carica papaya*. The outcome of an earlier study suggested that *Jatropha cureas* methanolic extract has immuno-modulatory results by enhancing the level of lymphocytes and macrophages in blood along with an increase in antibody titers. Manifestations from former studies recommended that a number of herbal medicines yield certain antioxidants which can help in the control of oxidative stress during inflammation. In patients with severe sepsis, modifications in hematologic system are generally observed with an evidence of surge in mortality. Anyhow, survival rate may be improved by timely diagnosis and therapy of disturbed hematologic system. A study indicated that platelet /neutrophil complexes become greater in initial phase of sepsis and decreased in severe sepsis as there is thrombocytopenia associated with sepsis. A research evaluated that the leaves of *Carica papaya* escalates the production of platelet count. Constituents of plants like Genistein, Epigallocatechin-3-gallate (EGCG), and Baicalein remarkably reduce high blood pressure, therefore, serve a potential role of hypotensive drug in septic rats (Usmani et al., 2021).

Salvia miltiorrhiza, *Astragalus membranaceus*, and *Angelica sinensis* which are Traditional Chinese medicines (TCM) have immune-modulatory or anti-inflammatory effects thus helping in the regulation and improvement of immune system. Different types of Traditional Chinese Medicines have been researched deeply. For examples, several researches reported vasorelaxant property, antioxidant potential, and antiplatelet aggregation activity of the rhubarb along with detailed mechanisms. Apart from this, certain other effects have been discovered, for example, prevention of over secretion of tumor necrosis factor- α (TNF- α), promotion of gastrointestinal electric activity and also intestinal peristalsis, endotoxin reduction, reduction of bacterial translocation and improved microcirculation. Several compounds of *Salvia miltiorrhiza* (a commonly used Chinese medicine) were extracted. It has been reported that these compounds possess particular activity against platelet aggregation, leukocyte adhesion, endothelial cell injury and release of oxygen radicals. Two proteins isolated from *Salvia miltiorrhiza* have antifungal activity. This Chinese medicine also plays efficient role in reducing over production of prostaglandins (PGs), neutrophil degranulation, and nitric oxide synthase induction (Liang et al., 2015).

In Malaysia, different plants have been utilized for therapeutic reasons based on various practices and culture. Here are some Malaysian herbal plants with their active components and potential therapeutic applications in sepsis.

Andrographis paniculata

A. paniculata is also known as King of Biters. It is a bushy therapeutic plant. It is widely distributed in Southern Asia and Southeast Asia. This plant is known as "*pokok cerita*" or "*hempedu bumi*" in Malaysia. The scientifically proved effects of this pant involve anti-inflammatory, antibacterial, anti-diabetic and antioxidant actions.

Zingiber officinale

Z. officinale is also known by the name of ginger. Among Indian and Chinese communities, its rhizome has been historically used for medicinal purpose. The ginger has a variety of advantages which include its anti-inflammatory, antioxidant and anti-carcinogenic effects along with prohibition of cardiovascular diseases.

Curcuma longa

In general, C. longa is called as turmeric. For so many years, turmeric has been utilized for culinary purpose and also in the Ayruvdeic tradition. Its rhizome appears to have numerous medicinal activities including antibacterial, antifungal, antiviral, anti-inflammatory, anti-diabetic, as well as antioxidant effects. A main compound present in its rhizome is curcumin which has been widely studied due to its antisepsis ability.

Piper nigrum

Investigations have reported that *Piper nigrum* holds hepatoprotective, antioxidant, antimicrobial, and anticancer characteristics. (Liew et al., 2020).

Some other Traditional Chinese Medicines (TCMs) include:

Rhubarb

Rhubarb contains organic acids, glycosides, anthracene derivatives, volatile acids and certain other active components. So it is used in Traditional Chinese Medicine. It has the ability to improve kidney function, digestive system, inhibits lung disease, and prevents antioxidant stress. In addition to this, it shows antiviral, antibacterial, anti-inflammatory and antitumor actions.

Berberine

One of the major effective constituents of *C. chinensis* is berberine. It is an alkaloid which is acquired from *C. chinensis*. This component demonstrates an inhibitory action when there is acute and chronic inflammation. C. chinensis and berberine can increase the phagocytosis of white blood cells in vitro and in vivo and partially stops the inflammatory reaction mechanism. Furthermore, berberine is helpful to prevent and treat sepsis induced multiple organ dysfunction syndrome (MODS).

Safflower Yellow

Toxins and heat cause blood stasis which have a remarkable role in the manifestation and development of sepsis. Removal of blood stasis and activation of blood circulation are aided by safflower. Safflower yellow (recognized effective constituent of safflower) possesses antioxidant, anti-inflammatory and immune function boosting qualities.

Ginseng

Ginseng holds chemical ingredients like ginseng polysaccharides, amino acids, volatile oils and ginsenosides. These components have pharmacological potential, for example, anti-oxidative, anti-fatigue and immunity boosting effects. A number of studies have been performed to investigate the actions of ginsenoside to prevent and treat MODS in sepsis, along with sepsis associated encephalopathy, lung damage, liver damage as well as myocardial injury (Zhang et al., 2023).

***Angelica sinensis* (Oliv). Diels**

The low molecular weight fraction of aqueous extract of *Angelica sinensis* (a Chinese herb) is beneficial against lethal experimental sepsis and endotoxemia in a dose dependent manner.

***Salvia miltiorrhiza* Bunge**

Salvia miltiorrhiza, a natural remedy which has been experimentally proved to interact with HMGB1. It was used traditionally for the treatment of cardiovascular diseases. It was reported to be defensive against lethal LPS-induced endotoxemia and sepsis by reducing HMGB1 proportion in vivo in a murine model.

***Glycyrrhiza Glabra* L. (Licorice)**

Rhizomes and roots are the principle therapeutic parts of licorice. Various studies have revealed that licorice has antiviral property against hepatitis C virus. Moreover, anti-inflammatory, antimicrobial and anti-oncogenic characteristics have been reported. Glycyrrhetinic acid (GTA) and glycyrrhizic acid (GA) are the compounds which may be isolated from licorice plant.

***Perilla Frutescens* (L.) Britton**

Rosmarinic acid (RA) can be extracted from *Perilla frutescens*. It has the potential to inhibit the release of HMGB1 and down regulate HMGB1-dependent inflammatory responses in endothelial cells of humans (Wyganowska-Swiatkowska et al., 2020).

A flavonoid which is apigenin is found in ample amount in plenty of vegetables and fruits. This flavonoid has demonstrated excellent effectiveness for the control of inflammatory response. Salidroside is obtained majorly from the root and rhizome tissues of *Rhodiola rosea* (rose). Several investigations mentioned that it possesses antibacterial, anti-inflammatory and anti-oxidative effects. Another flavonoid, baicalein is gained from the roots of *Scutellaria baicalensis georgi* (a Chinese herb). The anti-oxidative and anti-inflammatory properties of baicalein have been shown through different experiments. A non-flavonoid polyphenol, resveratrol has anti-oxidative quality. This component is present in fruits skin like berries and grapes. Pretreatment with resveratrol guarded mice against CLP-induced ALI (Song et al., 2023).

An exemplary therapeutic drug would weaken excessive harmful responses, help out in the clearance of microbes, and guard tissues, consequently assisting in organ preservation and function of system with increasing survival. Based on the preclinical studies, it can be proposed that polyphenols (PPLs) which is a group of chemicals found in abundance in plant based beverages and food, achieves the above mentioned criteria and carries the ability to manage sepsis. The largest group of phytochemicals is polyphenols (PPLs). Greater than 8000 are thought to occur and present in different amounts in majority plant derived foods (such as fruits, vegetables, spices along with legumes). Some examples include olive oil, green tea, soybeans, turmeric and red wine which have high content of polyphenols which contribute to their health benefits (Shapiro et al., 2009).

Classification and subclassification			Polyphenols	Source
Phytochemicals	Polyphenols	Flavonoids	Genistein	Tofu, soya
			Quercetin	Apple
			Naringenin, hesperidin	Citrus fruits
			Anthocyanins, cyanidin	Berries
			Glabridin	Licorice (*Glycyrrhiza glabra*)
		Nonflavonoids	CAPE	Propolis
			Oleuropein	Olive oil
			Curcumin	Turmeric

Classification and Sources of Polyphenols with Curative Ability for Sepsis (Shapiro et al., 2009).

Research in Herbal Medicines

To determine the safety and effectiveness of Traditional Herbal Medicines, there are limited clinical trials. The lack of research does not hinder many of the people from using them, given that these remedies are usually grounded in long cultural traditions. Ethical analysis of global herbal medicine research was published recently. They give rise to a number of scientific queries that enlighten the problems of performing research with herbal medicines globally. To find suitable ways to perform this kind of research is an existent challenge (Rivera et al., 2013).

Potential Risks Related to Herbal Medicines

It is believed by the public and some professionals of health care regarding herbal medicine that they are natural so they are comparatively safe. In spite of the fact that very little data is present in the support of this presumption. Studies have also highlighted serious consequences as a result of the side effects of particular herbal drugs. From the utilization of herbal medicine, numerous harmful and deadly complications have been disclosed. Majority of this data has been collected from health care centers and emergency rooms. These bad consequences of herbal products may happen by means of different mechanisms such as direct harmful effect of the herb, effects due to contamination, as well as interaction with some other herbs or drugs. Complications may occur due to contamination of heavy metals (such as arsenic, mercury, or lead). Besides this, contamination may be due to the undeclared pharmaceutical products which are illegally and purposefully added to the herb to attain a desirable effect (Rodriguez-Fragoso et al., 2008).

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Chapter 45

The Future of Chiropractic: And Then What?

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ABSTRACT

This chapter looks into the antecedents of the chiropractic care that has up to today become an established form of medical practice. It explores such aspects of chiropractic therapy as spinal manipulation, on which the system is based; holistic view of health; non-invasive nature of the treatment and the importance of the nervous system. The chapter also looks into the existing trends and some of the problems experienced in the field including the question of regulations and the public perception, and the place of chiropractors in attending human and animal patients. Moreover, it discusses the prospects of the future of chiropractic care as well as the possible trends and strategies may define its evolution in worldwide contexts of the healthcare market. The Six Pillars is presented as a way to establish directions for dealing with change in the future; this change has to be modelled and forecast within the chiropractic profession.

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INTRODUCTION

Chiropractic care is a branch of medicine that specializes in the identification, management, and avoidance of conditions affecting the musculoskeletal system, especially the spine. Chiropractic therapy dates back to the late 19th century, and its main focus has always been on manual adjustments and manipulations to rectify spinal misalignments. The theory behind this treatment is that the nerve system's disruption can have an impact on general health (Jenks et al., 2022). As per WHO, The field of chiropractic care is dedicated to the diagnosis, treatment, and prevention of conditions affecting the musculoskeletal system, especially the spine. Chiropractic care, which dates back to the late 1800s, places a strong emphasis on the health of the spine and how it affects the nervous system as a whole. Manual spine manipulation, or adjustment, is the mainstay of chiropractic care. Its goal is to return the spine to its natural alignment and function, which should reduce pain and enhance general health (Anonymous, 2023).

The phrase "chiropractic" refers to the use of manual therapy or spinal manipulation to cure a variety of illnesses. It is derived from the Greek words "cheir," which means "hand," and "praxis," which means "practice" or "done by". The field of veterinary chiropractic is still very new and is developing quickly. Chiropractic treatment focuses on the spine to slow the course of the illness. It is a fascinating and quickly developing therapy option for musculoskeletal discomfort in animal chiropractic care. It is a functional neurology-based integrated medical diagnostic and therapy approach (Haq et al., 2017). Although the philosophy and practice of spinal manipulation date back to ancient cultures, chiropractic was established in 1895 by Daniel David Palmer. He founded the Davenport, Iowa-based Palmar Infirmary and Chiropractic Institute in 1897. The idea behind the founding of modern animal chiropractic was that it ought to have a role in the treatment of animals. With veterinary and chiropractic degrees from Michigan State University and Palmer College of Chiropractic in Davenport, Iowa, respectively, Sharon Willoughby made significant contributions to the development of this concept. She made the decision to focus all of her efforts on improving animal chiropractic care and education not long after earning her Doctor of Chiropractic degree in 1986 (Eschbach et al., 2008; Cifuentes et al., 2011).

Chiropractic care has also come to be recognized in veterinary medicine as an effective adjunctive therapy for animals, especially when it comes to musculoskeletal problems. It treats a wide range of animals, with a concentration on treating horses and dogs. It is frequently used to treat ailments in dogs that affect movement as well as lameness, stiffness, and performance-related concerns in horses (Maldonado et al.. 2022).

Chiropractic Fundamentals and Concepts

Chiropractic therapy targets certain joints or anatomical areas with manually applied, high velocity, low amplitude forces (also known as adjustments) in order to produce healing effects in the articulations, muscles, and neurological reflexes. To maximize spinal joint neuromuscular performance, the aim of chiropractic care is to guarantee all spinal segments move smoothly and in unison (Eschbach et al., 2008).

Chiropractic care takes into account the wider effects of spinal dysfunction on the neurological system in addition to treating mechanical abnormalities of the spine. Research demonstrating the physiological benefits of spinal manipulation on the neural system, including enhancements in musculoskeletal and autonomic functioning, has provided support for this comprehensive approach (Bishop et al., 2019; Miller, 2022).

Key Concepts

1. Spinal Manipulation

One of the main components of chiropractic care is spine manipulation, sometimes referred to as spinal adjustment. It incorporates manual methods intended to treat vertebral subluxations, which are spinal misalignments that can impair nerve function and be a contributing factor in a number of health problems. Chiropractic theory places a strong emphasis on this procedure because it restores proper nerve function and enhances general health by correcting these subluxations (Miller, 2022).

2. Holistic Approach

A holistic approach to health is embraced by chiropractic therapy, which emphasizes how the body can heal itself when the spine is in the correct alignment. In addition to spinal adjustments, chiropractors frequently incorporate lifestyle recommendations like exercise, diet, and stress reduction into their patients' treatment regimens (Gyer et al., 2019; Miller, 2022).

3. Non-Invasive Treatment

The non-invasive and drug-free nature of chiropractic care is one of its main tenets. Without the need for surgery or medicine, chiropractors treat musculoskeletal issues with manual approaches. This method is especially appreciated for its capacity to address underlying problems with the spine and neural system in order to treat pain and other disorders (Bishop et al., 2019; Gyer et al., 2019).

4. Nervous System Integrity

According to chiropractors, general health depends on the nerve system's integrity being preserved. Spinal misalignments can cause a variety of health issues by interfering with the nervous system's ability to function. Chiropractic therapy seeks to rectify these subluxations in order to restore normal nerve function and support the body's natural ability to maintain health (Gyer et al., 2019).

Current Trends and Challenges

An increasing amount of research emphasizing the benefits of chiropractic care for treating neuro-musculoskeletal problems has influenced recent trends in chiropractic care. Current research hotspots include the integration of chiropractic therapy in controlling problems including headaches, back pain, and other musculoskeletal difficulties, according to studies like the bibliometric analysis by Song et al. (2024). Alongside this, chiropractic care has gained more respect in the medical world; yet, obstacles still need to be overcome before chiropractic therapy can be widely acknowledged and integrated into traditional healthcare systems (Riggs III, 2024). The emphasis placed by the chiropractic profession on evidence-based practices is another noteworthy trend. The increasing number of publications and research projects aiming at comprehending the mechanics and effectiveness of chiropractic treatments is indicative of the drive towards rigorous scientific validation of chiropractic procedures (Bishop et al., 2019; Song et al., 2024).

Challenges

1-Regulatory Issues

Globally, there are many regulatory obstacles for chiropractic care. Every country has a varied set of regulations for this profession, with differing recognition, educational requirements, and practicing scopes. For instance, whilst chiropractors are limited to physical therapy in certain areas, they have a broad scope of practice in others, including diagnostic authority. The widespread acceptance of chiropractic care and its incorporation into the larger healthcare system are hampered by this contradiction. In addition, the profession continues to face challenges from continuous discussions about the need for stronger regulations, particularly with regard to the training and certification of chiropractors (Riggs III, 2024).

2-Public Perception

The general public's opinion of chiropractic care differs greatly. Some people believe it to be a valid and useful therapy option, particularly for musculoskeletal conditions, but others are dubious because they don't know enough about it or because of inaccurate representations in the media and online. The skepticism frequently results from doubts over the effectiveness and safety of specific chiropractic procedures, especially those that entail spinal manipulations. Improving communication and public education to address these issues is crucial to improving the acceptance and reputation of the profession (Song et al., 2024).

Cases That Can Benefit From Chiropractic

In 2017, the American College of Physicians published updated guidelines recommending spinal manipulation as a primary treatment for both acute and persistent low back pain. Both in people and animals, chiropractic therapy has a high success rate in treating cases of acute and chronic low back pain. Chiropractic care is currently not the primary line of treatment for back discomfort in animals, though. Exercise restriction and pain medication are recommended as treatments for back pain in animals in Ettinger's Textbook of Veterinary Internal Medicine (Dator, 2009; LeFebvre et al., 2012; Marziani, 2018).

In a series of nerve root compression studies on animals, it was discovered that a little 10 mm Hg of compression, or roughly the weight of a dime, may reduce a nerve's conduction by 50% after 30 minutes and by 40% in the first 15 minutes. According to another research, this function decline could range from 60% to 75%. It took 15 to 30 minutes to recover to almost normal function after the compression was removed (Marziani, 2018).

Chiropractic Treatment Protocols

Depending on the ailment, whether it is acute or chronic, and whether the goals are preventative or chronic condition management, a chiropractor's recommended frequency of adjustments will vary. Different practitioners have different recommendations for the frequency of treatments. I typically meet patients every one to two weeks for a total of two to three treatments. If the patient is responding well, the intervals between treatments might be progressively widened in order to gauge effectiveness (Marziani, 2018).

In chiropractic therapy, more than one hundred techniques are used. The most common method employs osseous modifications and is referred to as diversified. A manual, high-velocity, short-lever thrust adjustment is included. The same outcome is also achieved with the use of an activator, a tiny, portable device. In order to restore joint mobility, the adjustment is directed towards a hypomobile motor unit. The next step is to apply a low-amplitude thrust with enough force to release fixations near the end of passive range of motion, or joint play. Every now and again while making the adjustment, there is a popping sound or "audible", and humans are more likely than animals to exhibit these. An audible signal is not necessary for a successful adjustment; it just signals a decrease in intra-articular pressure. In terms of contact points (spinous, mammillary, or transverse processes), direction, force, depth, and timing, the adjustment is quite precise (LeFebvre et al., 2012; Haq et al., 2017).

Each situation is different. While some patients with spinal arthritis may benefit from adjustments every four weeks, others may benefit more from treatments every twelve weeks. The author advises against waiting more than four to six months between adjustments because the spine is always moving and under tension. In severe circumstances, a few adjustments can be all that's needed to fix the problem, negating the need for continued chiropractic care. But it's important to remember that spinal nerve root compression can exist even in the absence of clinical symptoms and without producing pain (LeFebvre et al., 2012; Marziani, 2018).

Case Studies

1. A 14-year-old spayed female Boston terrier dog with polydipsia, constipation, widespread weakness, and a vertebral subluxation complex is managed and cared for by chiropractic adjustments.

The patient had a six-day history of polydipsia, constipation, and widespread weakness. Static and motion palpation were used in the examination. The patient also has a medical history of obesity, xerosis, and impacted anal glands. The dog was unable to walk or stand when it was brought in, and several spinal subluxations were found.

The patient underwent two visits for chiropractic evaluation and treatment with the goal of removing vertebral subluxations and regaining optimal nervous system function. The patient's ability to walk on their own improved after just one chiropractic adjustment, and right away there was a noticeable bowel movement.

For dogs with functional constipation, chiropractic care may be helpful. However, more studies assessing animal treatment plans are required to maximize the advantages of care. Chiropractic treatment was provided on a veterinarian's recommendation, and spinal adjustments were made by hand.

2. A study was conducted to assess whether a dog's tremors have subsided after receiving chiropractic therapy.

A male Great Dane puppy, three weeks old, showed up at a private veterinary and animal chiropractic facility with evidence of vertebral subluxation and orthostatic intention tremors.

A vertebral adjusting instrument was used to treat vertebral subluxations. Muscle tone, discomfort presence, and static and motion palpation were used to analyze the subluxations. The dog was put to sleep right away following low-level laser therapy and chiropractic adjustments. The dog began to exhibit noticeable improvement three days later, and the tremors disappeared two weeks later.

Three days after starting treatment, the dog's owner reported "wonderful improvement," saying that on the second day after treatment, the dog stood up and walked twice with "very minimal shaking." (Dunwoody, 2018).

Chiropractic care was given to numerous wild animals with a range of ailments. Rabbits with constipation and decreased activity, ferrets dragging limbs, Alpacas with forelimb lameness, Green Sea Turtles with dislocated shoulders, Cheetahs with impacted anal glands (anesthesia was used during the procedure), Llamas with pelvic limb lameness, Babirusas with immune-mediated polyarthritis, Julian Pigs with aggressive behavior, Komodo dragons with forelimb lameness, reduced cervical range of motion, and cervical torticollis on radiographs are some examples. Amazon parrot from St. Vincent without the capacity to use its right pelvic limb White-tailed deer, goat breeds with osteoarthritis, a leopard that self-mutilates the distal end of its tail, and a great horned owl that is incapable of closing its fingers on one pelvic leg (Marziani, 2018).

Chiropractic Contraindications

For evident pathological disorders, fractures, infections, neoplasia, metabolic issues, and non-mechanical issues, chiropractic treatment is contraindicated. Conventional veterinary treatment should be used to treat horses with medical or surgical issues; nevertheless, chiropractic care can play a significant part in rehabilitation by aiding in the restoration of normal neuromuscular and musculoskeletal function (Eschbach et al., 2008).

Within veterinary chiropractic medicine, there are a few minor contraindications, such as spinal neoplasia and pelvic or vertebral fractures. While it's not a contraindication, animals with spinal cartilage prolapses or those who have had back surgery need to be treated with competence and caution (Haq et al., 2017).

Acute episodes of pain related to osteoarthritis, impinged dorsal spinous processes, soft tissue damage, and joint hypermobility (joint subluxation and dislocation) are not recommended for chiropractic care. Cervical manipulation is not recommended in cases of spinal cord compression brought on by static or dynamic cervical lesions resulting from cervical vertebral instability. On the other hand, in the damaged spinal segments, chiropractic adjustment of the neighboring compensatory hypomobile vertebrae (VSCs) may enhance joint motion and lessen compression of the spinal cord (Eschbach et al., 2008).

The Future of Chiropractic

A number of significant developments and trends that are expected to strengthen the position of chiropractors in international healthcare systems will likely influence the direction of chiropractic care in the future. Chiropractic care is anticipated to become more and more important in the management of a variety of musculoskeletal conditions as patient demand for non-invasive, holistic treatments rises. This is especially true when it comes to sports medicine, chronic pain management, and preventive healthcare.

Since its inception as a complete alternative medicine idea 120 years ago, chiropractic care has evolved to include complementary medicine and, in certain jurisdictions, primary care status. At the moment, several nations have license and registration requirements for chiropractors as well as educational programs with varying standards and focus, most of which are housed in private institutions and only a small percentage of which are financed by government universities (Walker, 2016). A clear regulations, good governance, suitable laws, and established educational standards would be necessary for the profession to advance (Du Plessis, 2017; Bishop et al., 2019).

The future of the chiropractic profession must be mapped out using a deep and thorough analytical framework. The Six Pillars analysis is a priceless tool for delving into the intricacies of the chiropractic field and identifying potential future developments. This strategy is based on six interrelated pillars, each of which offers special perspectives and methods for navigating the chiropractic profession's future. This article provides useful insights for strategic decision-making and proactive adaptation by addressing the prospects and issues of the chiropractic profession through the use of mapping, anticipating, timing, deepening, and developing alternative pillars (Dator, 2009; LeFebvre et al., 2012; Bishop et al., 2019).

PILLAR 1 provides a basis for imagining potential opportunities and obstacles in the future by mapping the chiropractic environment and analyzing factors impacting its trajectory. In order to create future scenarios for strategic planning and shifting healthcare dynamics.

PILLAR 2 looks ahead to many future scenarios by analyzing future trends, disruptions, and paradigm shifts in the industry. In order to make sure that strategy and actions are in line to maximize effect and success.

PILLAR 3 identifies crucial transition points and the rate of change. With a focus on ongoing education, research, and professional growth.

PILLAR 4 expands the profession's knowledge and capabilities while giving healthcare professionals the tools they need to meet new challenges, spur innovation, and provide high-quality treatment.

PILLAR 5 is all about embracing new modalities and technologies, finding creative ways to adapt to evolving patient requirements, and making sure that the field is relevant and sustainable in the long run.

PILLAR 6 offers a path forward for the profession's transformation by tackling persistent problems and creating principles for evidence-based practice. Improved patient care outcomes and increased services are achieved through embracing technological advancements, addressing regulatory constraints, and improving collaboration with other providers (Dator, 2009; Cifuentes, et al., 2011).

Although the field generally produces skilled manual therapists who are decent professional citizens and contributors to their communities, there are still aberrant elements with deeply held outdated ideologies. These disorganized and lone elements have done immense harm to the profession's credibility and will keep doing so. As a result, the profession's standing is frequently bad when compared to other health professions, and public acceptance of it varies widely (Walker, 2016).

Keeping all of this in mind, how can the profession develop to establish itself as legitimate and equal stakeholders in the health sector? A career that can command the respect of patients, policymakers, and other members of the health sector? a field where it is accepted as an appropriate collaborator in the provision of healthcare services? If the chiropractors, especially the young members of the profession plan to tackle the above questions, the profession's standing will be improved to the point that people will view chiropractors and chiropractic as respectable collaborators in the delivery of healthcare. It is conceivable that this objective aligns with the hopes of our younger professionals who want to have long and honorable careers (Cifuentes, et al., 2011; Walker, 2016).

In a quantitative analysis involving numerous chiropractic care clinics, the chiropractic profession presents itself as competent to treat a broad range of illnesses, significantly more than just the ones that are more closely related to chiropractic care (such as back pain). Evidence-based practice seemed to be valued and embraced by a large number of clinics. They did, however, also present the profession as "natural" and as upholding the principles on which it was established. These clinics appear to want to have it both ways: to maintain their status as an alternative that supports a natural approach while simultaneously presenting chiropractic as an evidence-based treatment that conforms to the norms of established science. Customers may become confused as a result of the communication surrounding chiropractic therapy being associated with two somewhat different epistemologies (Cifuentes et al., 2011; Shelley et al., 2015).

Given the increasing acceptance of chiropractic therapy as a primary care alternative and its expanding popularity, future research should investigate the veracity of the claims from an evidence-based perspective. Even if the information that is currently available does not support most of the claims made concerning the "face" of chiropractic, a more in-depth investigation appears warranted. Future studies that look at the viewpoints of doctors or other people who recommend chiropractors could be beneficial as well (LeFebvre et al., 2012; Shelley et al., 2015).

The following are some crucial factors that must be considered in order to legitimize the chiropractic profession:

- For chiropractors, pre-professional education needs to be improved. Universities should, if feasible, be the site of chiropractic education. It is imperative that chiropractic education incorporates meaningful hospital access or work experience, such as hospital rounds, to enable students to witness patients who are genuinely ill and to observe the signs and symptoms that are taught in theory sessions. Chiropractic students require a multidisciplinary faculty of teachers, with physicians, physiotherapists, and other allied health professionals participating in their instruction.
- Creating a progressive identity is vital. It is necessary for chiropractors to specialize in treating musculoskeletal conditions, with a focus on treating spinal pain.
- A broadened area of specialization should be developed by the profession. A special interest area in the health sciences that chiropractic as a profession may contribute to other relevant health sciences globally should also be developed. Developing and refining evidence-based treatment, enhancing bone density, providing musculoskeletal care for the elderly and ageing, and improving posture through motor control are a few potential directions. Another crucial topic to consider is implementing implementation of this science to convert research findings into practical applications.
- Exclusion of the profession's absurd components.
- Both the profession and its members should support public health.
- Professionals should encourage reputable organized components of the chiropractic profession.
- The goal of the profession ought to be to enhance clinical practice.
- Evidence-based practice should be embraced by the profession.
- Research needs to be supported by the profession.
- To bring about change, individual chiropractors must exercise personal leadership (Walker, 2016).

Conclusion

Chiropractic care is set for even more growth and development in the future due to a growing trend of patients seeking natural drug-free types of treatments. It is for this reason that the chiropractic profession can improve its image and acceptance as well as better incorporation into present day health care: adopt emerging technologies, improve on its regulative frameworks, and improve communication and cooperation with the numerous other health care practitioners. It is noteworthy that the studied “Six Pillars” model provides chiropractors with the prospects for a strategic management of future change and development thrusts. However, as the profession changes and advances therefore it will be important to continue to remove such ideologies and adapt the public image of chiropractic care to assist in becoming a more accepted and important branch in world healthcare. Chiropractic has the potential of transforming to meet these challenges through the current crop of young chiropractors who can take the profession to even higher levels of practice.

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Chapter 46

Quality Considerations for Standardization and Authentication of Botanical Ingredients in Aquafeeds

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ABSTRACT

Aquafeeds and the use of botanical ingredients Over recent years, interest has been raised in the use of herbs, spices and plant extracts as feed additives to aquaculture feeds because they may offer advantages for improving growth promotion effects or nutrient utilization efficiency (NUE) whilst simultaneously enhancing fish health. But verifying quality, safety and legitimacy continues to be a struggle. This chapter will discuss key issues relating to quality control, standardization and authentication of these ingredients. Adjust from these to matters relevant in: e.g. variability of constituents and bioactive substances, contaminant presence, risk uncovered for adulteration/substitution etc.; The first chapter focuses on standardization strategies (quality standards), monographs and reference materials. Examples of authenticity specifications were macroscopic/microscopic assessment, chromatographic methods, spectroscopy procedures and DNA authentication techniques. Given this was a fishing village market very good agricultural and collection practices (GACP), good manufacturing practices (GMP), supplier qualification, sampling, testing protocols should be done in order to provide the homogeneity of composition. Contents of the book include discussions on regulatory facets, harmonization efforts and international organizations in setting standard are described. The consolidation of ingredient sources, the transparency through the supply chain and also documentations — in fact record keeping up to authenticating at every stage is given a primacy. Presentation of case studies showing what works, problems in implementation and lessons learnt in the use of QA measures. Future outlooks examine new analytical measurements, blockchain-sourced tracking offerings and responsible sourcing practices which help to highlight the shifting industry landscape. The chapter attends these considerations, therefore collaborating with an adequate and sustainable use of high-quality botanicals for nutritional purposes in aquafeeds favoring growth and productivity as to overall prosperity within the industry.

KEYWORDS		
Quality Considerations, Botanical Ingredients, Aquafeeds; Aquaculture	Received: 08-Jun-2024 Revised: 09-Jul-2024 Accepted: 12-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Aquaculture is one of the fastest growing industries worldwide with a key factor determining performance, health and efficacy being on feed quality fed to farmed aquatic species. To facilitate this process, there are rigorous quality control measures of the feed to ensure it provides all necessary nutrients required for the target species and does not contain any contamination or adulteration which would have possible detrimental effects on animal health and food safety. Total global production of farmed seafood, which reached 82.1 million tonnes in 2018 and now represents almost half (46%) of all fish produced worldwide, highlights the increasing importance and need for safe high-quality aquafeeds ~Aquaculture doesnt use freshwater (Jiang et al. 2022).

The botanicals in the form of various herbs, spices and plant extracts have become a potential focus of interest for their benefits like growth promotion, better nutrient utilization support and providing resistance to diseases. Natural components which used as bioactive compounds, prebiotics and immunostimulants can replace those synthetic additives (Dawood et al. 2022).

While botanicals offer advantages to human health, they are challenging in standardization and authentication due to their complicated chemical composition. Plant species, geographic origin, cultivation practices and processing methods would have an influence on the quality and consistency of these ingredients. Furthermore, there is the question of risk: will premium grade be more likely to suffer adulteration or substitution with cheaper and dangerous substances that should only evaluated with reliable authentication methods.

Botanical Ingredients in Aquafeeds

Types of botanical ingredients (herbs, spices, plant extracts): Botanical ingredients used in aquafeeds can be categorized into three main groups:

Herbs: It contains herbaceous plants or their parts e.g. leaves stems, roots. This category is really a dump-meeting for most balm and well-known, plant-derived supplements like turmeric (Curcuma longa), peppermint, garlic cloves (Allium sativum) as well treacle basedtokoro-gyoubumeisteri "Ginger ") (Mariappan et al. 2023). A study by Abdelrazek et al. (2017) aimed to evaluate de effects of dietary turmeric supplementation on growth performance and immune response in Nile tilapia (*Oreochromis niloticus*).

Spices: These are the dried fruit, seed, bark or root of a plant used to enhance flavoring. These include black pepper (Piper nigrum), cinnamon (Cinnamomum verum) and clove (Syzygium aromaticurn) (Karmakar et al. 2022). Studied the effect of dietary supplementation with black pepper on growth, antioxidant status and immune response in African catfish (*Clarias gariepinus*).

Plant extracts: Plant extracts, which essentially concentrated preparations are obtained from different parts of plants through extraction methods such as solvent extractions or supercritical fluid Exrtraction. Green tea extract (Camellia sinensis), grape seed extract (Vitis vinifera) and garlic extracts are still other examples (Presenza 2022).

Intended Functions (growth promoters, immunostimulants, etc.)

Botanical ingredients are incorporated into aquafeeds for various intended functions, including:

Growth promoters: Many phyto-constituents were reported to be having growth promoting activity in different kind of species by increasing feed efficiency, feed intake and overall gain in body weight. The growth performance and feed conversion ratio were significantly augmented in rainbow trout, for instance through diet suppletion with garlic powder (Adineh et al. 2020).

Immunostimulants: A number of the botanicals employed include bioactive components that stimulate an individual immune response in fish which helps protect against diseases and provides restorative healing benefits. Immunostimulant activity in aquaculture species of selected plant extracts: Olive leaf extract and Rosemary Extract (Mariappan et al. 2023).

Antioxidants: Polyphenolic substances, among other antioxidant compounds found in botanical ingredients can help to reduce the oxidative stress whilst at the same time improving overall aquatic animal health and well-being. Green tea extract supplementation reinforced the antioxidant capacity and enhanced environmental stress resistance in freshwater prawn (Liu et al. 2022).

Common Sources and Supply Chain Considerations

The systematic production process and sources of botanical ingredients for aquafeeds may vary with regions and the type or part of plant ingredient which depends on feeding purpose. Most of the herbs and spices are grown in different regions like India, China, South America whereas plant extracts could be obtained from various agricultural or industrial processes. Supply Chain factors that determine Quality Control, Traceability and Sustainability. A whole host of other concerns also need to be addressed along with resource-related questions, regarding issues such as environmental impact etc ensuring fair trade practices and compliance in respect of regulatory standards concerning botanically derived ingredients that are used within the production processes relating to plantmeal for aquafeed (Eroldoğan et al. 2023).

Quality Issues and Adulteration

Variable chemical composition, bioactive compounds: Botanical ingredients are a class of raw materials that can vary significantly in their essence content and the concentration of bioactive secondary metabolites (abundantly depending on plant genotype but also environmental factors during cultivation as well harvesting/processing methods (Dossou et al. 2021). This variability may have effect on the performance and fluctuation of targeted effects in aquafeeds .A study by Nyadjeu et al. (2021) with descriptors of physical variability epileothe chemical composition of garlic (Allium sativum), obtained from samples cultivated in different cultivars and cultivation conditions. Authors reported the quantitative variation in bioactive compounds like allicin, organic sulfur compound and these are responsible for the biological activity of garlic.

Botanical raw materials sometimes carry contamination of heavy metals, pesticide residues and microbiological contaminants since these substances are hard to avoid when growing the botanicals which combine a risk for animal health. A study by Glencross et al. (2020) Heavy metal study in different medicinal plants from different areas used as traditional medicine source was evaluated.

In references to antibiotic and pesticide residues, a review paper by Naiel et al. ,(2019). This studylooked at the incidence and concentration of pesticide residues in different spices, some of which are used in aquafeeds that we consume. They highlighted cases of non-compliance with maximum residue levels (MRLs) and stressed the need for good agricultural practices as well as monitoring programs in place. Secondly, the risk of microbiological contamination is significant because botanical ingredients can mention pathogenic bacteria, molds and mycotoxins. To assess the microbiological quality of different varieties of spices that were commercialized, some samples showed contamination with > 1 pathogen (e.g., Salmonella spp.; Escherichia coli; molds) which may pose health risk (Nascimento et al. 2024).

Standardization of Botanical Ingredients

To overcome this variability and quality issues of botanical ingredients in aquafeeds, it is important to develop quality standards / specifications. These rules must specify the limits that should be adhered to for these parameters in terms of chemical composition, bioactive compounds count etc., and control level (contaminants, microbiological quality) (Tangendjaja 2022).

They could develop monographs and quality control guidelines, for instance on a selection of medicinal plants that can be used as botanical ingredients in aquafeed (Salin et al. 2018). Monographs and multimodal reference materials are essential tools for ensuring standardisation of botanical ingredients. Monographs offer a sufficiently detailed information regarding the identity, quality and safety characteristics of individual botanical ingredients which is mandatory for manufacturers as well as regulators and control laboratories to use these Monos either directly from Western Herbal Ingredient Standards (WHISS) or collectively by integrating them into monograph system (Hodar et al. 2020).

Many scientists, as well organizations such as the USP (United States Pharmacopeial Convention), NIST (National Institute of Standards and Technology), and EDQM (European Directorate for tbe Quality of Medicines and HealthCare) are involved in creating reference materials to measure botanical ingredients (Glencross et al. 2020).

Importance of Identity, Purity, and Potency

The standardization of botanical ingredients in aquafeeds should focus on three key aspects: identity, purity, and potency.

Identity: Identity → confirming the plant based ingredients are properly identified thus avoiding adulteration or substitution by inferior quality, toxic etc. Microscopic investigation, chromatographic techniques and DNA barcoding are few of the analyitical methods which can help to identify botanicals (Negi et al. 2021).

Purity: Botanical ingredients must be free of impurities such as heavy metals, pesticide residues, microbial contaminants and adulterations. Purity specifications should be established when using these ingredients and strict testing protocols implemented to guarantee safety and efficacy (Gil et al. 2021).

Potency: Botanical Ingredients can prove useful in conditions where the activity of biological compounds is necessary and also they are used for their desired effects, which may be imparted because one or more active ingredients within them have a biochemical effect. This standardization of the potency is required so that bio-similar aquafeeds have similar biological activities and ultimately are efficacious. Analysis methods such as chromatographic techniques and bioassays can be used to determine the concentration of these active ingredients in botanical blends, thereby establishing ingredient potency (Nikooet al. 2023).

Standardization of botanical ingredients in aquafeeds can be achieved by defining monographs and reference materials as well identity, purity, potency etc. which will ensure that increased quality standards are established leading to good quality assurance, safety and efficacy for being used at a commercial scale in the production systems.

Authentication Techniques

For authenticating botanical ingredients in aquafeeds, some of the analytical techniques like use for guaranteeing their genuineness and quality. It can be used for the identification of plant species or to test contaminants, detect adulterants and also assess whether raw material has all its bioactive compounds as well it can identify levels in a formulation which are responsible. Some of the frequently used methods to authenticate macroscopically are those that involve morphological analysis and physical examination; it can be gross evaluation based on color, odour texture or some characteristic morphology. This will give initial hints of what material the substance is and whether it might be unique. Microscopic evaluation often requires the use of a microscope to see into botanical ingredients and then identify both internal structures as well as cellular features. This information can help to identify the diagnostic features such as certain cell types, starch grains or other anatomical feature quickly enabling identification and authentication of botanicals under examination. For the analysis and authentication of botanical ingredients, chromatographic techniques are one of the most sought after methods. Techniques such as High-performance Liquid Chromatography (HPLC) and Gas chromatograph-Mass Spectrometry (GC-MS), are commonplace tools for the chemical separation, identification and quantitation of phytochemicals within botanical materials (Farabegoli et al. 2018).

It presents an alternative method for the determination of polyphenols, flavonoids and alkaloides, among other bioactive compounds used as markers in analytical control with chromatographic techniques such as Hig Pressure Liquid

Chromatography (HPLC) to generate a chemical fingerprint (Gunathilake et al. 2022 The potential of GC-MS is especially well demonstrated in the field of volatile compound analysis (e.g., essential oils, terpenoids), which has great application prospects for authenticity and identification research on botanical compounds according to their specific chemical compositions (Sadgrove et al. 2022). Spectroscopic methods such as FTIR (Fourier-Transform Infrared Spectroscopy) and NMR Nuclear Magnetic Resonance spectroscopy have been successfully employed for the chemical structure analysis of botanicals (Monakhova et al. 2018).

FTIR spectroscopy can produce characteristic spectral peaks by the vibrational frequencies of various functional groups in a sample, which is useful for identification and authentication of botanical materials (Gezahegn2018). Methods based on DNA are increasingly being used for the identification of botanical ingredients, especially in cases where morphological or chemical traits might be inadequate and thresholds may have lost due to processing or adulteration. DNA barcoding is the application of a short, standardized DNA sequence as an identification tag for distinguishing species. The method can also be used for pharmaceutical and biologicals, even processed or powdered botanical material constituents to identify not only crudity level but intrinsic quality of the locality at the species stage (Vlachavas et al.2019).

The detection and quantification of particular plant species or adulterants in botanical ingredients can also be performed using a Polymerase Chain Reaction (PCR) as well as the real-time PCR methods. These methods rely on the amplification and detection of particular DNA based sequences to produce results determining whether target plant materials are present or absent. With the combination of all these methods, you can have a well-rounded assessment to better ascertain both identity and purity which is essential for high-quality botanical ingredients in aquafeeds. Quite often the selection of a method depends upon what botanical is being analyzed,how then that might affect authentication,and to which degreea particular analysis has resources and expertise. Adherence to stringent quality control practices is imperative for the safety, effectiveness and uniformity of botanical raw materials utilised in aquafeeds (Nogueira et al. 2020). The following strategies can be employed:

Good Agricultural and Collection Practices (GACP)

GACP (Good Agricultural and Collection Practices): It is the norms that apply to practices for cultivation, collection of geographical species on which they grow. The guidelines ensure good harvesting practice i.e.; planting/seeds selection suitable agro-climatic conditions with optimum soil type etc. these will produce quality yield free from contamination or illegal alien's materials. From the onset of production, GACP is designed to eliminate any potential for contamination, adulteration and quality variability.

Key elements of GACP include:

- Selection of Suitable Growing Areas and Environmental Conditions
- Sustainable, environment-friendly agriculture practices adopted
- Fertilizer, pesticide and irrigation water available for use
- Good harvesting and post-harvest handling practice compliance
- Proper drying and storage of drugs
- End-to-end supply chain documentation and traceability.

GMPs: Guidelines and Regulations for the Quality Manufacuring of Products "Good Manufacturing Practices" GMP should be applicable during the processing, formulation, packaging and labeling as well as storage of botanicals ingredients for feed in general with specific reference to aquafeeds (Teves and Ragaza 2016).

Key aspects of GMP include:

- Appropriate Facility Design, Equipment and Maintenance
- Enforcing Standard Operating Procedures (SOP)
- Training and Hygiene of Workers
- Quality control systems and rigorous testing.
- Documentation and Recordkeeping Requirements
- Recall Procedures and Corrective Actions

GMP guidelines for aquafeed have been described by the FAO and IFIF (Tacon2022). The 2014 INA Annual Conference agreed that it is essential to qualify and audit the suppliers of botanical ingredients in order to guarantee the quality, origin etc., for their use as raw materials by the aquafeed industry. This means that one scrutinizes the suppliers in accordance with whether or not they meet GACP, GMP and quality standards such as those referred above. Supplier Audits may consist of Site Inspections, Review on Documentation and Sampling and Analysis of supplied materials. Audits performed on a regular basis Check for possible quality issues Confidence risks Opportunities in the supply chainDetection of fraudValue added logistic operations Sampling and testing protocols: Robust sampling and testing protocol need to be implemented for the quality control as well authentication of botanical ingredients. They should be established following recognized standards and guidelines internationally, such as that provided by the International Standard Organisation (ISO) or Association of Official Analytical Chemists ARISING FROM HOMEOSTATIC REGULATORY MECHANISMS

One of the prerequisites for this step is to be able sampling in which you should have a complete, representative and unbiased samples i.e., considering factors such as lot size, homogeneity or potential variability within batch. These manufacturing controls may contain testing methodologies that function to help make certain the strength, uniqueness, and power of a product also helping determine possible contaminants as well as adulterants (analysis methods are discussed thoroughly in another chapter; chromatography-based strategies, spectroscopy techniques or DNA based-tests). According to the time of writing this review, regulatory frameworks and legislative rules surrounding botanical ingredients added in aquafeed depend on region/country, reflecting disparate regulations concerning priority setting as a function of regions. Knowing more about these regulatory frameworks are essential to comply and promote elements of trade in aquaculture products (Gómez et al. 2020).

For example, botanicals have been an issue on the table of regulators in the Aquafeed industry for a long while: The European Union has outlined that they are used to regulate feed ingredients at least when it comes to animal feeds including aqua-feeds via Feed Additives Regulation and its amending regulations. This legislation ensures that feed additives (including botanicals) placed on the market are listed in a catalogue of permitted substances and lays down requirements for assessing their safety, authorisation, and labeling (Dusemund 2020; You et al. 2024).

Asia and Latin America, for example, have their individual regulations as well as guidelines for the botanicals used in animal feed. Guidance from, for example the Association of Southeast Asian Nations (ASEAN) on traditional medicines and health supplements might provide some high-level insight that is relevant to botanical ingredients in aquafeeds (Aya 2017).

Challenges in Harmonizing Standards and Guidelines

Although regional regulatory frameworks exist, convergence of standards and guidelines for botanical ingredients in aquafeeds across different regions and countries is needed. (Woodgate et al. 2022). Challenges come from a variety of fronts such as:

Regulatory philosophies and risk assessment practices differ: Countries may have a different perspective on what level of acceptable risk they can live with, the evidence required for safety evaluation leading to variations in standards, thresholds or guidelines.

Cultural and tradition practices: Use of botanicals in aquafeeds may be affected by cultural, religion or traditional practices that vary from one region to another which is very complex when it comes for harmonization.

Resource: The development and implementation of harmonized standards/guidelines can be resource-intensive, particularly in countries/regions where there may be limited technical expertise, analytical capacity or funding to support this

Non-tariff trade barriers are often manifested in regulatory differences that can complicate efforts toward harmonization and cause headaches for the global movement of aquaculture products.

Role of International Organizations and Initiatives

For the same reason, international organizations and initiatives are established to promote harmonization in standards as they pertain to safe trade practices of aquaculture products worldwide (Ababouch et al. 2023). Some of the key organizations and initiatives in this regard include:

Codex Alimentarius Commission, a body set up by the Food and Agriculture Organization (FAO) of the United Nations jointly with WHO to develop harmonized international food standards, guidelines as well codes of practice such as those concerning animal feeding (Codex Alimentarius, 2023).

International Feed Industry Federation (IFIF): This is a world-wide organization for the animal feed industry, also including aquafeed. Its objectives are to harmonize the regulations of feed, encourage safety and environmental sustainability in the use of botanical ingredients (IFIF, 2023).

OIE World Organisation for Animal Health: In order to protect animal health and welfare, the OIE develops international standards and guidelines with respect to biosafety, biosecurity, as well sufferers of packanimal carcasses including those components relatingto animal feed safety a quality; such standards affect the approval of botanical ingredients in aquafeeds (OIE, 2023).

Regional initiatives: Several regional blocs or organizations such as the EU, ASEAN and MERCOSUR are working towards harmonization of regulations/standards for botanical ingredients (and other feed additives) utilized in aquaculture.

Traceability and Supply Chain Management

Product traceability and supply chain management are essential when guaranteeing the identity, quality, safety of botanicals used in aquafeeds. By working with robust traceability systems, by following sound supply chain management practices; you can better manage the risks of adulteration, contamination and quality variability. Traceability: to follow the movement of botanical ingredients along the complete supply chain starting from their plantation or collection and ending with product distribution (Glencross et al. 2024). There are several reasons why traceability is important, including:

Quality control and Risk management: where in case there is any quality issues, contamination or adulterations it's easy to ID the product from which farm/battery that was sourced.

Regulatory requires the Traceability system: Various governments as regulatory body possess trade norms and standards that direct firms to build up a specialized device for tracing plant based abstractions coming in feedstuff products which are safe, hygienic, and healthy.

Source verification: Traceability supports source-segregation claims, providing the path to traceable ingredients back through each step of the supply chain.

Part of the reason consumer confidence: Consumers are becoming more demanding with food and feed products, which includes wanting transparency in regards to where botanical ingredients are coming from for aquafeeds.

Authentication Methods at Different Stages

Depending on the level of authentication necessary at each stage, different methods can be used to authenticate that a product is genuine or not:

This will first just be a cultivation/collection stage, in which proper documentation of the botanical source, geographical origin (if available), cultivated or wild-collected plants should previously occur. Authenticity can be assessed based on visual, microscopic and DNA barcoding analyses.

Stage of processing and manufacturing: For the verification of identity, purity, and potency botanical ingredients in raw materials processed, during which are used different analytical techniques like chromatographic methods(ICP-MS etc) spectroscopic methods (FTIR,NMR), molecular biological technique based on DNA(PCR analysis), real-time PCR.

Distribution and RetailWhen transported to distribution, visual material review followed by spectroscopy for commercial assays such as the immunological speciation tests can be used at various stages of goods typically related in aquafeeds that typify their resistance.

Solid documentation and record-keeping is a core part of any traceability system. This includes keeping detailed records of:

1. Cultivation / Collection Info: botanical source, geographic origins or location, how the plant is cultivated (if known) like seasonal growth time year — any harvest dates and what are taken to account for handling.
2. Production information: Information about the processes, production data including batch numbers and stability testing results to meet with quality control standards etc.
3. Transport and storage data: Temperature records, exposure to light for transportation conditions and handling history.
4. Distribution and retail data: This includes information about retailers, distribution channels in addition to product recalls or complaints.

1. Through the proper use of traceability systems, authentication methods at different process points as well documentation and record-keeping practices in case it becomes necessary to verify regulatory compliance on a particular batchs Baliga BCC ingredients stakeholders within the aquafeed industry can work together tighter ensure...simply stated that only great quality herbal components which you hope for from providing via supply chain reaches.... By carefully managing botanical ingredient through appropriate product development/production processes Quality Aquarian Feed GRID. It ensures consumer confidence as well, which is important for the sustainability and reliability of aquaculture in general.

Case Studies and Industry Examples

Case studies and industry examples which can illustrate how to apply quality control measures, authenticate the use of botanical ingredients in aquafeed etc. The lessons learned from these real-world scenarios will prove invaluable to all aquaculture stakeholders.

Use Cases and Best Practices

Herbstreith and Fox: a German company for standardized botanical extracts to different markets even in aquacultureRanked 3 their quality control is strict and under the umbrella of GACP collecting practices, GMP manufacturing standards and multiple analyses to authenticate its contents are used. This commitment towards quality and traceability has made them one of the most reliable suppliers for botanical ingredients in aquafeed industry.

Also have a look at Biomin: This Company produces some of higher-grade feed additives and premixes, including their line of phytogenic feed additives that are made from botanical origin specifically for aquaculture. They implement stringently enforced, state-of-the-art quality control procedures along with identification and purity verification via chromatographic and spectroscopic methods. They have gone ahead to setup and strike partnerships with botanical suppliers which have them put in place measures for traceability of their products hence enforcing authenticity and quality..

Cargill Aqua Nutrition: One of the biggest names in aquafeed is Cargill Aqua Nutrition, and they have made use of botanical ingredients as part-feed formulations. They have introduced supplier qualification programs and stringent testing methodologies, as well as track and trace systems to guarantee the quality of non-synthetic botanical ingredients. Their dedication to high quality and sustainability has gained the trust of aquaculture producers around the world.

Challenges Faced by Aquafeed Manufacturers

Botanical ingredient quality variabilityOne of the biggest struggles in developing aquafeed formulations is that botanical ingredients have significant inherent variations from factors such as plant genetics, environmental conditions and post-harvest handling. Such variability can, therefore, impact the efficacy and consistency of targeted benefits in aquafeeds (Brugere et al. 2021).

Risks of adulteration and substitution: Adulterating or substituting botanical ingredients with lesser quality, as well as potentially harmful materials are major worries. This is something that can happen for monetary reasons or weak high-quality controls in the supply chain (Ichim and Booker 2021).

Regulatory compliance and harmonisation: With the different regulatory frameworks and guidelines for botanical ingredients relevant to various regions, aquafeed manufacturers might find it hard. Complying with diverse sets of standards and requirements can be convoluted, especially for businesses that work across multiple markets.
Analytical capabilities and skills: Enforcing advanced analytic technics for authentication/quality control mandates a tier of equipment, human capital manpower, and its associated know-how. However, resource-constrained aquafeed manufacturer's especially smaller ones might struggle in this space.

Lessons Learned and Recommendations

Tech in Aquaculture: Install Strong Quality Control Systems -Aquafeed manufacturers need to set up complete quality control systems such as a robust sampling and testing system, supplier qualification programs, traceability measures etc. This type of proactive approach can prevent risks and guarantee the uniform quality and genuineness botanical ingredients.
Ensure reliable vendors and industry partners: Working with well-established botanical ingredient suppliers, together with interacting extensively with industry associations as well as research institutes or regulatory bodies for knowledge sharing between stakeholders will aid learning from best practices to harmonized efforts in achieving this goal.
Adopt modern analytical methods: Keeping abreast of contemporary authentication techniques like chromatographic, spectroscopic and DNA-based assays should provide the aquafeed producers with reliable hammer for QC and Authentication.
Transparency and Traceability: Transparent and traceable supply chains for botanical ingredients will increase consumer trust, ensure regulatory compliance, and help to deliver more sustainably farmed seafood.
Focus on research and development: Continuous investments in RandD can lead to new advances that refine cultivation practices, processing methods, and analysis methodologies improving the quality of botanicals used for aquafeeds.

Future Perspectives and Emerging Trends

The road to using botanicals in aquafeed is a constantly changing landscape, influenced by improvements in analytic techniques, digital technologies and an increased focus on sustainability and emphasis on responsible sourcing. A view of the future and emerging trends in this area includes these components:
New approaches/tools available for analysis: The field of analytical chemistry is ever advancing, and novel techniques/technologies arise that could be applied to authenticating botanical inputs in aquafeed (e.g. food finger-printing).

Metabolomics and chemometrics — Metabolomics together with state-of-the-art multivariate statistical methods are ideally suited for global metabolite profiling, allowing a full chemical fingerprint of plant materials. This capability of the approach supports detection for exclusive chemical markers, adulterants and batch-to-batch consistency.

Hyphenated techniques such as liquid chromatography combined with mass spectrometry (LC-MS) or nuclear magnetic resonance detection (NMR-LC), can offer improved resolution, sensitivity and structural information for the identification/quantification of bioactive compounds in botanical ingredients (Wyss et al. 2019).

Imaging techniques: Hyperspectral imaging and Raman imaging are capable of nondestructive, spatially resolved analysis to detect contamination, adulterants (including those with the same biosources) or volumetric segmentation on quality variation in botanical materials/images/processes (Wang et al. 2021).

Block Chain and Digital Traceability Solutions: Block chain technology (BBN) could offer a substantial breakthrough in improving the supply chain transparency in botanical ingredients for aquafeeds by tracking and tracing the process digitally, therein offering new modelled opportunities to ensure quality assurances within various parts of this linkage with traceable transactions that can even be linked back or forward to see what was delivered when where part of which batch source (Cui and Gaur 2022.
This helps in blockchain-based traceability: Introduction of blockchain systems can help you build an unaltered,decentralized mode for all transaction which packs a complete chain-from the time botanical ingredients are cultivated/collected till they enter into making aquafeeds.
Internet of Things (IoT) and sensor technologies: IoT devices can be deployed throughout the supply chain for monitoring performance, controlling environmental conditions and quality assurance actions by providing accurate data based on real-time in addition to traceability (Sallamet al. 2023).
Digital product passports: Digital Product Passports — or digital twins to store comprehensive information about botanical ingredients, including references on their origin and processing, analytical data and certifications used to ensure supply chain transparency as well as authentication. (Van et al. 2023).
Sustainable botanical sourcing and supply chain: With the aquaculture industry expanding, there is a higher demand for sustainable botanicals with low environmental impact.
Sustainable agriculture and harvesting techniques: I have discussed about this in detail above as it is necessary for the future availability of a good quality botanicals (Ahirwar et al. 2020).
Conservation of biodiversity and rational trade programs: The conservation of biological diversity, as well as fair-trade activities to ensure that biological resources are sourced from countries based on the principles endorsed by indigenous communities and traditional knowledge holders is significant (Makita2016).

Novel botanic… ingredients through waste valorisation: Investment in circular economy : Processing and agricultural wastes represent vast opportunities for the creation of novel botanical actives Waste stream based innovation should promote principles of a Circular Economy aimed at promoting zero-waste generation (Ferronato et al., 2019).
Sustainable use and dosage optimization:: Moreover, the constant research of technologies aim to optimize the formulation and dosages in aquafeeds feeding those biomolecules try imply that maximum benefits can be obtained with regards to resource efficiency thus reducing environmental impact (Onomu and Okuthe2024).

Summary of Key Points

Novel utilization of botanicals in aquafeeds has many advantageous attributes including growth promotion, improved nutrient utilization or increased resistance against various diseases. Yet it is also challenging to maintain the quality, safety and organic identity of inputs because they might be essential oils made out from batches with different chemical compositions; they might have contaminants in them; or there could even be a risk that lots are being adulterated or replaced by another oil entirely.
Many strategies, techniques have already been talked in this chapter to cope these challenges.

1. Create standards on botanical ingredients by setting quality norms, drafting monographs and giving reference materials.
2. Methods of authentication like macroscopic and microscopic assessment, chromatographic methods, spectroscopic techniques and DNA based assays.
3. Strategies for quality control, like GACP (good agricultural and collection practices), GMP (good manufacturing practice standards) supplier qualification, as well as more stringent sampling and testing requirements.
4. Regulatory dimensions and harmonisation efforts, in collaboration with international organisations and on initiatives to converge standards/guidelines across regions.
5. Documentation, record-keeping and authentication at the origin or other critical points in a supply chain including traceability through the system.PostMapping of performance-mediated operational documentation.
6. Success stories, challenges and lessons learned from selected case studies with botanical ingredients in a product supply chain.
7. Outlook and emerging trends; novel analysis technologies, blockchain to traceability solution and sustainable sourcing practices.

Importance of Quality Control and Standardization

Because of these various reasons, quality assurance in regard to botanical ingredients used is via aquafeeds an essential factor.

Siege on animal health and welfare: Farmed aquatic species require an uninterrupted supply of nutrients, and contaminants, adulterants or substandard botanical ingredients can jeopardize this need as well as their overall condition thus lowering productivity while making them more susceptible to diseases which in turn may affect food safety.
Effectiveness and consistency: Standardization and quality control measures guarantee the biological activities are consistent, while also ensuring the expected effects of botanicals in this way that other ingredients perform reliably and predictably across all aquafeeds.
Consumer confidence and market access: There are rising pressures from consumer's as well regulatory authorities for transparency, traceability, upholding sustainability principles and quality assurance in a range of aquaculture products including feed ingredients used. Effective quality control builds consumer confidence and can help to develop markets for aquaculture products.

Today, some major strides have been made to overcome quality control and authentication challenges for botanicals used in aquafeeds; however, many of them are still need more research and collaborative work that require critical scientific attention along the supply chain.

Future Research Directions and Collaborations

While significant progress has been made in addressing quality control and authentication challenges for botanical ingredients in aquafeeds, several areas require further research and collaborative efforts:

This includes continued research to develop more standardized analysis methods and authentic reference materials for a greater number of botanical constituents, in order to better enable proper identification/support quality control efforts.
Novel analytical approaches: New methodologies, such as metabolomics and hyphenated techniques in combination with imaging methods or even artificial intelligence (AI), may provide new insights for sophisticated authentication and quality control strategies.
Regulatory harmonization: The concerted efforts from international organizations, regulatory bodies and industry stakeholders are pertinent to standardize the regulations/standards pertaining botanical ingredients used in aquafeed across different regions.
Assuring sustainable sourcing and consumption practices: Explore the sustainability of production, biodiversity conservation, fair trade agreements and circular economy models related to botanicals application in aquafeeds.

Promoting interdisciplinary collaboration: Sustain inter-play among scientists, aquafeed manufacturers, botanical suppliers, regulatory agencies and other stakeholders which might be critical for sharing of information such that resources are pooled to develop holistic approach in solving challenges relating to quality control and authentication

Focusing on quality control, standardization and responsible practices will allow for the maximum utilization of botanical ingredients within aquafeeds concurrently with ensuring safe, effective and sustainable operations in the global aquaculture market.

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Chapter 47

Use of Nigella Sativa (kalonji) against Arthritis

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ABSTRACT

Rheumatoid arthritis is a persistent inflammatory, gradually developing autoimmune disease with articular and systemic effects. It affects people of all races globally and has a prevalence of 0.5–1%. Numerous researches conducted in developing nations shows that disease prevalence is lower, between 0.1-0.5%. This illness has been observed to be more occurring in North America. However, black people in the Caribbean and rural sub-Saharan Africa have reported lower incidences. In the fourth century B.C., Hippocrates was the first to recognize rheumatic illnesses. The term "rheumatism" was first used in the first century A.D. by the Persian physician Guilliaume Baillou to describe a pain that was felt in all of the body's joints. It was described by him as musculoskeletal. It is a multifactorial disease characterized by pain and stiffness of joints. Its exact cause is not known but genetic and environmental factors are responsible for the ailment. Most RA patients have a homozygous form of the HLA-DRB1*04 epitope, which puts them at high risk of developing joint injury. PTPN22, STAT4 PADI4, , TNFAIP3, and TRAF1-C5 are additional loci linked to RA, while non-MHC risk alleles may account for just 3-5% of the genetic burden of RA. Activated T-cells with the MHC-shared epitope and HLA-DR4 alleles initiate the pathogenic process.

KEYWORDS		
Arthritis, Rheumatoid, Kalonji, Nigella, Uses	Received: 08-Jun-2024 Revised: 09-Jul-2024 Accepted: 10-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Rheumatoid Arthritis is a persistent inflammatory, gradually developing autoimmune disease, damaging numerous joints with localized as well as generalized effects (González et al., 2009). Most patients with RA experience joint demolition, serious physical ailment and many co-occurring disorders. Its exact reason is not known, but environmental factors and genetic are responsible for ailment. Onset of the disease can be at any age, with incidence mostly in the age between 40-60 years (Choy, 2012).

Characteristics of Rheumatoid Arthritis

RA is characterized by pain and stiffness of joints with their gradual degradation resulting in disability. Its distinguishing features include synovial hyperplasia with migration of inflammatory cells, formation of new blood vessels, and destruction of bone and cartilage. RA is caused basically due to deregulation of immune system including its both compartments (Radu and Bungau, 2021).

Prevalence of Rheumatoid Arthritis

Rheumatoid Arthritis is discernible throughout affecting all races worldwide with prevalence of 0.5-1%. Its incidence in North America and Northern Europe lies between 0.5-1.1%. Southern Europe countries have incident rate of 0.3-0.7%. Various studies have been performed in developing countries that indicate a lower prevalence of disease i.e. 0.1-0.5% (Alamanos and Drosos 2005). A higher prevalence of this ailment has been seen in North America. Nevertheless, lesser incidence has been seen in rural sub-Saharan Africa and Caribbean blacks. In Middle East countries, the incidence of disease is 0.3-0.4%. In Asian countries, there is lower prevalence of disease. In Japan 0.3%, China and Indonesia 0.2-0.3%, Taiwan 0.3%, Philippines 0.2-0.3%, India 0.7 % and Pakistan has low incidence rate of 0.1% (Alamanos and Drosos 2005). RA is very prevalent inflammatory autoimmune disease in elderly people (Singh et al. 2016). Prevalence of Rheumatoid Arthritis increases significantly with age. Its incidence rate is only 0.3% in individuals below age of 35. However, rate is greater than 10% in senior individuals that are above 65 (Alamanos and Drosos 2005).

History

Hippocrates was the first who identified rheumatic ailments in fourth century B.C. The word rheuma was launched to specify feeling of pain throughout the joints of the body in first century A.D. Guilliaume Baillou who was a Persian physician first gave the concept of rheumatism. He defined it as a musculoskeletal (that affects muscles, tendons and ligaments of bone and joints) syndrome. Joseph L Hollander first launched the term rheumatology in 1949. Clinical illustration and definition of Rheumatoid Arthritis was first given by Augustin-Jacob in 1800. Definition of Rheumatoid Arthritis was further modified and was reported in 1988 (Alamanos and Drosos 2005).

Causes of Rheumatoid Arthritis

RA is a multifactorial disease influenced by both environmental and genetic factors, but its real cause is not known. Pathogenesis of RA involve role of B and T cells and organized interaction of cytokines. The vital cytokine (IL-17) that enhances synovitis, produced from reorganization of T cells into Th17. B cells perform a key function in pathogenesis by releasing cytokines, production of autoantibodies, and antigen presentation (Choy, 2012).

Genetic Factors

Majority of RA patients have antigenic determinant of the HLA-DRB1*04 in homozygous form, they are at high risk of having joint damage. Other RA-associated loci are PTPN22, TRAF1-C5PADI4, STAT4, and TNFAIP3, although non-MHC risk alleles may denote only 3–5% of the genetic load of RA. Commencement of the pathophysiological process is done by triggered T-cells, exhibiting HLA-DR4 alleles with the MHC-shared determinant. Responsible T-cell antigens are either single or numerous, including viral or bacterial products. Cross-reaction of T-cell antigen with self-antigen leads to production of cytokines either by the stimulation of cytokines or by direct cell-to cell contact (Choy, 2012).

Environmental Factors

Environmental factors impart a significant role in the onset, severity and the progression of rheumatoid arthritis (Edwards and Cooper, 2006). Although many infectious agents have been involved in the disease process, current data imply smoking as a significant environmental risk aspect for the progression of the RA in HLA-DR4-positive individuals. The relation between smoking and RA seems to be dose-dependent which is evident from hefty smokers (Alamanos and Drosos 2005). It has been suggested that smoking perhaps produce an ample source of neo-antigens to enhance further autoimmune reactivity (McInnes and Schett 2007). Rate of RA is two to three times more in women compared to men. Hormonal factors are responsible for high prevalence in women. Difference in development of arthritis in identical twins definitely indicate the significance of non-genetic factors in development of disease and for this, infectious agents are logical explanation (Oliver and Silman, 2006). Infectious agents such as bacteria may spread throughout the body including joints. Neutrophils, as a part of innate immune response, may move to the affected joints and deteriorate matrix components while attacking invading organisms (Burrage, Mix et al. 2006). Infectious agents like rubella virus, Epstein Barr virus have been found to be involved in disease process (Alamanos and Drosos 2005).

Dietary factors could remarkably increase risk of developing disease. Certain diets have been suggested that have potential to decrease risk of ailment such as Mediterranean diet. Other lifestyle factors that provide protective effects against Rheumatoid Arthritis include cooked vegetables, olive oil and fish. Their lifelong consumption could provide safety from disease (Alamanos and Drosos 2005). Many other elements such as socio-economic status, education and stress affect the incidence of disease (Tobón, Youinou et al. 2010).

Pathogenesis of Rheumatoid Arthritis

RA progression begins in synovial tissues neighbouring the joints and later, it moves towards cartilage. IL-1 and TNF-alpha play a role in arthritis. They lead to production of enzymes MMPs that have ability to destroy all parts of extracellular matrix (Luyten et al., 2006). MMP1 is mainly produced by synovial cells that cover the joints and MMP13 is produced by chondrocytes present in the cartilage. MMP13 plays a multiple role by degrading not only collagen but also aggrecan, a proteoglycan molecule. Other MMPs such as MMP2, MMP3 and MMP9 are also produced in increased amount in arthritis and they detoriate non- collagen parts present in joints (Burrage et al., 2006). NF-kappa B activation is required for expression of MMP1 and MMP13 as well as inflammatory stimuli such as Interleukin-6, Interleukin-1 and TNF-alpha. In response to high level of IL-1 and TNF-alpha, raised level of MMP1 and MMP13 collagenases has been observed in arthritic tissue (Vincenti and Brinckerhoff 2002). Disease begins with stimulation of innate immune comeback that mainly involves activation of antigen presenting cells (dendritic cells) by foreign agent such as bacteria or virus or in response to self-antigen. Antigen offering cells such as dendritic cells or macrophages present antigen to T cells. As a result, T cells produce IL-2 and IFN-gamma which permeate the synovial membrane (Choy, 2012). B cells contribute by production of autoantibodies which form large immune complexes that lead to release of pro-inflammatory cytokines such as TNF-alpha. T and B cell activation lead to increased production of cytokines and chemokines which in turn produce more T cells, macrophages, and B cells (Vita et al., 2002).

Role of Cytokines in Rheumatoid Arthritis

Cytokines are molecules of smaller size that bring about communication among different cells that ultimately leads to movement of the immune cells and inflammatory cells into the joints. As these cells move into the joints, they are activated to generate products that results in tissue degradation (Arend, 2001). The actual job of these small molecules inside a complicated regulatory system are associated to particular immunological procedures that can enhance autoimmunity, chronic inflammation and tissue degradation (McInnes and Schett 2007). Hence the process of tissue degradation in rheumatoid arthritis requires the role of numerous cytokines which proceed in a complicated array as moderator of communication between different cells. Cytokines perform major part in the beginning of responsive synovitis, in the modification of this self-limited reaction into a hostile and tissue degradation procedure and further in the continuation of persistent synovitis. The same or dissimilar cytokines may play dynamic and complementary roles in these steps of the disease process (Arend, 2001).

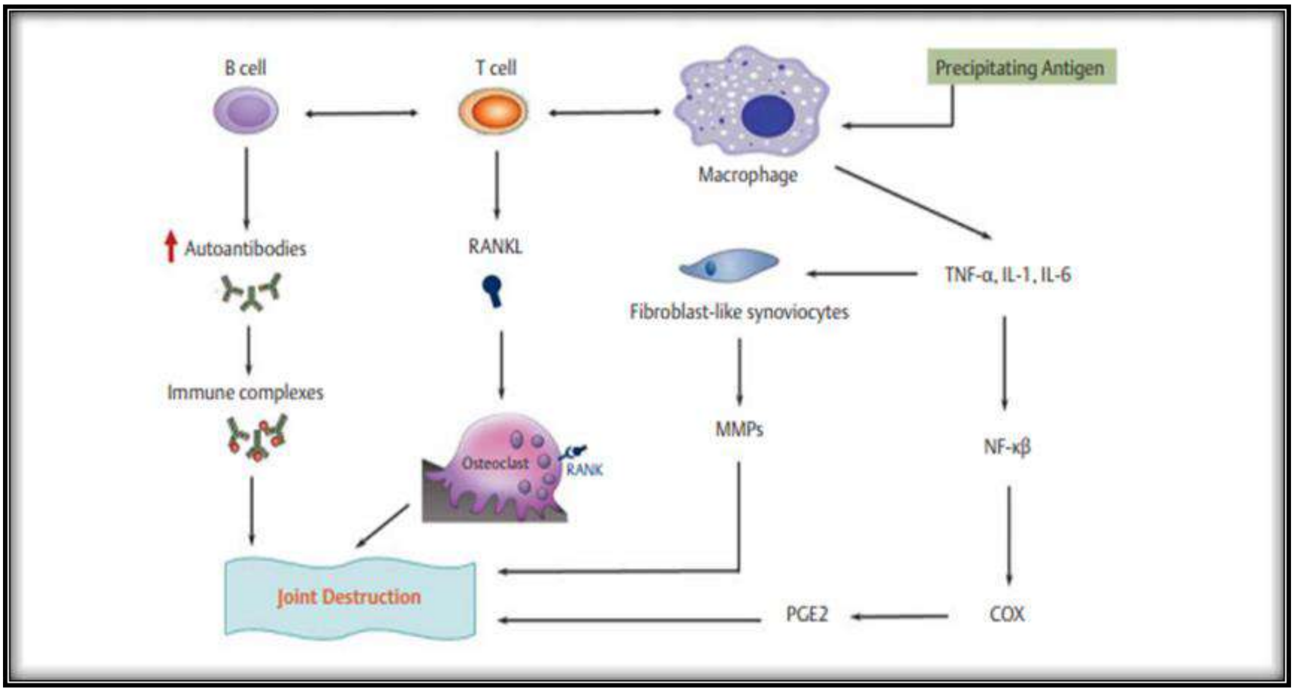

Fig. 1: Pathogenesis of Rheumatoid Arthritis

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Role of Pro-inflammatory cytokines- TNF- alpha and IL-1

These mediators perform a key function in the formation of the degenerative and inflammatory response. (Smolen, Redlich et al. 2005). Tumour necrosis factor-alpha, Interleukin-6 and Interleukin-1are the main moderators that are participating in migration of cells and inflammation (swelling) in rheumatoid arthritis (Choy, 2012). Tumour Necrosis Factor-alpha and Interleukin-1 perform major function in inflammation (swelling) and joint destruction that happens in rheumatoid arthritis. The pathological consequences of these mediators include migration of leukocytes into the synovium (leucocytes infiltration) which results in synovial hyperplasia, leading to activation of cells, destruction of cartilage and prevention of formation of cartilage matrix (Vervoordeldonk and Tak 2002).

IL-1

Interleukin-1α and Interleukin-1β are chiefly produced by macrophages; however, they can also be released by B and T lymphocytes and endothelial cells. Interleukin-1 can employ a range of generalized inflammatory responses such as inset of fever, wasting and also include formation of acute-phase proteins. Interleukin-1 also has ability to employ localized responses on cartilage as well as bone matrix synthesis. Furthermore, Interleukin-1 secondarily promotes joint damage by promoting fibroblasts to produce Interleukin-1, Interleukin-6 and Interleukin-8 (Dayer, 2003).

TNF-alpha

Tumour necrosis factor-alpha plays a more significant role than Interleukin-1 as it modulates discharge of pro-inflammatory cytokines in rheumatoid affected synovial tissue. It regulates release of other pro- inflammatory cytokines like Interleukin-6 as well as Interleukin-8. It promotes expression of prostaglandins (PGE2) and matrix metalloproteinase (MMPs) (Vervoordeldonk and Tak 2002).

IL-6

IL-6 specifically acts primarily on neutrophils with the aid of membrane IL-R which sequentially leads to swelling (inflammation) and joint damage by secreting proteolytic enzymes as well as reactive oxygen (RO) intermediates. (Choy, 2012). IL-6 promotes an acute phase reaction; however, in chronic(persistent) inflammation it has dual effects i.e. inflammatory and anti-inflammatory responses. Decrease amount of estrogen and androgen, that are also present in patients suffering from rheumatoid arthritis are related to raise levels of IL-6 (Hashizume and Mihara, 2011)

Role of Anti-inflammatory cytokines

These mediators are mostly considered as having immunoregulatory as well as inhibitory features. These cytokines are actually a chain of immunoregulatory molecules that have potential to regulate response of pro-inflammatory cytokines. In general, cytokines usually act in combination with particular cytokine inhibitors and receptors to control immune response in humans (Opal and Depalo 2000).

IL-4

IL-4 revert back cartilage degeneration generated by pro-inflammatory cytokines, impediment of angiogenesis (formation of new blood vessels); and bone resorption (Mobasheri, 2013). It performs a major role by deregulation of pro-inflammatory cytokines and aids to promote Th2 response (Dong et al., 2018).

IL-13

Interleukin-13 impedes secretion of various cytokines as well as chemokines. Interleukin-13 also has a pro-angiogenic response because it can trigger endothelial chemokines (Peluzzo and Autieri, 2022)). It performs a key role in deregulation of pro-inflammatory cytokines ((Hussein et al., 2021). It also has inhibitory characteristics similar to that of Interleukin-4. Its presence can be confirmed by immunostaining in synovial membrane of RA patients (Feldmann, Brennan et al. 1996).

Role of Regulatory Cytokine

IL-10

Interleukin-10 inhibits secretion of Interleukin-1 and Tumour Necrosis Factor-alpha with aid of Rheumatoid Arthritis mononuclear cells and impede cartilage damage. It can also inhibit release of Matrix Metalloproteinases. Interleukin-10 also prevents osteoclast growth and hence osteopenia (Szekanecz, Koch et al. 1998). It also perform a role in deregulation of pro-inflammatory cytokines and impediment of T-lymphocyte reaction (Isomäki and Punnonen 1997). Interleukin-10 is composed of two-fold features associated with development of inflammation (swelling) because it has both pro-inflammatory and anti-inflammatory features (Bevaart, Vervoordeldonk et al. 2010). Interleukin-10 also performs a regulatory function in progression of rheumatoid synovitis, based on the phase of disease (Arend 2001). It has significant anti-inflammatory as well as immunoregulatory features (Feldmann, Brennan et al. 1996).

Role of NF-kB in Rheumatoid Arthritis

Switching on of the NF-kB transcription family with aid of nuclear displacement of cytoplasmic network perform a key function in inflammation by its capability to enhance transcription of pro-inflammatory genes. It is thought to be a significant component giving rise to inflammation in chronic ailments such as Rheumatoid Arthritis (Tak and Firestein 2001). NF-kB is greatly switched on in synovial membrane of patients suffering from Rheumatoid Arthritis and may be a crucial element shielding cells from apoptosis, hence bringing about synovial hyperplasia (Tak, Gerlag et al. 2001).

Treatment Modalities for Rheumatoid Arthritis

Variety of drugs and anti-inflammatory agents account for the panacea of arthritis are accessible in the market. Some of them target cytokines, while others target related enzyme or proteins in inflammatory disease. Before discussing mode of action of non-steroidal drugs. It is important to first discuss the major targeted inflammatory protein and its function in the body.

Cyclooxygenase

Cyclooxygenase (COX) is the enzyme that assist in the catalysis of arachidonic acid in the biosynthesis of the prostaglandins (PGS) (Fitzpatrick, 2004). Metabolic products of arachidonic acid have significant role in various processes occurring in living organism including immunological and inflammatory functions, angiogenesis, ovulation and platelet accumulation in the body. There are two basic kinds of Cyclooxygenase-1 (COX-1), Cyclooxygenase, and Cyclooxygenase-2 (COX-2). COX-1 is present in almost every cell type including cells of duodenum, jejunum, ileum, renal cells, cells of large intestine and cells of stomach and lungs. The main role of COX-1 is to produce cytoprotective prostaglandins including PGE2 and prostacyclin, which play crucial role in maintaining probity and integrity of gastrointestinal mucosa (Fitzpatrick, 2004)**.** COX-2 is not produced continuedly in every cell type. It is produced because of some stimuli and expressed in specific cells only. COX-2 is used for signaling pain and inflammation. Some intracellular and extracellular stimuli are needed for its propagation. Following stimuli are responsible for the expression of COX-2 enzyme. LPS (lipopoly-saccharide) of bacteria, tumor necrosis factor (TNF), serum, converting growth factor alpha (TGFa), epidermal growth factor, interleukin like IL-1, retinoic acid, arachidonic acid, platelet activating factor (PAF) and endothelin. Following treatment, COX-2 level returns to normal within 24 ± 48 h. Its high level for longer duration causes serious complications in the body(Chen, 2010).

Nonsteroidal Anti-inflammatory Drugs (NSAIDS)

Studies have shown that Nonsteroidal anti-inflammatory drugs (NSAIDS) target the prostaglandin synthetase in the cyclooxygenase pathway. In Stomach, prostaglandins secrete bicarbonate and mucus, thus maintain mucosal cell turnover and mucosal blood flow. Inhibition of prostaglandin synthesis in stomach result into mucosal injury and gastric ulceration (Adinortey et al., 2013). Their way of targeting COX-1 is either by covalently modifying the enzyme or by competing for active site as a substrate. Prostaglandins are involved in physiological function of body; therefore, their blockage leads to chronic and undesirable side effects in the body. Gastrointestinal ulceration, bleeding and perforation are the life threating side effects of NSAIDS. It has been reported that frequent and daily users of NSAIDS have a greater chance of developing gastrointestinal and renal problems as compared to non-users. The rate of getting gastrointestinal complications is threefold high in daily users. PGI2 or PGE2 produced as a result of loss of COX-1 activity in stomach leads to chronic and severe gastric mucosal damage and ulceration in stomach (Wallace and Vong, 2008)

Nigella Sativa

Characteristics

Nigella sativa also known as kalonji, black cumin, charnushka, belongs to Ranunculaceae family is a flowering plant indigenous to Eastern Europe and western Asia, but can be easily full-grown in other areas like Europe, North Africa and Myanmar. It enhances the taste in different cuisines. The Nigella genus is miniature of the Latin word niger "black" which refers to the tint of the seed. The particular label sativa is translated as "cultivated "In English language, Nigella sativa is also known as by the variety of the names such as black caraway, black cumin, black seed and fennel flower.

Description

The average size of *Nigella sativa* plant reaches up to 20–30 cm (7.9–11.8 in) tall and they possess sharply divided and linear leaves but they are not threadlike. The delicate white and pale blue flower having five to ten petals can be seen on the tiny plant. The fruit of *Nigella sativa* is characterized as huge in size and pumped-up capsule comprised of three to seven integrated follicles (El-Morsy and Osman, 2021). Each fruit encompasses a massive number of seeds which put to use as spice for cuisines and sometimes in the substitute of *Bunium bulbocastanum* (black cumin).

Culinary Use

The dry-roasted seeds add taste to meal. The black seeds are also used as essence in bread products. In Bengali cuisine, the spice mixture (panch phoron) also contains these seeds. Nigella enhances flavour in tresse cheese, a braided string cheese called majdouleh in the Middle East. It is also marked safe for use as a spice, natural seasoning, or flavouring by The Food and Drug Administration of United States and it includes Nigella sativa in Generally Recognized as Safe (GRAS) list.

History

The medievalism evidence of *N. Sativa* cultivation traces back about three thousand years. These seeds were found in different sections of the world like ancient Egypt and the Tomb of Tutankhamun. *N. sativa* may have been used to flavour food in the condiment of the Old World. The Muslim physician Avicenna pronounced *N. Sativa* as a panacea for dyspnea in his The Canon of Medicine. In the Middle East, *N. Sativa* was used as local medicine.

Chemical Nature

Out of total conformation of *N. Sativa* seeds, 32% to 40% are oils, these comprise of Linoleic acid, Palmitic acid, Oleic acid, and Trans-anethole. In the minor ingredients, it includes Nigellidine, Nigellicine, and Nigellimine N-oxide. While from aromatics it possesses thymoquinone, p-cymene, Dihydrothymoquinone, Carvacrol, α-thujene, α-pinene, Thymol, β-pinene and Trans-anethole. Protein and various alkaloids are existing in the seeds. quinone, p-cymene (7%-15%), Carvacrol (6%-12%), 4-terpineol (2%-7%), t-anethol (1%-4%), Sesquiterpene longifolene (1%-8%) α-pinene and Thymol etc (Mukhtar et al., 2021). Furthermore, *N. Sativa* seeds tolerate potential to anticancer agent such as alpha-hederin, a water soluble pentacyclic triterpene and saponin. Additionally, some compounds e.g. Carvone, Limonene, Citronellol were also found in minor amounts. The pharmacological properties of *N. Sativa* are because of quinine constituents. On stowing, TQ yields Dithymoquinone and higher Oligocondensation products. The proximate composition of seeds of N. Sativa shows that protein is 26.7%, fat holds 28.5%, carbohydrates are 24.9%, and crude fibres maintain 8.4% and total ash accounts for 4.8 %. The seeds are also bearing good number of various vitamins and minerals like Cu, P, Zn and Fe etc (Albakry et al., 2022).

Traditional Use

N. sativa has marked for traditional use such as for the curing of a variety of diseases relating to digestive tract, respiratory system, liver and kidney function, cardio vascular system as well as for general well-being.Avicenna mentions in the "The Canon of Medicine" that black seeds integrate the body's energy and aid in recovery from fatigue. In Indian and Arabian civilization, Black seeds and their oil create a long history of folklore usage as food and medicine. The seeds have been traditionally used in Southeast Asian and the Middle East countries for the handling of several diseases and ailments counting asthma, rheumatism, bronchitis, and related inflammatory diseases. Its other uses earned Nigella the Arabic approbation 'Habbatul barakah', symbolizing the seed of blessing (Nunez, 2024).

Medical Research

The other clinical research on these seeds found that it does not support strong evidence that *N. Sativa* has a short-term benefit on dropping systolic and diastolic blood pressure (Albakry et al., 2022). Despite significant use of *N. Sativa* in traditional medicine practices in Africa and Asia, there is inadequate high-quality clinical evidence to indicate that consuming the seeds or oil can be used to treat human diseases.

Nigella sativa contains various compounds, including thymoquinone, which have been shown to perform antioxidant properties. These compounds aid in neutralizing injurious free radicals in the human body, potentially dipping oxidative stress and inflammation. The main active compound in *Nigella sativa*, Thymoquinone, has demonstrated anti-inflammatory effects in several studies. This is useful for conditions categorised by inflammation, such as arthritis, asthma, and certain skin disorders (Toor et al., 2024).

Respiratory Health

Research suggests that *Nigella sativa* may have benefits for respiratory health. It has the potential to assuage symptoms of asthma and allergies, possibly because of its anti-inflammatory and bronchodilator properties.

Diabetes Management

Some studies indicate that *Nigella sativa* may support normalise blood sugar levels and recover insulin sensitivity in persons with diabetes. This could be accredited to its antioxidant properties, as well as its potential to enhance glucose uptake by cells (Toor et al., 2023).

Cardiovascular Health

There is sign to suggest that *Nigella sativa* may have constructive effects on cardiovascular health. It may assist reduce blood pressure and cholesterol levels, dropping the risk of heart disease and stroke (Adinortey et al., 2013). Additionally, its antioxidant properties may protect against oxidative damage to blood vessels.

Anticancer Potential

Thymoquinone has been considered for its potential anticancer effects. Research shows that it may obstruct the development of cancer cells and encourage apoptosis (programmed cell death) in various categories of cancer, counting breast, prostate, colon, and pancreatic cancer. However, more research, including clinical trials, is needed to confirm these findings and determine the optimal use of *Nigella sativa* in cancer treatment (Almatroodi et al., 2020).

Antimicrobial Activity

Nigella sativa has also been considered for its antimicrobial properties. It may have antibacterial, antifungal, and antiviral effects, which could be beneficial for combating infections caused by pathogens.

Treatment for Arthritis

Anti-inflammatory Properties

Nigella sativa comprise of compounds like thymoquinone that have demonstrated anti-inflammatory effects in studies. Inflammation performs a key role in the progression of rheumatoid arthritis, contributing to joint pain and damage (Toor et al., 2023). By reducing inflammation, *Nigella sativa* may help alleviate symptoms associated with RA.

Pain Relief

Some research suggests that *Nigella sativa* may have analgesic properties, meaning it could help relieve pain associated with arthritis. This could improve the quality of life for individuals with rheumatoid arthritis by reducing discomfort and stiffness in the joints.

Antioxidant Activity

Oxidative stress is concerned in the development and progression of rheumatoid arthritis (Albakry et al., 2022). *Nigella sativa's* antioxidants properties may support neutralize free radicals and reduce oxidative damage to joint tissues, potentially slowing the progression of the disease.

Immunomodulatory Effects

Rheumatoid arthritis is an autoimmune condition characterized by an overactive immune response that targets the body's own tissues. Some studies suggest that *Nigella sativa* may have immunomodulatory effects, meaning it could help regulate the immune system and reduce the abnormal immune response seen in RA (Albakry et al., 2022). .

Joint Protection

Nigella sativa may help guard joint tissues from damage triggered by inflammation and oxidative stress. By preserving joint health, it could potentially slow down the progression of rheumatoid arthritis and prevent further deterioration of the joints.

Reduction of Autoimmune Response

Rheumatoid arthritis is followed by an autoimmune response in which the body's immune system erroneously attacks its own tissues, particularly the synovium (lining of the joints) (Darakhshan et al., 2015). Some research suggests that *Nigella sativa* may modulate the immune response, potentially reducing the severity of autoimmune reactions and the associated joint damage.

Combination Therapy

Nigella sativa may complement conventional treatments for rheumatoid arthritis. Some studies have investigated its use alongside conventional medications, such as disease-modifying antirheumatic drugs (DMARDs) and nonsteroidal anti-inflammatory drugs (NSAIDs), to enhance their effectiveness or reduce their side effects (Darakhshan et al., 2015).

Improved Quality of Life

By reducing pain, inflammation, and joint stiffness, *Nigella sativa* could improve the overall quality of life for individuals living with rheumatoid arthritis (Adinortey et al., 2013). Enhanced mobility, decreased reliance on pain medications, and better management of symptoms may contribute to a better sense of well-being and daily functioning.

Potential for Disease Modification

While current treatments for rheumatoid arthritis focus primarily on managing symptoms and slowing disease progression, there is growing interest in therapies that can adapt the course of the disease itself (Mousavi et al., 2024). Some researchers speculate that *Nigella sativa* may have disease-modifying properties, but more evidence is needed to support this claim.

Safety and Tolerability

Nigella sativa is generally considered safe when used in appropriate doses, with few reported side effects. Unlike some conventional medications for rheumatoid arthritis, which may cause gastrointestinal issues, liver toxicity, or other adverse effects, *Nigella sativa* is often well-tolerated. While these potential benefits are promising, more research, particularly clinical trials involving human participants, is needed to fully understand the efficiency of *Nigella sativa* in the treatment of RA (Mousavi et al., 2024). Additionally, it's important to consult with a healthcare professional prior using *Nigella sativa* or any other herbal supplement as a treatment for arthritis, especially if you're already taking medications or have other medical conditions.

Conclusion

Nigella sativa has shown anti-inflammatory, analgesic as well as immunomodulatory and RA lesion reducing effects in studies including in vitro, in vivo and clinical trials. Studies proved the efficiency and safety of *N.sativa* in the rheumatoid arthritis patients by reducing pain and inflammation in the joints of patients. Anti-oxidant properties of N. sativa have also been tested and are shown to be remarkable as it reduces oxidative stress in animal models as well as clinical trials. Research has shown that thymoquinone, the major and active component in Nigella sativa is responsible for its anti-inflammatory, anti-oxidant and analgesic properties. Combination therapy using Nigella sativa with non-steroidal anti-inflammatory drugs or stem cells would be more effective in the treatment of RA. Further in vitro and in vivo studies are needed to confirm the efficacy of nigella sativa against RA.

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Chapter 48

Curcuma longa L: A Promising Drug against Respiratory Disorders

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ABSTRACT

Spices and herbs have used since historic times to improve the flavor of edible food. Apart from this, these are also utilized to prevent and treat chronic health conditions. Turmeric is a well-known culinary spice and also herbal remedy. For many centuries, turmeric (*Curcuma longa* L.) has been utilized to add color and flavor to the food. Along with this, it has been utilized in traditional healing practices to treat skin diseases, digestive disorders, wounds and respiratory problems in India and China. Turmeric has been extensively used traditionally for respiratory and gastrointestinal problems like cough, cold, asthma, throat irritations, flatulence and chronic diarrhea. Because of the existence of various chemical components (such as proteins, starch, vitamins, volatile oils, curcuminoids and curcumin), this plant is considered to have the potential to act like a medicinal plant and having a broad range of pharmacological characteristics. Many phytochemicals are present in turmeric. Curcumin (diferuloylmethane) is the active constituent of turmeric which possesses many therapeutic qualities. While, the defensive actions of this constituent of turmeric were examined in various pulmonary diseases like chronic obstructive pulmonary disorder (COPD), acute respiratory distress syndrome (ARDS), pulmonary fibrosis and asthma in animal studies. The administration of powder of turmeric by oral route notably alleviated cough and asthma. Also, fresh rhizomes appeared to be efficient against dyspnea, whooping cough and other coughs. Over the last 50 years, the safety, efficacy and pharmacokinetics of curcumin have been studied widely in clinical evaluations. Curcumin has less solubility, stability and bioavailability. Researchers are now struggling to solve all these issues by modifying it and also checking it by combinational therapeutics.

KEYWORDS
Inflammation, Turmeric, Curcumin, Treatment, Curcuminoids

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Introduction

Throughout the human history, natural products from plants have been utilized for several reasons. Having co-evolved with animal life, these natural products are acquired from plants which are billions of years old. Higher plants form many of these substances as secondary metabolites for their natural defense against infection and disease. Several of the natural plant products possess biological or pharmacological properties which can be utilized in pharmacological discovery of drug and its design. Plant originated medicines retain a significant part in the health maintenance of different cultures, including modern as well as ancient cultures. Ayurveda which is known as the Indian system of holistic medicine mainly utilizes plant derived formulations or drugs to treat a number of diseases including cancer (Prasad and Aggarwal, 2011). Valuable effects of herbs or spices involve antioxidant, anti-inflammatory, gluco-regulatory, anti-thrombotic and anti-hypertensive actions. Polyphenols are one of the main component of spices and herb. Few of the above mentioned characteristics are associated with polyphenols and they are involved with the attenuation of metabolic syndrome (Panickar, 2013).

Curcuma longa Linn. (*C. longa*), also commonly named as turmeric is a member of the Zingiberaceae family. It has an extensive history of possessing therapeutic qualities against several ailments. In Ayurveda as well as Unani medicine, *Curcuma longa* has been employed for jaundice and obstruction of liver as well as applied for inflammation and ulcers externally. In addition to this, it is used as an antiseptic and for many other problems such as cold, cough, asthma, bronchitis, indigestion, dental issues, blood purification, skin infection, wounds, tumor, and hepatic disorders. *C. longa* possesses curcumin which is its principle constituent. Curcumin is popularly known because of its therapeutic ability against various diseases (Fuloria et al., 2022). The major route for the administration of *C. longa* is by oral administration. Apart from this, it can be used either through inhalation or topically. It can be applied topically to treat wounds, bruises, boils, blistering, acne, eczema, ulcers, parasitic infection, hemorrhages, skin diseases and insect bite (Labban, 2014). Curcuminoids, borneaol, zingiberine, sabenene, phellandreen, cineol, sesquiterpenes as well as essential oils are present. Other than this, turmeric also possesses carbohydrates, proteins, fats, fibres, vitamins and minerals. Turmeric has been extensively used traditionally for respiratory and gastrointestinal problems like cough, cold, asthma, throat irritations, flatulence and chronic diarrhea (Gilani et al., 2005).

Composition

The known significant species of genus Curcuma are *Curcuma zedoaria* Rosc. (Zedoary), *Curcuma angustifolia* Roxb, *Crucuman aromatica* Salisb. (Vana Haridra), *Curucma caesia* Roxb. (Kali Haridra), *Curcuma amada* Roxb. (Amaragandhi Haridra) and *Curcuma longa* Linn. (Haridra). These grow in various parts of the world. In Hindi, *Curcuma longa* Linn. is known by the name of' 'Haldi'. It is a tall herb and cultivated across the tropical and other regions in India. In Indian homes, *Curcuma longa* Linn. is used as therapeutic plant in day to day practice for different illnesses (Krup et al., 2013). *Curcuma longa* contains curcumin (diferuloylmethane) which is the potent principal curcuminoid. The other two curcuminoids include bisdesmethoxycurcumin and desmethoxycurcumin and several volatile oils including zingiberone, atlantone and tumerone. Further components are proteins, sugars and resins. The curcuminoids are the polyphenols. These are also accountable for the yellow color of turmeric (Ansari et al., 2020).

History

Turmeric has been described as an important plant in old scriptures. It has been used for over 4000 years and is described as 'Indian saffron'. It is also predominant in prehistoric Indian medicine, Ayurveda. Without any doubt, the utilization of turmeric as a medicine, paint and condiment has extended to a lot of countries. Turmeric has digestive characteristics and also used for flavoring. It is distinctly regarded by the Hindus and offered in many temples as "Prasad". Different uses of turmeric have been mentioned by great earlier Indian doctors. Dioscorides, who was a Roman Army Greek scientist also talked about turmeric. Europeans discovering the Asian continent took turmeric to the West in the 14th century. The powdered and crushed turmeric rhizome was routinely used in Asian cooking, fabric dyeing, cosmetics and medicine for 4000 years. Approximately 40 species of *Curcuma* are native to India indicating their origination from India. Though, in tropical Asia nearly 70 to 110 species have been recorded and the most diverse are found in Thailand, India and Myanmar. Some species are scattered in Australia, China and the South Pacific. While others are raised in all tropical regions (Abd El-Hack et al., 2021).

Pharmacokinetics

In animals, the pharmacokinetics evaluations indicated that when curcumin is administered orally, 40 to 85 percent of it passes unchanged through the gastrointestinal tract. Much of the absorbed flavonoid is being metabolized in the mucosa of intestine as well as in liver. As it has less absorption rate, so to increase the absorption and anti-inflammatory activity, curcumin is many times formulated with bromelain. Curcumin has an approximate bioavailability of 65% after oral administration. It is metabolized by means of glucuronidation. It inhibits cytochrome P-450 isoenzyme 1A1 (Kumar and Sakhya, 2013).

Therapeutic Properties of *Curcuma longa*

Curcumin has captured significant scientific attention during the recent years as a result of its broad range of valuable pharmacological characteristics. These include antioxidant, anti-inflammatory, anticancer, anti-mutagenic, anti-infective, anti-angiogenic and anti-diabetic properties. A number of publications are present in the literature which describe the useful role of curcumin to prevent and treat chronic conditions such as atherosclerosis, Alzheimer's disease, different type of cancers, diabetes type-2 and multiple sclerosis (Karlowicz-Bodalska et al., 2017).

In Ayurvedic medicine, *Curcuma longa* L. has been used for a long time to treat inflammatory diseases (Boskabady et al., 2020). Turmeric has demonstrated variety of biological activities including anti-inflammatory, anti-viral, anti-bacterial, anti-protozoal, anti-fungal, antioxidant, anti-diabetic, anti-mutagenic, anti-ulcer, hepato-protective as well as analgesic effects. Inflammation and irritation associated with allergies and inflammatory skin conditions can be prevented when curcumin is used topically. The anticancer, anti-inflammatory and antioxidant effects of curcumin might be employed clinically for the control of carcinogenesis, rheumatism and oxidative-stress associated pathogenesis. Curcumin has been used clinically to overcome post-operative inflammation. Studies on the safety evaluations show that curcumin and turmeric both are well tolerable at an elevated dose without imposing toxic actions. So, both curcumin and turmeric have the ability for the manufacturing of modern medicine to treat several diseases (Nisha and Anbu, 2017).

Health Benefits

C. longa is employed to alleviate dental issues along with digestion problems including pain or discomfort in the upper abdomen and acidity, gas, ulcers, as well as indigestion. Furthermore, it reduces the hallucinogenic effects of hashish and other psychoactive drugs (Fuloria et al., 2022). *Curcuma longa* as a medicinal herb has a background to be used in medicine in view of the fact that it has anti-inflammatory, anticancer antimicrobial, antioxidant together with analgesic characteristics. Turmeric possesses two classes of secondary metabolites i.e. curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) and the other is turmeric essential oils (TEO). Turmeric's active constituent, curcumin is highly pleriopiotic molecule. Curcumin acts as antimicrobial agent against various strains of viruses, bacteria and fungus and works by targeting their membrane efficiency. On the other hand, it works against different types of cancers by targeting molecular markers. Moreover, this constituent also demonstrates effective results against a number of diseases such as neurodegenerative diseases and rheumatoid arthritis. It can also restrain cataractogenesis induced by selenium and ionizing radiations. Curcumin may target different signaling pathways. It assists to cure different types of cancers such as pancreatic, gastric, prostate, endometrial, lungs, ovarian, leukemia, ovarian and oral cancer. Treatment like chemotherapy and radiotherapy are considered effective for cancer. But medicinal herbs have the ability to treat threatening diseases. Medicinal effects have also been demonstrated in diseases like neurodegenerative diseases, cataract and musculoskeletal pain. Curcumin has less solubility, stability and bioavailability. Researchers are now struggling to solve all these issues by modifying it and also checking it by combinational therapeutics. When curcumin is incorporated with piperine, ascorbic acid it provides more effective results. Numerous formulations are developed with the assistance of nanotechnology to reduce its size and to combine with nanoparticles to make it more efficient and useful (Gul and Basheer, 2016).

In Ayurvedic medicine, turmeric is a widely known remedy for a number of respiratory problems (for example, allergy, asthma and bronchial hyperactivity), liver disorders, diabetic wounds, cough, sinusitis and runny nose (Prasad and Aggarwal, 2011). Turmeric appears to have hepato-protective effect just like silymarin. The hepato-protective action of turmeric is fundamentally an outcome of its antioxidant characteristics along with its potential to reduce the production of pro-inflammatory cytokines (Kumar and Sakhya, 2013). Oil of turmeric as well as ether and chloroform extracts incorporate antifungal activity. Crude ethanol extract also has antifungal effect. Oil of turmeric appears to be effective against *Fusarium moniliforme*, *Penicillium digitatum*, *Aspergillus flavus* and *A. parasiticus*. Healthy level of cholesterol is beneficial for the prevention of cardiovascular problems and other major health issues. High level of cholesterol can be harmful for health, therefore people are always exploring ways to reduce the level. Investigations have demonstrated that simply adding turmeric to season your food can markedly lower cholesterol levels in blood. Previous studies proposed that turmeric may aid in the prevention of atherosclerosis (building up of plaque which can block arteries and contribute to heart attack or stroke) (Verma et al., 2018).

Throughout the world, curcumin is well-known and utilized for numerous possible health benefits. Turmeric which has curcumin has been used in curries, presented as tea in Japan, used in China, used in cosmetics in Thailand, served in drinks in Korea, used as anti-inflammatory in Pakistan and India, and used as an antiseptic in Malaysia. In the USA, it is also used in chips, cheese, mustard sauces, and butter. Some different types of products at hand include curcumin capsules, ointments, tablets, soaps, power drinks, and cosmetics. The United States Food and Drug Administration classified the curcuminoids as "generally recognized as safe" products. Moreover, clinical evaluations have described great tolerability as well as safety profiles at doses varying from 4000-8000 mg (Abd El-Hack et al., 2021).

***Curcuma longa* for the Treatment of Respiratory Disorders**

Turmeric is one of the most powerful natural healers. It is used for the removal of mucus from throat. In China, India and other Southeast Asian countries, turmeric is a traditional remedy for the treatment of colds, asthma, and is applied as an ointment, paste, or poultice for scabies, insect bites, bruises, boils, and other skin lesions. Orally, turmeric is administered for other conditions, such as pain, bleeding, jaundice, diarrhea, rheumatic disorders, epilepsy, menstrual problems, and respiratory tract infections. A pinch or turmeric mixed with organic ghee is applied to the mucus lining of nose to stop the sniffles. It also ceases bleeding from nose, aids to clear the sinuses, re-establishes a more acute sense of smell, and assists to purify the brain and mind (Bhowmik et al., 2009).

Aside from this, the defensive actions of curcumin were examined in numerous pulmonary diseases like chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), asthma as well as pulmonary fibrosis in animal studies. Curcumin decreased the production of interleukin-1β (IL-1β), interleukin-8 (IL-8), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), matrix metalloproteinases-2 (MMP-2) and matrix metalloprtoeinases-9 (MMP-9) in mice and in A549 cells infected with influenza A virus. These cytokines aggravate acute lung injury (ALI). Curcumin @ 20 mg/kg orally markedly stops ovalbumin (OVA)-induced airway constriction and airway hyper-reactivity to histamine in sensitized guinea pigs. In the mouse model of asthma, curcumin @ 2.5 mg/kg and 5 mg/kg by intranasal route remarkably decreased bronchoconstriction. In addition to this, in rats, the extract of *Curcuma longa* (1.5 and 3 mg/ml) decreased tracheal contractile response to OVA and maximum response to methacholine. Along with this, it also reduced interstitial fibrosis. Standard therapy with curcumin capsule (500 mg BD daily for 30 days) in patients with bronchial asthma notably improved forced expiratory volume one second (FEV1) in contrast to the standard treatment. For bronchial asthma, curcumin is suggested to be used as an add-on treatment (Babaei et al., 2020).

Curcumin can reduce or prevent the inflammation of respiratory tract induced by bacterial or viral infections and also decrease the extent of inflammation of animal skin in preclinical studies. Chronic obstructive pulmonary disease (COPD) is a progressive airflow limitation disease associated with consistent inflammation of respiratory system, particularly in the airways and lungs. It can be a result of long-term exposure with gases and toxic particles like smoke or air pollutants. In animal model, the preclinical investigations showed that the anti-inflammatory activity of curcumin can decrease and relieve respiratory inflammation and oxidative stress occurred as result of exposure to soot or other pollutants of air. Over and above that, curcumin is helpful to reduce allergic asthma by suppressing the PPARγ/NF-κB signaling pathway in respiratory mucosa to hinder chronic obstructive pulmonary disease (COPD). Acute lung injury can result from the clinical application of radiotherapy or chemotherapeutic drugs and contribute to pulmonary fibrosis. Treatment with curcumin can lower the extremity of pulmonary fibrosis (Fu et al., 2021).

Former studies indicated the bronchodilatory as well as preventive effects of this plant and its components on respiratory diseases (Boskabady et al., 2020). The effectiveness of volatile oil of turmeric as an oral drug in the treatment of bronchial asthma was reported in a clinical trial. The administration of powder of turmeric by oral route notably alleviated cough and asthma. Also, fresh rhizomes appeared to be efficient against dyspnea, whooping cough and other coughs. In coryza and catarrh, the act of inhaling burning turmeric fumes results in abundant discharge of mucous and allows immediate relief. In bronchitis, the parched and powdered root is given. Acute lung injury (ALI) is a pulmonary disorder caused by bacteria, sepsis, or intestinal ischemia. Acute lung injury (ALI) is marked by an inflammatory response resulting in alveolar damage, edema, accumulation of neutrophil, including hemorrhage. The most severe form of it is acute respiratory distress syndrome. Curcumin manifests anti-inflammatory activity by the regulation of inflammatory cytokines (Satpathy and Parida, 2023). The antioxidant and anti-allergic activities of curcumin together with related compounds (such as glycosides, reductants and bis-demethoxy analogs) have recently been examined. Their outcomes recommend that the curcumin's hydroxy groups have an important function in exhibiting both the anti-allergic and antioxidant effects (Kurup and Barrios, 2008).

Since previous times, turmeric is extensively utilized in respiratory disorders. It is anti-purulent and anti-inflammatory in nature. It is very beneficial for the treatment of bronchial asthma. A fume of Haridradi dhumvarti (fumes wick) is provided in congestion and asthma. Majorly, the chemical components of turmeric (such as tumerones, curcuminoids, tetrahydrocurcumin, and curcumin) have an anti-asthmatic action. At times, it has been observed that boiled Haridra in milk (mixed with jiggery) is offered internally in cough and rhinitis. In cough and cold, a piece of lightly burnt rhizome is given for chewing. In sore throat, throat infection and catarrhal cough, decoction of rhizome is also used for gargle (Bhattacharjee et al., 2017).

Curcumin may have a role to play in the treatment of COVID-19 according to scientific research. The scientific evidence indicates that curcumin (the chief curcuminoid ingredient present in turmeric) may decrease inflammation and also provide protection against oxidative stress. It also possesses antifungal, antibacterial, wound-healing as well as hypoglycemic qualities. As part of a new method of drug development to enhance the bioavailability of curcumin, important technologies like nanoparticles, liposomes, adjuvants, along with phospholipid complexes are being investigated. It has been frequently utilized for sore throats, coughs as well as for respiratory disorders as a home remedy. It could be an outstanding immune-booster against SARS-CoV-2 therapy. The critical proteins of SARS-CoV-2 can be inhibited by turmeric spice. Therefore, it could be utilized as a medicinal drug against SARS-CoV-2 by the inhibition of important SARS-CoV-2 virus proteins (Jyotirmayee and Mahalik, 2022).

Asthma and allergy both are pro-inflammatory diseases, stemming from inflammatory cytokines. The rhizomes of turmeric have been used for a long time to treat asthma and allergy in Asia, particularly in India. In Thailand, it has been also utilized for the treatment of skin diseases in addition to itching. Curcumin's hydroxyl groups have shown to reduce the allergic reactions. Moreover, it possesses beneficial activity against asthma by extending the narrowed air pathway and enhancing the antioxidant capability (Kocaadam and Şanlier, 2017).

Toxicology of Curcumin

Curcumin has been stated as a "generally recognized as safe" compound by Food and Drug Administration (FDA). According to Joint FAO/WHO Expert Committee on Food Additives (JECFA) and European Food Safety Authority (EFSA) reports, 0-3 mg/kg is the adequate daily intake (ADI) value of curcumin. There are few worries about the relationship between inhibition of some enzyme working in metabolism of drug, potential impairment of DNA, chelation of iron and intake of curcumin. Anyhow, further research is required to be performed to investigate these relationships (Kocaadam and Şanlier, 2017).

Future Prospects of *Curcuma longa* L.

Turmeric possesses antioxidant, ant-inflammatory, anti-mutagenic, neuro-protective, anti-fibrotic and antibacterial properties. As a pharmacological agent, the prime drawback of *Curcuma longa* L. is its mediocre bioavailability when orally administered because of less intestinal absorption and fast hepatic metabolism through glucuronidation and instant excretion through bile and feces. In several animal models, the studies demonstrated that inhalation and intra-peritoneal injection have greater bioavailability and efficiency as compared to oral administration. Future studies directed toward understanding the action of turmeric on the visual circuit pathway of pulmonary disorders and the protective role of *Curcuma longa* L. might address the probable mode of action of herbal intervention against pulmonary disorders (Satpathy and Parida, 2023).

Conclusion

In Ayurvedic medicine, turmeric has been used since long time with many biological applications. In Ayurvedic medicine, turmeric is widely known therapy for a number of respiratory problems (for example, allergy, asthma and bronchial hyperactivity), liver disorders, diabetic wounds, cough, sinusitis and runny nose. Curcumin can be recognized as a potent curative agent for a number of health problems like inflammatory conditions and many types of cancer. As a result, its therapeutic potential is a matter of great interest. Over the last 50 years, the safety, efficacy and pharmacokinetics of curcumin have been studied widely in clinical evaluations. The results from many clinical studies indicated that curcumin may be effective for the prevention and treatment of a number of diseases. Curcumin is less costly than drugs and considered a safe natural product. Curcumin has been shown in preclinical investigations to lower the extent of inflammation in animal skin as well as prevent or minimize respiratory tract inflammation induced by bacterial or viral infection. The main obstruction in using curcumin as a therapeutic agent is its limited systemic bioavailability, but researchers are trying to discover the most effective method of application.

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Chapter 49

Immunostimulation and Stress Reduction in Farmed Fish Fed Herbal Extracts

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ABSTRACT

Given the rapidly expanding aquaculture industry, where intensive culture practices are used and stress related to exposure to diseases leads animals with decreased immunity against pathogenic organisms,, mutualistic bacteria should be considered as potential probiotic agents in commercial fish. Finally, Immune stimulant prophylactic and strategic agents to enhance the health product quality of fish. In this chapter, the mechanisms of action that allow herbal extracts to exert beneficial properties in farmed fish are summarised. These immunomodulatory properties of SCFAs include interactions with immune cells and their receptors, regulation gene expression as well as signaling pathways or the modulation of gut microbiota and intestinal immunity. They help to boost both innate and adaptive immune responses, as well as regulate age-related stress-induced physiological consequences. The practical applications in aquaculture are highlighted, including diatary supplementation to prevent and manage diseases/structural adjust during stressful periods/integrate with other health strategies. This publication contains case study examples that demonstrate effectiveness in survival, immune measurements and stress markers across diverse farmed species. These challenges are in terms of variability in bioactive content, potential interactions with feed ingredients and medications as well regulatory acceptance (and consumer acceptance). Additionally, novel sources for herbal immunostimulant development and promotional strategies in terms of both synergism with other categories of stimulants essentially combined natural adjuncts are focused. We provide a review of the potential benefits, in stimulation and stress mitigation terms, that herbal extracts offer as natural sustainable alternatives to be used for producing healthy fish under improved welfare conditions together with enhanced productivity.

KEYWORDS		
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INTRODUCTION

Importance of Maintaining Fish Health in Aquaculture

Maintaining the health of farmed fish is crucial in aquaculture operations for several reasons:

1. Economic Loss: Diseases and poor health status may cause economic losses in terms of low growth, high mortality rate and increase cost to treat (Naylor et al. 2023).

Contribution to global food security: Aquaculture plays a vital role in the world's growing demand for safe, nutritious and sustainably produced food by providing highly digestible proteins (Chary et al. 2024). The rationale here is that you need to have a supply of fish products in order for them to meet the ever-growing demand which can only be built and maintained through maintaining good health.

Environmental sustainability diseased fish can pass illness to wild stocks of fi9sh which could have a disruptive effect on the ecosystem (Satkar et al., 2024). If fish disease is not managed properly, it may threaten the whole aquatic environment.

Impacts of Stress and Disease on Fish Productivity

Key statistics on aquatic animal health and stress in regard to diseases can take a heavy toll of fish farm productivity:

1. Diminished growth rates: Stress and disease can discourage your fish from growing to their maximum size (Sadler et al., 2024). This may cause low yields and economic loss for fish farmers.
2. More deaths: This can lead to diseases and more fish mortality which decrease the number of fishes in general bestowed on increased production (Assefa and Abunna 2018).
3. Poor feed conversion: Fish which are stressed or unwell may have a reduced appetite and poor feed conversion, resulting in suboptimal growth İnd increased production costs (Mateus et al. 2017).
4. Streses and diseases can also have adverse effects on reproductive performance of spawning females with potential impact on the availability of good quality ova/larvae for restocking (Rato et al. 2018).

Potential Benefits of Herbal Extracts as Feed Additives

Using Herbal Extracts As Feed Additives in Aquaculture have attracted the attention because:

1. Immunostimulatory properties: Different plant-related compounds like polysaccharides, flavonoids and alkaloids are proven to stimulate the immune response of fish which leads in increasing resistance against diseases (Mariappan et al. 2023).
2. Antioxidant and anti-inflammatory: Plants containing a great amount of antioxidants (e.g. polyphenols) could protect fish against oxidative stress, inflammation that leads to the promotion of health in these animals (Akbari et al. 2022).
3. Growth promoter: Several herbs reported to induce growth in different fish species by enhancing feed efficiency, nutrient utilization and regulating growth parameters (Saleh et al. 2018).
4. Local stress reducers: Some plant extracts may be adaptogenic, allowing the fish to better handle stressful conditions and maintain homeostasis all along (Kamal et al. 2017).
5. These plant compounds have shown to possess antimicrobial and antiparasitic properties, which can be useful in the prevention of diseases into aquaculture (Mariappan et al. 2023).

However, it is worth mentioning that the effectiveness and safety of herbal extracts as feed additives are affected by different factors such as plant sources, extraction methods or/and fish species. However, just like with any natural compound used in aquaculture operations samples that truly demonstrate efficacy must be proven under the guideline of proper scientific research and regulatory scrutiny

Fish Immune System and Stress Response

Overview of the Fish Immune System (innate and adaptive)

1. The fish immune response is a sophisticated and complex network of cells, tissues and molecular mediators that interact in an interconnected system to protect the organism from pathogens crossing through body barriers while keeping homeostasis. It consists of two interconnected branches, one belonging to the adapted immune system and another from the innate immune System (Mokhtar et al. 2023).

Innate Immunity

- Physical barriers: The skin, scales and mucus are physical barriers that keep pathogens from entering the body (Reverter et al. 2018).
- Cellular components: phagocytic cells including macrophages and neutrophils that engulf pathogens; non-specific cytotoxic cells, such as natural killer (NK) cells, which kill infected or malignant host-cells (Mukherjee and Ghosh 2016).
- The humoral components: complement system mainly composed of different protein, thereby used for opsonization tagging the pathogenic proteins with phagocytosis and they may directly lyses them. Innate immunity also involves antimicrobial peptides, such as defensins and cathelicidins that are effective in their ability to disrupt microbial cell membranes (Hoseinifar et al. 2020).

Adaptive Immunity

- Adaptive Immunity (Humoral)- Antibodies(Immunoglobulins) from B- cell to neutralize pathogens or target them for killing (Abós et al. 2020).
- Recall the Different Types of Immunity: This type includes T lymphocytes, which include cytotoxic t cells and helper t cells (Cao et al. 2023).
- Initiation: Adaptive immunity generates immunological memory, which future encounters with the same pathogen can invoke in a rapid and vigorous response (Yamaguchi et al. 2019).

The adaptive and innate immune systems interact such that the first system provides rapid but non-specific responses, while the second one offers specific reactivity with long-lasting memory.

Stress Physiology and the Hypothalamic-pituitary-interrenal (HPI) Axis

In fish as in other vertebrates, the HPI axis is the main neuroendocrine system involved in stress responses. Or rather, it includes a dance between the hypothalamus and pituitary gland up to some interrenal cells (which are basically adrenal glands).

Activating the Stress Response

The brain senses stressors that is changes in the environment or handling of infection and releases corticotropin-releasing hormone (CRH) from hypothalamus (Yıldız and Seçer 2017).

Pituitary Involvement

The hypothalamus then produces corticotropin-releasing hormone, or CRH that circulates in the blood to stimulate the pituitary gland to release adrenocorticotropichormone (ACTH) into system (Lu et al. 2022).

Interrenal Cell Response

In addition, ACTH stimulates the interrenal cells of head kidney (which is analogous to adrenal gland in mammals) for synthesis and secretion of the principal stress hormone cortisol by teleosts (Lu et al. 2022).

Cortisol Effects on Your Body

Cortisol is important for regulating numerous physiological processes such as metabolism, osmoregulation and immune function which potentially help the fish to deal with acute stressors (Tort and Balasch 2022).

Even though the HPI axis is necessary for proper stress responses, its excessive or chronic activation can have deleterious consequences; i.e., immunosuppression and growth inhibition

Effects of Stress on Immune Function and Disease Resistance

2. Given the devastating effects of stress on the immune system, it is clear that fish must build up internal suboptimal responses and predispose themselves to pathological processes (Kumar et al. 2022).

Acute Stress Effects

- In general, acute stress can augment aspects of innate immunity such as phagocytic activity secretory potential of antimicrobial peptides and leukocyte mobilisation.
- This acute intensification is considered a temporary short-term boost that the organism provides itself due to evolution in order for it to anticipate any damages or infective health situations affiliated with stressful experiences.

Chronic Stress Effects

- Chronic stress, when persisted for an extended period or chronic lead to reduced disease resistance and can suppress both innate and adaptive immune responses.
- High levels of cortisol suppress lymphocyte proliferation, decrease antibody production and reduce cytokine expression, all leading to an impaired adaptive immune response.
- The balance of pro-inflammatory and anti- inflammatory cytokines can also be disrupted by chronic stress, thus increasing vulnerability to infections as well as hyperinflammatory conditions.

Increased Disease Susceptibility

- Stress-induced immunosuppression could render fish more susceptible to viral, bacterial and parasitic infections, thus having negative effects on their health and productivity.
- Chronic stress also can increase the susceptibility to infections and decrease the ability of your immune system to clear pathogens.

Hence, in aquaculture settings it is of utmost importance to deal with the stress load and strengthen disease defense mechanisms among farmed fishes, which may help improve quality of stock and prevent outbreak development due compromising immunity.

Herbal Extracts and Their Bioactive Compounds

Types of Herbs and Spices used as Immunostimulants (garlic, turmeric, ginger, etc.)

Garlic (Allium sativum)

Sulfur-containing compounds, such as allicin in garlic (Gar.any.sativum L), and its immune effect has been widely studied these days are being paid attention to for their potential application against bacterial diseases in different fish species like trout (Valenzuela-Gutiérrez et al. 2021; Abozaid et al. 2024).

Turmeric (Curcuma longa)

To have immunostimulant, antioxidant and anti-inflammatory activities curcumin has been described as the major curcuminoid in turmeric against fish (Bhadra et al. 2024).

Ginger (Zingiber officinale)

These bioactive compounds known as gingerols and shogaols in gingers showed immunomodulatory and growth-promoting effects in aquaculture (Megbowon et al. 2024).

Other Herbs and Spices

- Astragalus (Astragalus membranaceus), Withaniasomnifera (Ashwagandha), Origanum vulgare (Oregano), Rosmarinus officinalis (Rosemary), and Echinacea purpurea have also been explored for their potential immunostimulant properties in fish (Dhama et al. 2018).

Classes of Bioactive Compounds (polyphenols, alkaloids, terpenoids, etc.)

Polyphenols: Flavonoids, phenolic acids and tannins are some of the polyphenolics in many fresh herbs and spices (Elumalai et al. 2020). These compounds exhibit antioxidant, anti-inflammatory and immunomodulatory properties that may improve immunity in aquaculture species.

Alkaloids: Alkaloids, such as berberine, piperine, and capsaicin, are nitrogen-containing compounds found in plants like goldenseal, black pepper, and chili peppers. Some alkaloids have demonstrated antimicrobial, immunostimulant, and growth-promoting properties in fish (Almarri et al. 2023).

Terpenoids: Terpinen, are present in a variety of herbs and spices like thyme, oregano, licorice as monoterpenes diterpens,d; triterpernes These compounds have been found to exhibit antimicrobial, antioxidant and immunomodulatory activities rendering them as potential candidates for use in aquaculture (Elumalai et al. 2020).

Further compounds: Other bioactive compounds are also found in spices and herbs such as; saponins, lectins, polysaccharides which may influence the immune system of fish due to their immunostimulant effect on other animals (Vijayaram et al. 2022).

Extraction Methods and Standardization

Water, ethanol, methanol and other types of solvents as well maceration and decoction are the most used systems regarding these herbal recipes. This has led researchers to investigate more advanced techniques, such as supercritical fluid extraction (SFE), ultrasound-assisted extraction and microwave-assisted extraction. Herbal extracts must be standardized to guarantee that they convey comparative quality assurance, safety and effectiveness. High-performance liquid chromatography (HPLC), gas chromatography–mass spectrometry (GCMS) and nuclear magnetic resonance (NMR) are used to detect the phytochemical profile of extracts. Standardization parameter can be the concentration of particular markers, total phenolic content or antioxidant activity et cetera. The bioactive constitution, and consequently the probable effects of a herbal extract are subject to considerable variations in relation with e.g. plant source; cultivation conditions; extraction methods or standardization processes applied. Robust characterization and rigorous quality control is required in order to ensure that herbal extracts can be incorporated reproducibly and safely into aquaculture feed formulations (Tangendjaja 2022).

Immunostimulatory Effects of Herbal Extracts

Modulation of Innate Immune Parameters (phagocytic activity, respiratory burst, etc.)

For instance in several fish species, many herbal extracts like garlic, ginger and turmerica have shown to stimulate phagocytic activity of macrophages as well blood neutrophils. In addition, the high phagocytic activity facilitates pathogen and cellular debris clearance associated with improved immune defense. Some herbal extracts are capable of triggering the respiratory burst activity in phagocytic cells to generate killing reactive oxygen species (ROS) and nitrogen species (RNS), which can eliminate pathogens that have penetrated into tissue. Astragalus membranaceus and Withania somnifera extracts were shown, for instance, to boost respiratory burst levels of fish cells. For example, some herbal extracts may lead to the induction of antimicrobial peptides such as defensins and cathelicidins which are important human immune response molecules acting against bacteria, viruses or fungi. For example, extracts from garlic (Allium sativum), ginger (Zingiber officinale) and oregano have been observed to stimulate the expression of certain AMP genes in fish (Kumar et al 2022).

Regulation of Cytokine Production and Inflammatory Responses

Cytokines are important small molecule intermediates that allow the immune system to produce and express itself more widely, but herbal extracts can tune various cytokine productions through their elaborated work. In the case methods have been robust in that extracts were able to stimulate pro-inflammatory cytokines, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF) α), what can include the additionally enhance entity inflammatory response recruiting immune cells necessary for conducting infection. More extracts can be anti-inflammatory through the control of inflammation mediators like prostaglandins and leukotrienes. Herbal extracts often possess high levels of polyphenolic components that serve as powerful antioxidants and anti-inflammatory agents, capable to counteract oxidative damage and excessive inflammation taking place in fish (Dziewulska et al. These effects, in turn, can promote immune homeostasis and protect tissues from damage by the chronic inflammatory responses that are common with age (Mokhtar et al. 2023).

Enhancement of Specific Antibody Production and Cellular Immunity

Certain herbal extracts have been documented to improve the production of certain antibodies (immunoglobulins) in fish, which suggests their ability to trigger humoral adaptive immune response. Extracts from Withaniasomnifera and Astragalus membranaceus have for example been found to enhance antibody titers in a number of fish species. A number of herbal extracts have shown the ability to modulate proliferation and activity of lymphocytes particularly T cells and B cells, integral components responsible for cellular immune adaptive responses. Plant derived extracts such as curcumin and gingerol induced T-cell proliferation, cytokine production improving cell mediated immunity in fish. Due to several factors such as plant source, extraction techniques used or whether the extracts were tested in vitro or in vivo; different fish species might show varied immunostimulatory actions of herbal usage. Moreover, the pathways responsible for these effects are likely modulated through extensive interactions between various bioactive compounds in extracts with an array of immunological components. More in vivo and in vitro studies are needed to reveal exactly how different herbal extracts modulate the immune activities of cultured aquaculture species (Zhang et al. 2020).

Stress-Mitigating Effects of Herbal Extracts

Antioxidant Properties and Reduction of Oxidative Stress

Most of herbal extracts are rich in antioxidant compounds, including polyphenols (e.g., flavonoids and phenolic acids), carotenoids and vitamins CandE which can scavenge free radicals and reactive oxygen species (ROS) thus alleviating oxidative stress in fish. Environmental stressors, pathogens or metabolic disturbances can cause oxidative stress inducing cellular damage and therefore compromising the immune function resulting in an increased risk of diseases. Efficacy of the Antioxidants in Herbal Extracts Several recent studies have demonstrated that herbal extracts with antioxidant potential such as turmeric, ginger and green tea reduce oxidative stress markers while enhancing activities/expressions of various antioxidant enzymes systems in fish (Hoseinifar et al. 2020).

Modulation of Cortisol and other Stress Hormone Levels

In fish, cortisol is the major interrenal stress hormone which could be synthesized and secreted into circulation from their respective organ in response to a range of osmoregulatory perturbations. Some herbal extracts have shown to highly regulate/plain cortisol in fish, whether by reduction or maintenance within normal levels. For instance, extracts from Withaniasomnifera (Ashwagandha) and O.sanctum(Tulsi) have been found to reduce cortisol levels in fish during stress (Nazeemashahul et al. 2024).

Besides cortisol, certain plant extracts have also been found to alter the levels of other stress-related hormones like catecholamines (epinephrine, norepinephrine) which play a role in fight-or-flight. In such a condition, herbal extracts by modulating hormones of stress response may help in the maintenance of physiological homeostasis and thwart disadvantageous consequences brought on chronic stress (Ciji and Akhtar 2021).

Influence on Metabolic and Behavioral Responses to Stress

Metabolic changes, such as shifts in energy metabolism, protein synthesis and immune function are common responses to stress-induced physiological trade-offs in fish. Herbal extracts, by influencing various metabolic parameters like glucose levels, lipid profile or enzyme activities had the capacity to counteract these changes induced due to stress as observed in one of our previous studies.

Under stressful conditions, fish exhibit abnormal or maladaptive behaviors including decreased feeding activity erratic swimming and increased aggression. The aforementioned properties could reduce stress-induced behavior changes in fish by improving their overall well-being and anxiolytic (anti-anxiety) effects, but more relevant investigation is needed. For instance,net anxiolytic effects on fish have been reported for various phytopharmaceuticals, including the extracts of Valeriana officinalis (Muniandy 2018; de Mendonça et al. 2022).

Note, herbal extracts from different plant sources as well the method of extraction in addition to dose and type NOS for fish species may cause differences in stress-mitigating properties. Furthermore, the actions of these extracts on stress-induced changes in neurochemistry might result from intricate interactions between a variety of bioactive compounds within them and numerous physiological systems implicated in mediating the effects triggered by stress. In vivo and in vitro studies need to be conducted based on proper experimental design which are essential to know the activities of particular herbal extract against stressors in aquaculture species. These immunomodulating properties likely stem from the polyphenols, flavonoids and terpenoids making up the bioactive compounds found in herbal extracts that may act directly on immune cells or receptors(nodes sensei). These interactions can vary the immune response fish (López et al. 2020).

Polyphenols can promote the growth and function of immune cells, such as lymphocytes (antibody producing B-cells), macrophages, and neutrophils. Cytokines Cytokines, signaling molecules that mediate the adaptive immune response , might be influenced by flavonoids. Phagocytic activity of immune cells, an essential step for purging pathogens, can also be regulated by terpenoids. Gene expression and signal pathway regulation: Herbal extracts may regulate gene expressions especially responsible for the immune response, also altered stress-related pathways in fish (Ahmadifar et al. 2021).

Various plant products are known to elicit effects on activation of transcription factors including nuclear factor-κB (NF-κB) and activator protein 1 (AP-1), leading to modulation in the expression of various genes associated with inflammatory pathways as well as immune responses. HTAs may therefore act on the hypothalamic-pituitary-adrenal (HPA) axis, which can dial down cortisol levels_loan repayment_cc by exacting psychological stress. Many of the herbal compounds are able to interfere with these enzymes and decrease oxidative stress, inflammation through inhibiting cyclooxygenase-2 (COX-2) [levels]or inducible nitric oxide synthase(NO), as a response you can see decreased levels in inflammatory mediators Nhu et al. 2020; Zheng et al. 2022).

The gut microbiota is key to the health of fish and their immune function. Herbal extracts have the ability to influence and shape intestinal immunity through changing the composition, function of gut microbiota. One of the mechanisms through which certain herbal compounds can affect enteric dysbiosis is selective stimulation of beneficial gut bacteria, like lactic acid microbiota for a high-production profile in antimicrobial compound and immunological modulation. Herbal extracts can enhance intestinal functions, maintain the balance and function of the gut barrier to prevent pathogen invasion and toxic translocation in vivo, which helps improve local inflammatory response in intestine tract so as it promotes active mucosal immunity. In addition, some herbal compounds can modulate the production of antimicrobial peptides (AMP) and cytokines in intestinal mucosa, so as to enhance local immune function (Zimmermann and Wagner 2021).

Factors Influencing Efficacy

Factors affecting the potency of herbal extract in farmed fish as immunostimulants and stress-reducing agents are:

Fish Species and Life Stage

Fish are different and each responds differently to the same herbal extract, depending on its physiology, immune system and metabolism. This, in addition to the life stage of the fish also plays a role on how herbal extract effectively works. Example: Immunostimulatory effects of herbal extracts from Phyllanthus amarus and Ocimum sanctum in Asian sea bass (Lates calcarifer) against Vibrio harveyi. They found that the herbal extracts increased immune parameters, i.e., respiratory burst activity and complement activity--but variably between fish species (Subramani et al. 2023).

Dosage, Duration, and Administration Method

The effectiveness of herbal extracts can also be highly dosage and duration dependent. Taking too little or not taking it for long enough may have no consequence, but if you took too much of Benadryl Tablets and also had damage as a result further treatment is likely to be advised (Zhu 2020). To illustrate, effects of the herbal extract Withaniasomnifera in rohu (Labeorohita) on stress and immune responses were evaluated by feeding through diet. A dietary supplementation of W. somnifera extract was found to significantly elevate different immune parameters (e.g., respiratory burst activity, serum lysozyme, and antimicrobial complement), accompanied by reduced stress indicators as measured through cortisol levels (Gupta et al. 2021; Trivedi et al. 2024).

Environmental Conditions (temperature, salinity, etc.)

The effectiveness of the herbal extracts might be influenced by environmental factors, as temperature, salinity and water quality have effects on fish physiological state and their immune response. As an example, the effects of dietary supplementation containing herbal extract (Andrographis paniculata) on immune response and disease resistance of Asian seabass (Lates calcarifer) exposed to different salinity levels. They concluded that the herbal extract was able to improve immune parameters and enhance disease resistance against Vibrio parahaemolyticus infection in both freshwater reared fish but depending on a dose-dependent variation with brackish water condition (Susanto et al. 2024).

The performance of most herbal extracts as immunostimulant and stress reducers in farmed fish could be varied due to the reasons like type of herbs, species or life stages of fishes treated, dose rate administered and duration treatment made. These factors may influence the beneficial effects of herbal extracts in aquaculture practices which should be carefully taken into consideration.

Practical Applications and Case Studies

Research reports varying from in vitro to experimental studies have been reported which focus on dietary supplementation of herbal extracts for improved disease resistance and immune response, overall performance etc. in various farm raised fish species. Efficacy ofdietary supplementationofherbal extracts A.indica and O. sanctum toprotect goldfish (Carassius auratus Linnaeus, 1758) against Aeromonas hydrophila infection The results showed that the addition of these plant extracts to fish diets significantly increased survival rates, hematological parameters and blood activities (serum lysozyme activity, antiprotease activity), superior metabolic and hematic responses including serum respiratory burst) compared to those fed with this basal mixture without plants (Semwal et al. 2023).

The potential of herbal extracts for fish stress reduction in handling, transport and other aquaculture practices have been explored. The impact of supplementation with the herbal extract, Phyllanthus amarus on stress and immune responses in grey mullet (Mugil cephalus) subjected to transportation injury. The study indicated that in fish receiving diets with P. amarus extract, lower cortisone and glucose levels but higher respiratory burst activity, lysozyme activity as well as complement activities were detected relative to the group control, indicating the stress reducing properties of this herbal supplement along with its immunomodulatory effects against a viral infectionlehemomediatedimmunity (Viral Nervous Necrosis) (Mariappa et al. 2023).

The herbal extracts have immense practical applications and case studies that show herbals as effective immunostimulants and stress-reducing agents in aquaculture. Nevertheless, it has to be considered that the efficacy of herbal extracts depends on fish species as well as dosage level and influence significant differences due application method or environmental conditions. Hence, additional studies and optimization are needed to exploit the properties of herbal extracts best in individual aquaculture scenarios. Bioactive compound content and standardization issues: Herbal extracts are mixtures of different complex bioactive compounds, they can vary greatly due to differences in plant species, geographical locations, agroclimatic conditions and extraction methods. Such variance can translate to differences in the extracts, which may be difficult for them to standardize as well as that they put on stringent quality control measures. In order to solve this issue, much work is being accomplished about identifying and quantifying the bioactive ingredients leading to health effects of herb extracts. Standardization protocols and analytical techniques such as high-performance liquid chromatography (HPLC) and mass spectrometry are discussed for herbal extracts to identify the gross chemical composition (Sarmiento et al. 2024).

In addition, scientists are trying to adopt modern biotechnological strategies using plant cell culture techniques and metabolic engineering that can help produce uniform as well as standardized herbal extracts with clear profiles of these bioactive compounds.

Consumers and regulations oversee the use of herbal extracts in aqua feeding. The use of herbal extracts as feed additives or therapeutic agents needs a lot long term safety and efficacy data which may be only satisfied by some regulatory agencies. One area of concern in some regions may be the possibility of contaminants or residues in herbal extracts, and the importance for that information to appear on labels among other disclosures. A final factor to consider is consumer acceptance; some consumers may be wary of the use plant-based additives in farming an animal product, whilst others may view them as naturally derived preferred to synthetics. Meeting these challenges requires a coordinated effort by researchers in public health, regulatory agencies and industry partners. It is necessary to conduct safety and efficacy trials, allow standardization methodologies as well use lap transparency for communication with consumers prior herbal extracts get approval from regulatory bodies especially in public perception (Throne-Holst 2023).

These emerging trends and future directions explore the diverse efforts to identify new sources of herbal extracts, design combination schemes for increased efficacy, and take benefit from advanced omics technologies in order to better comprehend the underlying mechanisms. These developments will be effective in the novel application of herbal extracts that can improve fish health, disease resistance and overall productivity in aquaculture.

Potential Applications in Sustainable Aquaculture

Utilization of herbal extracts in aquaculture supports sustainable and eco-friendly approach. Natural compounds represent an effective means of supplementing synthetic immunostimulants and antibiotics, reducing the likelihood(s) for promoting AMR (antimicrobial resistance), as well as environmental contamination. The inclusion of herbal extracts in aquafeed and health management practices can aid to overall industry sustainability by enhancing fish health, welfare coupled with reduced reliance on synthetic compound utilization.

Future Research Opportunities and Collaborations

Great strides have been made in comprehension of the role of plants extracts for aquaculture but some issue area is there to be solved. This will involve issues such as variation in bioactive compound content and the requirement for standardization, potential interactions with other feed ingredients or medications, and regulatory considerations along with consumer acceptance.

Future research should focus on:

1. Identifying the active principles accountable for herbal extracts therapeutic effects and devising the standardization protocols.
2. Examining interactions between herbal extracts and other feed inputs or medications in current use for aquaculture.
3. Diversifying clinical safety and efficacy studies to bolster regulatory clearances beyond proven food-safety with consumers.
4. Development of new herbal extracts and sources, combining with other immunostimulants as well health management options.
5. Unscrambling clinical pharmacology utilizing omics-centric strategies to define the molecular constituents mediated by herbs contributing to immunomodulatory/anti-stress effects.

To move this subsector of sustainable aquaculture forward, interdisciplinary collaborations between academics and industry stakeholders from private sectors as well regulatory agencies will also be essential for a broad scientific background of herbal extracts applications. These partnerships can enable the sharing of information to deal with relevant issues and make recommendations for proper usage of these natural compounds in boosting fish healthiness production.

Summary of Key Findings

Utilization of moderate plant extracts to boost the fish immune response and lower resistance in farmed-freshwater fishes has gained much attention because it is thought to help improve health conditions, production capacity. Studies have shown that herbal extracts can interact with immune cells and receptors, modulate gene expression and signaling pathway of cellular function or regulate gut microbiota alongside intestinal immunity. These are examples of the mechanisms by which herbal extracts provide a part of their immunomodulatary and stress mitigating effects. In a wider perspective, many are the investigations entailing practical applications of herbal extracts for dietary supplementation within aquaculture to prevent and cope with diseases in addition to stressful situations (e.g., handling, transport) as well as their association with other health management strategies. Studies include case reports of enhanced survival from bacterial infections, improved immune parameters and reduced stress indicators.

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Chapter 50

Green Pharmacy: Botanical Remedies for Animal and Human Well-being

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ABSTRACT

Over 5000 years, herbs have been used for healing spans with over 85,000 plant species identified for their medicinal properties. Traditional systems such as Ayurveda and Traditional Chinese Medicine (TCM) have long used botanical remedies for holistic health management. Currently, approximately 75% of the global population is utilizing herbal remedies. Despite challenges in regulatory frameworks and standardization due to integrating botanical drugs into modern healthcare, their potential benefits in managing chronic conditions, and the rising demand for sustainable practices. However, traditional medicine contains essential botanical remedies but faces ecological threats from overexploitation. Ayurveda and TCM systems share common philosophical approaches to health which focus on balance within the body. Comparative studies show both common and unique ways by using plants, emphasizing the need to preserve ethno botanical knowledge. This preservation is crucial for maintaining cultural heritage and biodiversity. Plants have been essential in drug discovery and are serving as sources of bioactive compounds. The increasing herbal medicines demand is driven by their affordability and potential sustainability. However, research on plants such as ginseng emphasizes the need for rigorous quality control to ensure the efficacy and safety of herbal products. Herbs are also used in animal health practices to address concerns over synthetic drug residues and resistance. Worldwide acceptance of plant-based medicine remains to propagate as well as is supported by scientific validation of effective treatments. Developing countries are rich in medicinal plant species that are crucial in meeting global pharmaceutical needs. Ongoing research and regulatory efforts aim to ensure the efficacy, safety and sustainability of herbal remedies used in the healthcare of both humans and animals.

KEYWORDS
Botanical remedies, Animal and human wellbeing, Ayurveda, Traditional medicine

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INTRODUCTION

Humans have been utilizing herbs for healing purposes for many centuries and the historical records indicate that the medicinal use of natural products dates back at least 5000 years (Jamshidi et al., 2017). However, western medicine contains a shorter history duration a few hundred years. Currently, the medicinal properties of more than 85,000 plant species worldwide have been identified. The WHO predicted certain herbal remedies and nearly 75% all over the world population consumes for medicinal purposes (WHO, 2019). Herbal medicines are defined through the Food and Drug Administration (FDA) and encompass substances extracting out from garden-fresh as well as from dried out floras and plant fragments and extracted out as collective chemical constituents of plant foundation, macroscopic fungi, algae also their amalgamations (Khan and Abourashed, 2011). These drugs are formulated as solutions, powders, tablets, capsules, topicals, injectables, etc (Dahab, 2020). Consequently, this drug category can exhibit numerous characteristics including composite mixes as well as absence of well-defined bio-active components (La Mesa et al., 2020)

Historically, natural products have played integral roles in various native medicinal methods like, (TCM) Traditional Chinese Medicine and also Indian herbal medicines (Ayurveda) (Patwardhan et al., 2005). The empirically-dependent treatments stay used to inhibit or treat holistically particular ailments and their signs which offer complementary alternatives to modern medicine (Lee et al., 2018). However, a significant portion of scientific examination dependent on herbal medicines is underscored by current medical research happening during twenty first era that focuses on rejuvenation as well as global validation of their efficacy and safety (RH, 2015). Furthermore, standardized biomass and manufacturing processes are continuously being developed through innovative methodologies (Van dam et al., 2008). Humans have relied on nature for sustenance, shelter, and healing throughout recorded history and one of the oldest and most enduring forms of treatment is herbal medicine which highlights our deep-seated connection with the natural world (Lewis, 1996). Due to the increase in the population, individuals seek alternative and holistic approaches to health and wellness which is a noticeable resurgence of interest in herbal medicines in recent years (Salmon, 2022). Herbal medicine utilizes plants and plant extracts to treat various illnesses and promote overall well-being known as botanical medicine (Jamal, 2023).

With the rise of pharmaceutical drugs and advances in Western medicine, the popularity of herbal remedies gradually waned (Andrew, 2014). The numerous reasons driving the growing popularity of herbal medicine (Pan et al., 2013). The demand for sustainable and environmentally friendly practices is rising and has also contributed to the popularity of herbal medicines (Dubey et al., 2004). Despite pharmaceutical drugs being involved in complex chemical processes and producing waste herbal medicines rely on sustainable resources and have a minimal environmental footprint (Espro et al., 2021). In recent years, contemporary healthcare systems have accepted the herbal medicine (Mosihuzzaman, 2012). Furthermore, integrative medicine combines conventional medical practices with complementary therapies such as herbal medicine become increasingly prevalent in hospitals and clinics worldwide (Debas et al., 2011). The potential benefits of incorporating herbal treatments into comprehensive treatment plans are widely recognized by medical professionals for chronic conditions that may benefit from a holistic approach (Jamal, 2023).

The interest in herbal medicine resurgence does not signify a rejection of modern medicine but rather an acknowledgment of the evidence-based approaches to healthcare and the valuable contributions of both conventional (Cant, 2020). People are rediscovering their connection to the natural world and are exploring ancient remedies that have withstood the test of time by appreciating nature's therapeutic power (Jamal, 2023). Herbal medicine contains a fascinating history that examines the reasons behind its effectiveness and explores the diverse range of medicinal plants used across cultures (Li and Weng, 2017). Additionally, the incorporation of plant-based medication interested in up-to-dated healthcare live outs as well as considerations regarding potential interactions with prescription pharmaceuticals, and safety issues (Rivera et al., 2013). Whether well-being or a healthcare professional exploring enhanced alternative therapies by joining understanding and embracing the therapeutic potential of herbal medicine (Andrew, 2014). Herbal products are gaining widespread acceptance as valuable agents with various therapeutic properties and treatments for numerous conditions (Pan et al., 2013).

Natural herbs have been extensively used in treating and preventing various ailments and the accumulated knowledge has contributed to the development of new herbal remedies that offer health benefits with minimal or no side effects (Sofowora et al., 2013). This rich tradition spans different systems of medicine including traditional Indian, European, Japanese Kampo, traditional Chinese, and traditional Arabic (Ansari, 2021). These systems encompass not only herbal treatments but also pharmaceuticals derived from minerals and metals and substances derived from animals (Kapoor, 2010). Botanicals comprise plants and plant products containing active ingredients sourced from various plant parts or other plant materials that are formulated for medicinal use to treat diverse ailments (Tiwari, 2008). Since prehistoric times plants have been utilized as medicinal remedies due to their healing properties documented over millennia and are dating back over 5000 years to the era of ancient Sumerians who recorded their knowledge on clay tablets (Halberstein, 2005).

Botanical medicine plays a crucial role in outmoded as well as current therapeutic methods along with treatments like (TCM), flower essence therapy, naturopathy, aromatherapy, homeopathy as well as Indian herbal medicine system (Bone and Mills, 2013). Within numerous emerging nations, botanics fulfill essential healthcare needs are fulfilled by botanicals and with significant usage observed in Africa and Asia (Mudau et al., 2022). However, several drugs have been derived from botanical sources in modern medicinal practices such as Artemisia represents artemisinin, for malaria treatment they used annua, foxglove is used for cardiac glycosides for cardiac arrest and Galega officinalis is used for Isoamylene guanidine, that leads towards synthesis of metformes for diabetes treatment (Koul et al., 2017). In contrast, the combination underscores a growing recognition within the medical community of the efficacy and importance of botanical medicine (Talalay, 2001). Moreover, herbal or botanical sources offer natural products among the most popular supplements used due to their efficacy in treating various conditions that remain debated due to a lack of controlled studies (Khan and Ahmad, 2019). This chapter provides a review of the literature on the significance of botanicals by highlighting current challenges in this field and exploring opportunities for the advancement of botanical drugs with a particular focus on market dynamics, regulatory frameworks, and modernization efforts.

Botanical Remedies in Traditional Medicine

Herbal medications are vital to treat various ailments such as millennia which are playing a crucial role in promoting health and well-being (Sen and Samanta, 2015). However, a significant increase in global demand for plant resources and resulted in the endangerment of various plant's germplasm resources because of ecological destruction and degradation (Ogwu et al., 2014). This can lead to a gradual decline in agronomic yield as well as source of various species and studies are focusing on therapeutic herbs to recognize species by same phytochemical constituents or else active ingredient contented by facilitating qualitative and quantitative substitution (Moyo et al., 2015). Moreover, these global efforts are essential for the sustainable utilization and protection of medicinal plant resources that face extensive exploitation driven by high commercial demand (Chen et al., 2018).

World Health Organization defined the outmoded medication as encompassing awareness, and abilities based on indigenous notions, opinions along with capabilities from various values (Ogwu et al., 2014). However, this knowledge is utilized for maintenance of well-being as well as inhibit, identify, recover, give bodily as well as cerebral ailments (George, 2024). Moreover, many scholars have extensively reviewed and compared Ayurveda and TCM and are noting their distinct but lengthy traditions in utilizing medicinal plants for therapeutic purposes (Koul et al., 2017). These systems share many botanical drugs that are employed for similar or different therapeutic applications using varied processing methods (Chen et al., 2016).

Ayurveda and TCM shared a similar philosophical approach to treat diseased conditions which are considered humanoid body's components and the fundamentals of the world (Gasseholm, 2012). The humanoid body consists of basic around which world's penta components (water, metal, earth, wood, and fire) operate in balanced yang and yin state (Chopra and Doiphode, 2002). In Ayurveda, the humanoid body stays supposed that it consists of 3 powers (tridoshas) — vatta, pitta, and kapha — each governed by two elements from the pancha mahabhutas (Patwardhan et al., 2005). Furthermore, physiological balance and various processes are regulated within the body by these triodes' maintenance (Patwardhan et al., 2005; Kim et al., 2011). Several aspects can provide deeper intuitions into earliest medical texts as well as their underlying principles through detailed comparative studies (Sox et al., 2024). Plants with similar therapeutic activities but belonging to different species within the same genus can serve as substitutes for each other and such investigations are valuable (Stefano, 2020). For instance, various species of Aconitum various species found in India and China share similar medicinal usages then species such as Aconitum carmichaeli Debx (Kakkar et al., 2023). Cultivated widely in China could substitute for endangered species (Rawat et al., 2016). The given example demonstrates how knowledge about medicinal flora from different traditional systems can mutually advantage every system (Sarivastava and Vikash, 2010).

Traditional Chinese Medicine (TCM) and Ayurveda contain distinct diagnostic principles and guides for the use of different herbs for similar therapeutic purposes. Moreover, TCM and Ayurveda used various species but for varying therapeutic effects (Patwardhan et al., 2005). Such as, rhizome of *Curcuma longa* L. is known as Jianghuang in Chinese and is used in TCM to promote blood circulation, stimulate menstruation, and alleviate pain (Jaiswal and Liang, 2016). However, *Curcuma longa* L. (Haldi, and Haridra in Sanskrit) is valued in Ayurveda for treating respiratory issues, rheumatism, inflammation, menstrual problems, colds, coughs, and skin (Patwardhan et al., 2005). The leaves of Haridra are traditionally used to aid digestion, reduce bloating and gas, and as a culinary flavoring agent and are noted for their antimicrobial properties (Arutselvi et al., 2012). Similarly, Asparagus roots of different species are employed in both TCM and Ayurveda for diverse therapeutic purposes (Jaiswal et al., 2016).

Herbal medicines hold enduring efficacy and yet their widespread adoption for disease management remains limited despite their potential (Bone, 2013). Ethnic and rural communities play a crucial role in preserving ancient medicinal knowledge associated with plants and preventing it from fading into obscurity (Block et al., 2015). Revitalizing herbal medicine requires its integration into mainstream modern healthcare by ensuring adherence to rigorous safety and efficacy standards contains significant challenges (Yin et al., 2013). Additionally, the natural products are continued to serve as inspiration for drug discovery with nearly 80% of drug molecules having origins in natural sources or being natural product derivatives (Payyappallimana, 2010). However, approximately 50% of newly approved drugs have been based on natural compounds since 1994 and are underscoring the pharmaceutical importance of plant-derived substances (Gielecinska et al., 2023). Herbal products also serve as popular nutritional supplements and offer essential nutrients like vitamins, minerals, micronutrients, and antioxidants that are deficient in the diet (Bennett and Sturmberg, 2018).

Scientific Research on Botanical Remedies

Plants are fundamental in pharmacotherapy and have served as a rich source of bioactive compounds essential for drug discovery since the 19th century (Suntar, 2020). However, the pharmaceutical industries have shifted towards synthetic and combinatorial chemistry-based libraries for high-throughput screening and a significant proportion of new drug objects approved between 1981 and 2010 were derived from or inspired by natural products (Sarivastava and Vikash, 2010). In addition, plants form the basis of herbal medicines known as phytopharmaceuticals or botanicals due to their role in drug discovery as shown in Table 1 (Suntar, 2020). Herbal preparations are vital for traditional medical systems worldwide and in regions where conventional medicine is inaccessible to 70% of the population and are making herbal remedies their primary healthcare option (Anand et al., 2019). Traditional systems like Ayurvedic medicine in India, Kampo in Japan, Traditional Chinese Medicine (TCM), and Unani in the Middle East and South Asia are widely relied upon (Bennett and Sturmberg, 2018). The herbal treatments' affordability, local availability, and potential sustainability make them increasingly relevant amidst rising healthcare costs and all are explained in Table 2 (Bhusnure et al., 2019)

In the contemporary herbal historical period there has been a steady global increase in demand for traditional herbal medicines and botanicals over the past two decades, even in industrialized nations (Suntar, 2020). Due to their complex composition, herbal extracts and mixtures are believed to interact synergistically, enhancing solubility, and bioavailability, and potentially influencing multiple disease pathways, which is advantageous in chronic, multifactorial diseases (Balunas et al., 2005). Although proving these effects experimentally is challenging, the popularity of herbal medicines continues to rise. Many traditional medical systems aspire to integrate into mainstream healthcare by necessitating evidence of safety, efficacy, and quality that meets public health insurance standards (Ogwu et al., 2014). However, many challenges are posed by regulatory variations globally for herbal medicinal products. Herbal products are also marketed across countries as dietary supplements, functional foods, cosmetics, or medical devices, and each category is subject to different regulatory frameworks (Thakkar et al., 2020). For instance, dietary supplements are regulated under the Dietary Supplement Health and Education Act (DSHEA) in the USA which allows marketing without premarket approval based on efficacy and safety data required for medicinal products. Despite drugs being dietary supplements cannot make health claims but can use structure-function claims and are often ambiguous (Hernandez et al., 2004).

Table 1: Immune mechanisms of herb-induced Immunostimulation (Suntar, 2020)

Herb	Mechanism of immune stimulation
Spirulina	• Increases NK cell activity. • Activates Toll-like receptors and increases NK-mediated IFN secretion via elevated IL-12 and IL-18 • Increases gene expression of cytokines IL–8, MCP-1, MIP-1α, MIP-1β, IP-10, TNF–α, IL-1β, and the enzyme COX-2. • Acts on Th1 cells and increases production of Th1 cytokines, such as IL-2 and IFN-γ.
Aphanizomenon flos-aquae	• Activates NK Cells. • Activates NF-kappa B and increases TNF-α and IL-1β expression
Chlorella	• Increases TNF-α and IL-1β expression. • Augments Th1 cells response. • Increases NK cell activity and production of IFN-γ and IL-12.
Echinacea	• Increases extracellular cytotoxic effects of macrophages to similar levels compared to IFN-γ. • Increases production of various interleukins, including IL-1, IL-10 and TNF-α. • Stimulates NK cell activity and increases antibody-dependent cell cytotoxicity.
Alfalfa	• Novel epitopes created by L-canavine-laden aberrant proteins trigger autoantibody production or cytotoxicity.

Table 2: Reports of activation of autoimmune skin disease following ingestion of herbal supplements (Bhusnure et al., 2019)

Herbal supplement	Autoimmune skin disease
Food supplement containing *Spirulina platensis*, *Ginkgo biloba*, and ginseng	Pemphigus vulgaris
supplement containing *Spirulina platensis, Alphanizomenon flos-aquae*, organic cayenne pepper, and methylsulfonylmethane	Dermatomyositis
Spirulina	Mixed immunoblistering disorder with features of bullous pemphigoid and pemphigus foliaceus confirmed via histopathology and direct/indirect immunofluorescence
Spirulina	Dermatomyositis
Echinacea	Erythema nodosum
Echinacea	Pemphigus vulgaris
Alfalfa	Systemic lupus erythematosus
Isalean (contains alfalfa and a proprietary enzyme blend of *Aspergillus oryzae, Rhizopus oryzae, Trichoderma longibrachiatum, Saccharomyces cerevisiae, Bacillus subtilis, Ananas comosus, Aspergillus niger*)	Dermatomyositis

Notably, efforts are ongoing to harmonize global regulations within the European Union and worldwide. Moreover, herbal medicinal products present unique challenges throughout their production by ensuring quality, safety, and efficacy from cultivation and processing to manufacturing and are demanding tailored quality control measures at each stage (Fan et al., 2012). China, Korea, and Japan have been using the root of Panax ginseng Meyer for centuries to treat conditions like tiredness, exhaustion, and weakness, and to aid recovery during convalescence. Over the past half-century, understanding of ginseng's pharmacology enhanced due to extensive research focusing on its active components including ginsenosides which were first identified in 1963 (Patwardhan et al., 2005). Ginsenosides are categorized into 20(S)-protopanaxadiol and 20(S)-protopanaxatriol groups based on their chemical structures. Moreover, the quality and composition variability of these components depends on factors such as plant species, cultivation methods, and plant part used (Fan et al., 2012). The pharmacokinetics of ginsenosides are unraveled by the continued research efforts and are supporting their observed efficacy in clinical studies (Bagchi, 2014). Upon oral administration, intestinal microflora metabolizes ginsenosides into compound K believed to be the principal active constituent. Ginsenosides undergo enterohepatic recirculation and are primarily excreted via feces after liver metabolism (Ghosh et al., 2019). Numerous in vivo and in vitro studies have explored ginseng's effects like antioxidative properties, neuroprotection, immune modulation, anticancer activities, and benefits for cardiovascular health and metabolic functions (Al-Harrasi, 2022).

Applications of Botanical Remedies in Animal Well-being

Plants have been utilized for health and medicinal purposes for millennia and pinpointing the exact origin of their medicinal use is challenging (Gulati et al., 2019). However, plants are consistently served as the primary source of drugs and treatment strategies across various traditional medicinal systems (Sahoo et al., 2010). India is renowned for its rich biodiversity and boasts numerous medicinal plant species utilized in systems like Ayurveda, Siddha, and Unani to combat a wide array of diseases (Nazir et al., 2019). Nature has provided medicines not only for humans but also for animals and birds since the dawn of life (Buhner, 2020). The animals have this innate ability to self-medicate with herbs called Zoo pharmacognosy which reflects an ancient practice that persists today (Huffman, 2022). Traditional and folk medicine worldwide relies heavily on plant-based therapeutic entities by encompassing approximately 75% of all remedies used. However, the use of plants surges in animal health practices driven by concerns over synthetic drug residues, high costs, and drug resistance (Robson and Baek, 2009). The organic livestock production systems particularly marked this trend. Now, plant-based medicines and products are employed widely to enhance health and serve as curative agents either alone or in combination with other treatments (Dawkins and Yan, 2010).

Herbal plants are utilized not only as health enhancers but also in the treatment of various infections, surgical interventions, gynecological issues, and animal ailments like bovine mastitis. These plants encompass the bioactive compounds that are vital for enhancing livestock productivity and reducing environmental pollutants (Hernandez et al., 2004). Moreover, the importance of traditional medicine is recognized by the World Health Organization (WHO) which advocates for further exploration and integration of these practices into veterinary care, particularly in developing countries. The potential benefits in modern healthcare are underscored through the resurgence of interest in medicinal plants for treating diseases and improving animal productivity (Al-Harrasi, 2022).

In animal diets or extracts, the practical use of herbal supplements depends on various factors like animal species, age, and intended production purpose. Each herb contains distinct biological substances through varied mechanisms that exert different effects (Kuralkar et al., 2021). Additionally, the phytogenic feed additives are a key mechanism that involves beneficially influencing the gut microflora ecosystem by controlling potential pathogens (Dawkins and Yan, 2010). This microbial eubiosis stabilization in the gastrointestinal tract indirectly enhances digestive capacity in the small intestine. Consequently, phytogenics alleviate immune stress in animals during critical periods and increasing the availability of essential nutrients for absorption and supporting optimal growth within their genetic potential (Hernandez, 2019).

In recent years, herbal plant feed additives have garnered increased attention as alternative feeding strategies to replace antibiotic growth promoters. Studies have shown that extracts from herbs such as sage (Salvia officinalis), thyme (Thymus vulgaris), and rosemary (Rosmarinus officinalis), along with blends containing carvacrol, cinnamaldehyde, and capsaicin, improve feed digestibility in poultry (Hernandez et al., 2004). These improvements are attributed to properties like appetite stimulation, digestion enhancement, and antimicrobial effects, suggesting that herbal extracts can serve multiple functions in animal health management. For instance, the growth responses of birds to essential oil supplementation remain debated and some studies are reporting enhanced growth parameters while others show no significant effects. Essential oils are used to stimulate digestive enzymes and impact lipid metabolism and fat digestibility (Kuralkar et al., 2021). In contrast, the use of herbal plants and phytogenic compounds in animal nutrition is gaining importance due to their perceived safety, efficacy, and natural origins. However, the mechanisms of action, optimizing dosage and application methods and ensuring safety and compatibility can be understood thoroughly by further research along with animal diets before widespread adoption in animal feed practices (Hashemi and Davoodi, 2011).

Applications of Botanical Remedies in Human Well-being

Humanity has relied heavily on plants not only for sustenance but also for healing purposes throughout history. Natural products have played a crucial role in advancing modern medicine by dating back to the eighteenth century when digitalis glycosides were first used to treat cardiovascular disorders and willow bark was popular for managing pain and fever (Hernandez et al., 2004). The search for new therapeutic agents from natural sources has led to significant discoveries such as antibiotics, anticancer agents, anti-inflammatory compounds, and pain relievers. Terrestrial plants provide a renewable resource for discovering novel biomolecules with therapeutic properties due to the diverse structures and biological activities of their constituents (Kuralkar et al., 2021).

The safety concerns related to herbal ingredients are understood by acknowledging their origins, the regulatory frameworks guiding their production, and the criteria available for making informed decisions about their authenticity, efficacy, and safety in their intended use (Hashemi and Davoodi, 2011). However, current practices are insufficient to ensure consumer confidence and protection because the global interest in herbal medicine grows and reports of adverse effects increase. Therefore, to address these issues both international and national policies are being developed and implemented (Bhatt, 2015). Traditional pharmacopeias have evolved based on empirical testing over time, and many people worldwide rely on herbal remedies for their primary healthcare needs. The popularity of herbalism is expanding globally, with the industry projected to grow significantly in this century (Pandey and Saxena, 2019). Increasingly, these remedies are being clinically evaluated to establish their effectiveness. Some herbs have been found to contain specific biologically active compounds that validate their therapeutic value and have even led to new drug discoveries (Singh, 2020).

Consequently, there's a growing trend towards "designer foods" that incorporate medicinal herbs and other additives to enhance perceived health benefits in the health food industry. However, the composition and potential effects of these products are inadequately informed by consumers. For instance, certain additives such as psyllium in soy powder products can affect nutrient absorption and interact with medications by underscoring the importance of clearer labeling and consumer education. Moreover, herbal ingredients require comprehensive regulatory frameworks, improved consumer education, and transparent labeling practices associated with understanding safety concerns to ensure informed choices and safe use (Jana et al., 2018).

The raw medicinal plant materials quality depends significantly on agricultural and field practices that oversight policies in the country of origin, and the manufacturer's ability to detect potential issues. The final product value is influenced by factors like cultivation techniques, harvesting, post-harvest processing, transport, and storage (Bhatt, 2015). The cultural practices differences can affect how herbal remedies are diagnosed and evaluated for efficacy potentially leading to regional variations even when using the same plant species (Pandey and Saxena, 2019). The origins of medicinal systems, plant availability, and external influences on formulation and application are influencing the practices (Hashemi and Davoodi, 2011).

Future Directions and Challenges

Herbal medicine is widely used extending beyond developing countries with 70% of doctors in France and Germany regularly prescribing herbal remedies (Wang et al., 2024). The US FDA’s guidelines for herbal supplements sales have fueled a booming market. Natural products or their derivatives accounts for 60-80% of newly approved antibacterial and anticancer drugs (Ahmadifar, 2021). Examples include penicillin from plant mold and belladonna in ophthalmology treatments. Rauvolfia serpentine known as Indian snake root, contributed to modern tranquilizers and hypertension medications (Talebi et al., 2022). Approximately 25% of modern pharmaceuticals trace their origins to traditional medicine (Caipang, 2020). The efficacy of herbal treatments require quality standards and evidence evaluation (Ogunkalu, 2019).
Countries like China and India rich in medicinal plants are crucial in meeting global pharmaceuticals needs (Serra, 2021). Research on tribal medicines and efforts to document their use highlight the global demand for plant derived products enhancing public awareness and improving health outcomes (Basit et al., 2020).

Conclusion

In conclusion, the chapter emphasizes the profound historical and current significance of botanical remedies in both human and animal healthcare. For centuries, plants have served as a primary source of therapeutic agents, and their medicinal use dates back at least 5000 years. Despite the dominance of pharmaceutical drugs, there is a noticeable resurgence in the interest and use of herbal medicines due to their sustainable, holistic, and often synergistic properties. Traditional systems like Ayurveda and Traditional Chinese Medicine (TCM) provides the valuable insights. Moreover, the use of botanical remedies promotes productivity and reduces synthetic drug dependence in animal health. Globally, the interest in herbal remedies grows, and evidence-based approaches become paramount to fully harnessing their potential for well-being across all species.

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Chapter 51

Herbal Remedies to Replace Tilmicosin in Poultry

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ABSTRACT

Poultry has been used as a protein source in many countries around the world as an alternative to beef and mutton. The spread of chronic respiratory diseases results in a great loss of poultry production. *Mycoplasma gallisepticum* is one of the major microbial agents causing chronic respiratory infections in poultry. Tilmicosin is widely used to treat chronic respiratory infections in poultry and after five to seven days of regular treatment the bird gets better. The use of antibiotics against the *Mycoplasma gallisepticum* gives very satisfying results but the long term use of these antibiotics produce resistance in the microbial agent against these antibiotics. This situation comes up with a new solution which is the use of herbal medicine to treat poultry flocks. The concept of using herbal products against diseases is not new, in China many herbal products have been used to treat many medical conditions for almost the last 4000 years. Many herbal products including Andrographolide, Chinese herbal medicine formula, *Lonicera japonica* extract, Meniran Extract, Methanol extracts Garlic, Glycyrrhiza and Neem, and Extract of Indonesian wild ginger are being used to treat chronic respiratory diseases. There is no risk of resistance while using herbal medicine also there are no hidden side effects of them.

KEYWORDS		
Chronic respiratory disease, poultry, herbal products, *Mycoplasma gallisepticum*, tilmicosin, Andrographolide, Chinese herbal medicine formula, *Lonicera japonica* extract, Meniran Extract, Methanol extracts Garlic, Glycyrrhiza and Neem, and Extract of Indonesian wild ginger.	Received: 19-Jun-2024 Revised: 03-Jul-2024 Accepted: 10-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

The huge problem in the treatment and the control of *Mycoplasma gallisepticum* is the development of different phenotypic variations. Also the current situation of the antibiotic resistance of different bacteria makes it difficult to control the disease. Tilmicosin is widely used against the *M. gallisepticum* in poultry for a long time. The long term use of antibiotics in poultry results in the development of resistance in the poultry industry. The use of antibiotics as a growth promoter in poultry is another way to resist (Gharaibeh and Al-Rashdan, 2011). Antibiotic residues in milk, meat and eggs is another side effect of long term use of antibiotics and the aftermath of this is the transfer of antibiotic resistant bacteria to the humans. Other side effects include allergic reactions, immunological and pathological reactions. Vaccination and antibiotics are the only way to treat the chronic respiratory diseases but the resistance of the bacteria against the antibiotics impart the need for another way of treatment. This results in the use of herbal medicine to treat different diseases including *M. gallisepticum* infections. The use of herbal products as a treatment regime is incredibly increasing worldwide (Ishfaq et al., 2021).

Tilmicosin against CRD in Poultry

For a long time, macrolides have been used against different bacterial infections. These antibiotics did their actions by inhibiting the synthesis of bacterial protein. The antibiotic binds to the ribosomal RNA of bacteria and stops the protein synthesis (Vester and Douthwaite, 2001). Tilmicosin is a macrolide which is a broad- spectrum antibiotic. Tilmicosin has a bacteriostatic effect which is synthesized from tylosin only for veterinary use. Tilmicosin is very effectively used against *Mycoplasma* spp. and many Gram-positive organisms (Prescott and Baggot, 1993). In poultry, Tilmicosin is used to treat many chronic respiratory infections caused by *M. gallisepticum* (MG), *Mycoplasma synoviae*, *rhinotracheale*, and *Pasteurela multocida* (Figure 1) (Jordan and Horrocks, 1996; Kempf et al., 1997; Varga et al., 2001).

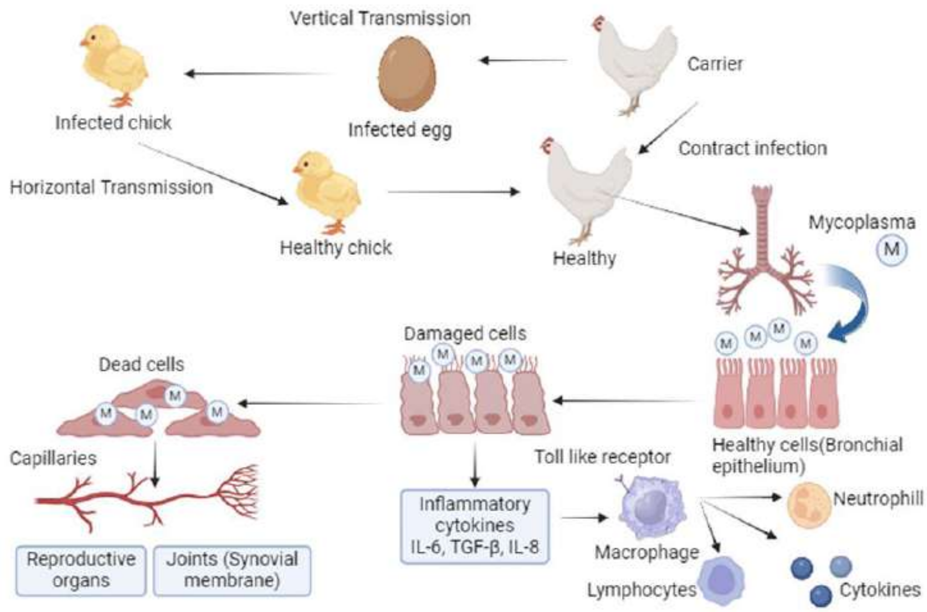

Fig. 1: Transmission of *Mycoplasma gallisepticum* and its pathogenesis (enters in the airways and destroys the cilia of epithelial cells, systemic invasion, causes immunosupression, srops protein and DNA synthesis) in poultry.

Mode of action of Tilmicosin

The classification of antibiotics is based on their mode of action as all types of antibiotics for example penicillin, cephalosporin, tetracycline, macrolides, aminoglycosides, and quinolones have different ways to response against the microbial agents. Tilmicosin belongs to the macrolide, a group of antibiotics which is isolated from a bacteria belonging to genus Streptomyces, present in soil (Riviere and Papich, 2013). Macrolides did their work by inhibiting the biosynthesis of protein in bacteria (Fig. 2). Tilmicosin is basically prepared from desmycosin after chemical alterations (Yazar et al., 2001).

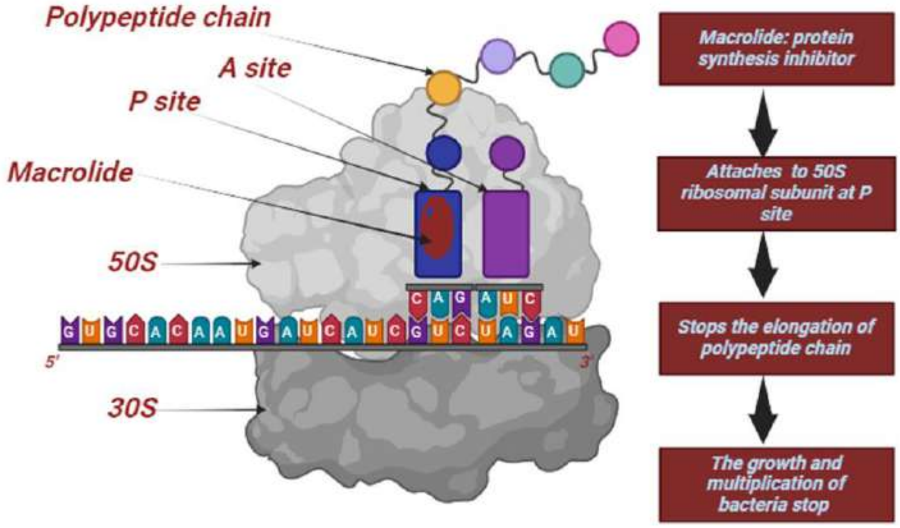

Fig. 2: Mechanism of action of Macrolide (Tilmicosin).

Uses of Tilmicosin in Poultry

The use of tilmicosin in water has very promising effects on chicken against MG including decrease in the formation and degree of lesions on the air sacs (Charleston et al., 1998). The use of tilmicosin at a dose rate of 20mg/kg of body weight for the clinical outbreaks of the MG is thought to be the best way of treatment. This protocol should be followed for five days continuously (Garmyn et al., 2019). The broiler chicken treated with tilmicosin and lincomycin has less or no mean gross air sac and microscopic tracheal lesions compared to those chickens which were untreated. This clears the fact that tilmicosin has very effective results against the mycoplasmosis in chickens (Amer et al., 2009). It is shown by a study that the spiramycin also shows good results against MG in broilers. It reduces the microscopic and gross lesions and also decreases the severity of arthritis. The clinical signs of the disease in treated flock was much lower as compared to those infected flock which is untreated (Elazab et al., 2021). Many studies reveal that the tilmicosin promisingly reduces microscopic lesions and also decreases the re-isolation rate at 20% and in some other findings the re-isolation rate decreases upto 0% (Abd El-Ghany, 2009; Zakeri and Kashefi, 2011).

Herbal Treatment Options Instead of Tilmicosin in Poultry

The term polypharmacology means the action of an antimicrobial agent at more than one target simultaneously, the latest approach of modern drug discovery (Anighoro et al., 2014; Kuenzi et al., 2017). Through this way natural products are used for treatment (Figure 3) of different diseases which is way better than the same old drugs which are single targeted (Ho et al., 2018). Natural products with the phenomenon of poly-pharmacological profiles defend the host against many diseases with novel therapeutic benefits (Fang et al., 2018; Ishfaq et al., 2021; Wang et al., 2022). The treatment of MG with vaccines is no more effective (Yang et al., 2021). The humoral response of the vaccine against MG is neither as effective nor can clear the pathogen which in turn results in the failure of the vaccine. The genetic variation of MGis also the cause of vaccine failure (Matyushkina et al., 2016). Antibiotics or antimicrobial agents can stop the microbial agent but only for a small period of time. As soon as the drug delivery stops the recurrence of infection is confirmed (Gharaibeh and Al-Rashdan, 2011). These circumstances lead to the need of another effective way of treatment which is not only cheap but also safe to use. The herbal medication is the safest way for treatment of many infections including mycoplasmosis.

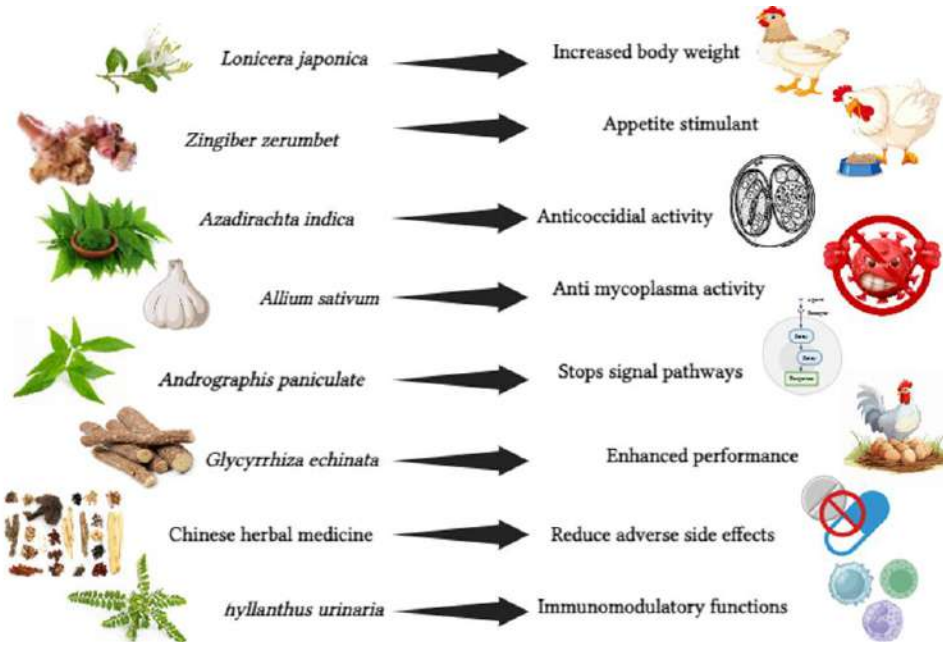

Fig. 3: Herbal treatment options in poultry.

Andrographolide

The main etiological agent for the chronic respiratory disease in chicken is MG The primary symptoms of the chronic respiratory disease is the inflammation of the respiratory tract and apoptosis. Andrographolide (Andro) is a small natural compound. It is famous for its natural properties including Anti-inflammatory action and anti-pathogenic effect (Luo et al., 2022). *Andrographis paniculate* (*A. paniculate*) has been used in China, India, Japan, Korea, and some other Asian countries for the last 2000 years as a medicinal food. It is known to treat many diseased conditions in humans for instance myocardial ischemia, pharyngitis, and respiratory diseases (Dai et al., 2019). Andro is a small natural molecule which was extracted from Traditional Chinese Medicine which was made up from *A. paniculate* (Kim et al., 2019). The natural molecule of Andro works by inhibiting the protein expression of MG which in turn decreases the adhesion of MG to the chicken lungs and AEC ll. It has been proved through many studies that MG causes inflammation of the air sac, tracheal tissue and lungs. It also causes damage to the chickens (Wu et al., 2019; Niu et al., 2020). It is confirmed that the administration of Andro is safe in chickens and AEC ll and have no adverse side effects. Andro is considered a very effective herbal product against MG as it stops the signal pathways of JAK/PI3K/AKT in the chicken.

Chinese Herbal Medicine Formulae

Recently Chinese herbal medicines have gained scientists' interest with their little toxicity and side effects. Beyond these effects there is no drug resistance and no drug residuals associated with the Chinese herbal medicine (Maryam et al., 2020). In China the use of Chinese herbal medicine to deal with different diseases is almost 4000 years old (Yi and Chang, 2004; Xutian et al., 2009). Old data of use of herbal medicine shows that for the treatment of chronic respiratory disease, a single Chinese herb has very prominent effects (Niu et al., 2020; Zou et al., 2020; Zou et al., 2021). Besides this the Chinese herbal formulae is made by using traditional Chinese medicine formula principles which helps to reduce the adverse side effects and helps in getting better therapeutic benefits (Su et al., 2016). This use of this formula to treat chicken has no deleterious effects on the health of normal chicken but it can enhance the performance of the chicken which is infected by MG. It also repaired the damage caused by MG to the air sac and tracheal tissue of the chicken. The histopathological data shows that the Chinese herbal formulae also helps in repairing the inflammation of lung and trachea and inhibits the expression of inflammatory cytokines induced by MG (Wang et al., 2022).

Lonicera japonica **Extract**

Herbs and spices have amazing properties which include antioxidant, antimicrobial, anti-helmintic, immune modulator and growth promoting abilities. These properties belong to the biologically active components of these herbs for instance terpenoids, phenolics, glycosides and alkaloids (Huyghebaert et al., 2011). *Lonicera japonica* Thunb is a very famous medical plant also known as the Japanese honeysuckle. It has many pharmacological and broad spectrum biological properties which includes anti-oxidative (Kim et al., 1994), anti-tumour (Yip et al., 2006), hepato-protective (Hu et al., 2008), antiviral (Houghton et al., 1993), anti-inflammatory (Lee et al., 1998), and antibacterial activities (Shan et al., 2007; Rahman and Kang, 2009; Shang et al., 2011). The primary natural extracts of *L. japonica* which act as natural medicine against many diseases are essential oils, organic acids, flavones, saponins, iridoids, and inorganic elements. The most important compound of *L. japonica* is the chlorogenic acid which is a bioactive organic acid. The chlorogenic acid is found in rich amounts in the flower bud of *L. japonica*. It has various pharmacological effects against many diseases. Many research studies show that the pharmacological effects of *L. japonica* extracts have amazing results in the chickens infected with MG. The results of use of *L. japonica* against MG is as good as achieved by tylosin tartrate. It reduces the chance of body weight loss in chickens infected with MG. Also in the FCR of birds shows that the use of plan based medicinal products have almost the same outcomes as the chemotherapeutic drugs (Giannenas et al., 2003; Saini et al., 2003). To get the best results, chlorogenic acid was given in drinking water to the poultry flock infected with MG at a dose rate of 190ug per day per bird. The liquid chlorogenic acid is prepared at a rate of 1g/ 1000 ml of water which is then used in drinking water for poultry flock. Various studies show that the use of chlorogenic acid results in increased body weight, less individuals with the infection of MG (Müştak et al., 2015).

Meniran (*Phyllanthus urinaria*) Extract

Currently the use of herbal medicine is widely spreading around the globe specially to treat the disease which affects the production of livestock. Among many of the herbal products used for treatment of animal diseases, Meniran plats are specifically used for the treatment and prevention of chronic respiratory disease. Meniran (*Phyllanthus niruri Linn*) has been known for the possession of bioactive compounds which have antimicrobial activities. These bioactive compounds are terpenoids, alkaloids, flavonoids, saponins, and tannins (Sreenivas, 1999). The statistical data of various researches shows that the use of Meniran extracts in chicken infected with MG, the body weight increases and the feed conversion ratio (FCR) decreases which shows the excellent performance of the flock (Hidanah et al., 2017). When the chicken is infected with chronic respiratory disease or MG bacteria, it results in a low weight gain and high feed conversion ratio. This happened due to the low appetite which in turn results in less feed consumption by the bird (Bell and Weaver, 2002). Meniran contains chemical compounds which help in enhancing the bird's appetite (Sutton, 2011). Some studies show that Meniran plants also have the benefits of immunomodulatory functions (Gunal et al., 2006). This means that they can help in repairing and restoring the immune system against diseases (Sreenivas, 1999). The natural compounds of Merinan extracts including alkaloids and tannins are well known for their inhibitory response against the microbial agent (Wahju, 2004). The Merinan plant also has the active compounds of phenol class such as flavonoids, alkaloids, saponins, and tannins. Among all the compounds, flavonoids are the one with the ability to denature proteins. With the ability, flavonoids destroy the cell wall proteins of the bacteria which changes its permeability (North and Bell, 1990).

Methanol Extracts Garlic, Glycyrrhiza and Neem

By using the micro dilution method, the minimum inhibitory concentrations (MICs) was determined for the methanol extracts. Herbal plants which include garlic, Glycyrrhiza and Neem were used for the methanol extracts against the three isolates of MG. The procedure was done at the University Diagnostic Lab, University of veterinary and animal sciences, Lahore. The protocols given by (Al-Momani et al., 2007) were used to do this procedure only with minor changes. The results of the study by (Muhammad et al., 2015) reveals that garlic has no adverse side effects on the two isolates of MG. These results were very close to the (Al-Momani et al., 2007) data according to which *Allium sativum* (garlic) shows anti mycoplasma activity against almost six different Mycoplasma species. This shows that garlic can be used in poultry for its amazing therapeutic activities against many gram positive and gram negative bacteria especially against MG (Bakri and Douglas, 2005). Studies show that the aqueous garlic extracts have astonishing therapeutic activities and protect the host from various gram positive and gram negative bacteria (Iwalokun et al., 2004).

Extract of Indonesian wild Ginger

In Indonesia, three species of wild ginger are very popular which are as follows: *Zingiber zerumbet* (L.) Smith with local name lempuyang gajah, *Zingiber amaricans* BL. with local name lempuyang pahit and the *Zingiber aromaticum* (Vahl.) with local name lampuyang wangi. The size of every part of the plant is different from one another in all three species. *Zingiber amaricans* is the smallest among all of them. The rhizome of *Zingiber zerumbet* L. Sm. is well known for its high efficiency as an appetite stimulant, its rhizome is much bigger in size with yellow flesh. The rhizome of *Zingiber amaricans* BL. is also used to enhance appetite but it is smaller in size with bitter taste. In the case of *Zingiber aromaticum*, the rhizome is fragmented and used for its effective results as a slimming agent (Wahyuni et al., 2013). The phytochemical studies about *Zingiber zerumbet* are still ongoing and reveal that the plant is of much Importance. Different compounds were isolated from the plant including sesquiterpenes (Kader et al., 2010; Yob et al., 2011), terpenoid, flavonoids (Nag et al., 2013), tannins (Prakash et al., 2011), and some aromatic compounds. Volatile oil from the rhizome of *Zingiber zerumbet* have different chemical compounds for example zerumbone, humulene, camprene, a-caryophyllene and champhene (Dai et al., 2013).

Conclusion

The resistance of microbial agents against antibiotics is one of the major issues faced by the practitioners and farmers all over the world. This alarming situation draws the attention of pharmacists to find an alternative and better way to fight against the bacteria. This ends with the discovery of herbal products which have been used in many Asian countries for the last 4000 years. Herbal products have many beneficial effects with almost no adverse side effects. The use of herbal products in poultry gives wonderful results and the production increases. Poultry is a source of protein used in many countries but the antimicrobial resistance causes a serious economic loss to poultry industries. The chronic respiratory diseases result in weight loss and mortality of the flock. The herbal products and treatment methods used to fight against the MG and the results are very satisfied.

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Chapter 52

Dynamic and Chronic Diseases: Homeopathic Perspectives

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ABSTRACT

Homeopathy, a significant element of healthcare in the 19th century, has recently experienced a worldwide resurgence. Following a period of gradual decrease, homeopathy is now gaining popularity worldwide, highlighting the pressing necessity for scientific validation of its mode of operation and efficacy. Homeopathy utilizes formulations of medicines that produce similar effects in healthy individuals as the symptoms, clinical signs, and pathological states observed in the sick. Homeopathic medications are manufactured by successive dilutions and shaking and are often administered in potentized forms. Currently, the practical use of homeopathic research in the field of high-altitude medicine for various dynamic and chronic diseases is still in its early stages. With increasing attention to alternative therapeutic approaches, several clinical investigations have been carried out in the field of homeopathy. This chapter provides a concise overview of scientific discoveries and identifies areas that require additional research to develop homeopathic treatments for dynamic and chronic diseases, as well as their underlying physiological circumstances. This chapter provides an evaluation of important homeopathic treatments, such as homeopathic coca, *Aloe vera*, and other possible options for treating several ailments.

KEYWORDS		
Homeopathy, Homeopathic perspectives, Chronic diseases, Natural medicine, History of homeopathy	Received: 17-Jun-2024 Revised: 25-Jul-2024 Accepted: 09-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Homeopathy is a widely practiced form of complementary and alternative medicine (CAM) that is highly prevalent in Europe. In the 18th century, the German doctor Christian Friedrich Samuel Hahnemann did systematic clinical tests that led to the idea. Hahnemann made various observations and changed the treatment theory known in medicine as "the rule of similars." After a slow decline, homeopathy is now becoming more famous around the world. The efficacy of this therapeutic method and the exact way in which ultramolecular or high dilutions (HDs) work are, however, still up for debate. Further research is essential in this area. The subject of how homeopathy could be integrated with traditional medicine emerges in light of its all-encompassing approach and the scant proof of its efficacy (Ling, 2019).

This is particularly relevant in clinical areas where the therapeutic effectiveness of conventional medicine is uncertain or to expedite the treatment of conditions where a wait-and-see approach is typically followed. To achieve successful integration, it is crucial to have a comprehensive understanding of the subject matter (Ling, 2021).

Homeopathy: Person-cantered Therapy

Homeopathy is a clinical-therapeutic approach that seeks to restore health in all organisms, including humans, plants, and animals. Its originator, Samuel Hahnemann, first articulated the concepts that underpin it in his seminal work 'Organon'. The concept of similarity also referred to as the 'law of similars', asserts that a homeopathic treatment can effectively cure a patient who displays symptoms that are like those caused by the same medicine in experiments conducted on a healthy person (Huang, 2019). Traditional homeopathy requires selecting a single treatment that has a distinct set of effects and can address all of the patient's energy, bodily, and mental symptoms. Hahnemann's therapeutic concept focused on treating the patient holistically, considering not only their illness but also their entire being, including the physical body and the disturbances in the vital force that animate it with sensitivity. In modern terms, this approach can be described as a comprehensive and intricate therapeutic approach that considers the complete and complex nature of the individual (Huang, 2021).

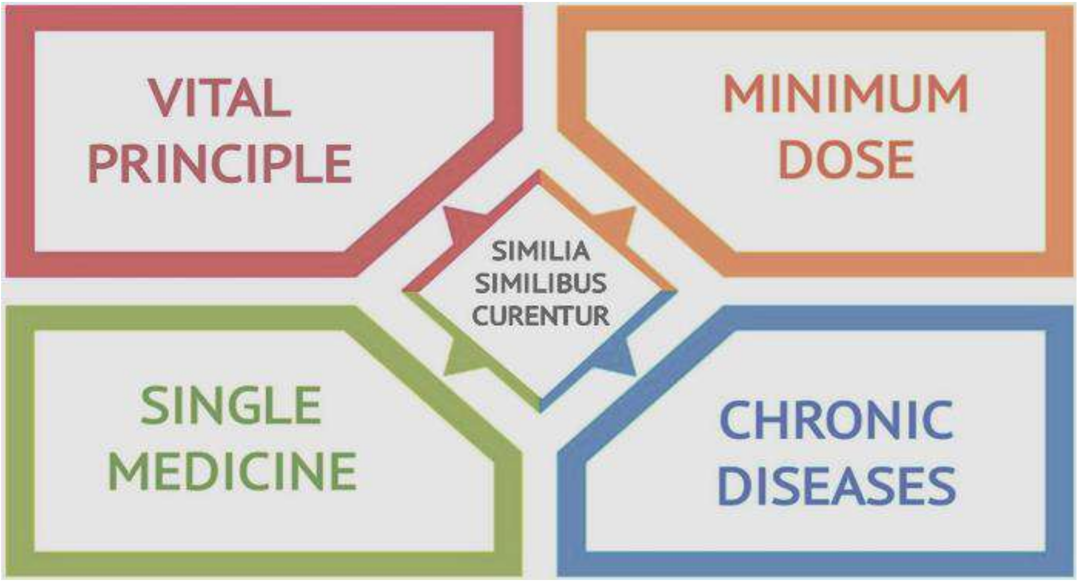

Fig. 1: How Law of Similar work in Practice

It is important to highlight the degree to which traditional homeopathic treatment, dating back to Hahnemann's era, has consistently focused on treating the entire individual. A famous American homeopath in the 1800s, James Tyler Kent (1849–1916), anticipated how important it was to treat the whole person, including their emotions, thoughts, and spirit, as well as their actual body. It consistently appears as a unified and natural occurrence, yet it has various components (Ling, 2021). Alexis Carrel, the Nobel Prize laureate in medicine, asserted that the sick individual has been categorized into several areas, each requiring its specialized practitioner (Pagliosa and Ros, 2008). A specialist of this nature dedicates their efforts to the examination of a minuscule portion of the human anatomy. However, their intense focus on one specific area results in a lack of knowledge regarding the remainder of the body, to the extent that they cannot be considered to possess complete expertise in even this particular aspect. Both medicine and society need to treat the patient as a whole, with both their mental and physical parts (Zulfugarova et al., 2023).

Historical Background

The concept of resemblance, which forms the basis of homeopathy, has its origins in ancient times and may be found across centuries of medical history. One of the first advocates of what is now known as rational medicine in the Western Hemisphere was Hippocrates, who lived between 460 and 367 B.C. (Daukes et al., 2005). He conducted empirical research and discovered that the sickness develops as a result of similarity, and it may be effectively treated by utilizing similarity (Huang, 2020). The substance that induces urinary tenesmus in healthy individuals is the same substance that alleviates it in those who are ill. Coughing and urine tenesmus are both triggered and resolved by the same substance in an identical manner. German naturalist physician and philosopher Theophrastus Bombastus von Hohenheim, better known by his pen name Paracelsus, presided over this school of thought from 1493 to 1542 (Wiegant, 1994). The person created the theory of signatures, or "signa naturae," which holds that particular characteristics of plants or minerals, including their forms or colors, can be used to deduce a plant's or mineral's medical properties (Marian et al., 2008). For instance, plants with pointed leaves are believed to be effective for alleviating stabbing pains, while Euphrasia flowers, resembling irises, are thought to be beneficial for treating eye ailments. Similarly, topaz, due to its yellow hue, is believed to be a suitable remedy for jaundice. These are just a few examples of the doctrine's principles (Du and Knopf, 2009).

The inaugural comprehensive textbook on homeopathy, titled "Organon of Rational Art of Healing," was published in 1810. In 1819, a second version of the book was published under the title "Organon of Healing Art". Subsequent editions were released until the sixth edition was published after the author's death in 1921. Two additional essential works on homeopathy are "Materia Medica Pura" and "Chronic Diseases". Materia Medica Pura is a collection of reports on "homeopathic proving" that was published in six volumes. The first book was published in 1811 and the last volume, book VI, was released in 1827 (Mastrangelo, 2006). The revised editions of volumes I and II were released in 1830 and 1833, respectively (Poitevin et al., 1988). These volumes contain a total of 61 medications (Steinsbekk et al., 2006; Viksveen et al., 2017). There was a total of 37 individuals who provided evidence or proof. In Hahnemann's work titled "Chronic Diseases," he provides a detailed and revised explanation of the therapeutic approach to patients based on the hypothesis of "miasms" (Hariharan et al., 2021).

Traditional Methodology

Lots of people still think that Hahnemann's first book, The Organon of Healing Art, is the most important thing to know about how to use the homeopathic method. This may be the only book that has been around for two hundred years and is still useful in current medicine. This remarkable phenomenon could be attributed to either the neglect of updating this particular medical field or the inclusion of timeless principles in its theoretical framework. In the world of medicine, this work represents the first attempt to organize the laws and regulations dictating what is considered healthy and harmful (Ling, 2020). The ideas in the Organon are what Hahnemann mostly bases his support for using homeopathy to help both short-term and long-term illnesses. During a clinical examination, a homeopathic physician focuses on finding a remedy whose etiology matches the patient's symptoms at the time of the disease (Guajardo et al., 1999).

The Materia Medica and the Repertory are two tools that the doctor uses to reach this goal. The first is a list of physical, mental, and sensory effects that happen to a lot of healthy people when they try a certain drug. The second, on the other hand, is essentially a catalog of symptoms and the corresponding homeopathic treatments linked to those symptoms. Indeed, two individuals can have comparable yet not identical symptoms in response to the same pathogenic agent (Rutten et al., 2013).

By correlating the pathophysiology of homeopathic remedies to the patient's symptoms, the test helps the physician tailor the treatment as much as possible. Not only should one be aware of the symptoms and indicators that are present, but also of the circumstances in which they worsen or improve ("modality"), the feelings they arouse, the time of day they occur, and other related elements. This phenomenon explains why different people with the same disease may need different homeopathic treatments (Ernst, 2008). The doctor carefully records the patient's medical history and looks at the patient as a whole, considering each person's unique traits, and is not primarily motivated by a strong moral stance. Instead, it is because of the practical implications of finding the right treatment based on the principle of similarity. As has been seen in other areas of health, the homeopathic approach fits with the ideas of modern complexity sciences. It is different from molecular medicine, which tends to be reductionist (Miles, 2009; Stub et el., 2022).

Dynamic Approach to Acutely Ill Patients

Acute diseases typically manifest with a restricted range of symptoms that exhibit minimal variation across different individuals. Therefore, the application of the concept of similarity is more straightforward and the available options for cures are decreased. Undoubtedly, the patient's particular responses such as the type of perspiration, fluctuations in temperature, thirst, and weakness are consistently observed, aiding the homeopath in selecting the most appropriate medicine. Hahnemann posited that acute diseases arise from abrupt changes in the expression of the vital principle. These pathologies typically have a variable but generally short-term progression (Milgrom, 2008). The user's text is enclosed in tags. He divides acute manifestations into two groups: (a) unique diseases, like injuries, illnesses brought on by sporadic factors (like heat, cold, or overeating), or the exacerbation of long-term conditions; and (b) prevalent diseases, which impact many people at once and can happen sporadically or as an epidemic. To treat acute disorders efficiently, a doctor must first identify the most likely underlying cause of the illness before choosing a drug that uses the concept of similars to address the patient's symptoms holistically (Oberbaum et al., 2005; Hart-Davies et al., 2024).

The Approach to Chronically Ill Patients

In homeopathy, giving each patient a personalized treatment needs a deep understanding of the Materia Medica and the use of the Repertory. When dealing with situations like these, it is necessary to apply the law of similars (Schmidt, 2009). As part of the medical exam, it is important to look at the patient's current clinical appearance as well as any changes in symptoms that have happened over time, as well as the patient's family history and any other signs of disease (Bell et al., 2012). In the past, Hahnemann had outlined that the systematic approach to treating patients who suffer from chronic illnesses should take into consideration a variety of factors. Some of these factors are the patient's age, sexual activity, family bonds, lifestyle, habits, social life, and moral and intellectual character. However, because this method of treating chronic illness is so complicated, the choice of a successful cure can be made by looking at certain traits that have become clear over time. Some of these are miasmas, temperament, and sensitive types (Mezzich and Salloum, 2008; Kettler, 2024).

Miasms

Hahnemann, after two decades of practicing homeopathy, started addressing the underlying issue of chronic illnesses that did not show improvement or only showed partial improvement despite the use of seemingly appropriate remedies. He documented his findings in the publication called "Chronic Diseases" (Bowker et al., 2006). Hahnemann, upon making this observation, proceeded to modify his hypothesis and propose the presence of unidentified exogenous agents (referred to as 'miasms') that, upon infecting the organism, initiate the manifestation of a range of symptoms. Currently, this concept appears to have significant limitations. Nevertheless, it is crucial to bear in mind that the knowledge about bacteria as agents of disease was virtually non-existent before 1860 when Pasteur made his groundbreaking discovery. Thus, the main topic of the debate centered on miasmatic ailments, which are caused by miasms or 'effluvia'. These miasms are organic particles present in the air that are emitted from marshes (Farzaei et al., 2014). Only a few of individuals speculated that these infectious agents could be living organisms. Hahnemann belonged to this exclusive group of individuals: In 1831, 35 years before Pasteur, he defined miasm as follows during a study on the treatment of Asian cholera: "The cholera miasm finds a suitable environment for its reproduction and multiplies into a much larger generation of extremely small, imperceptible, living organisms that are highly harmful to human life, which is likely the contagious substance of cholera". According to Hahnemann, a miasm has such a strong impact on the body that it makes the body unresponsive to homeopathic medicines that are chosesn based on the symptoms observed during a medical examination (Belcaro et al., 2014). These symptoms are merely a component of a multifaceted condition that necessitates a comprehensive understanding to provide appropriate treatment to the patient. From this perspective, the many symptoms observed throughout the patient's life are considered as a progression of an initial "infection". It is important to examine this progression to achieve a comprehensive and long-lasting cure. Throughout the history of homeopathy, numerous iterations of the miasms idea have emerged, and it continues to be a topic of extensive debate. Although it is obsolete in terms of current pathology, it is still employed in certain educational institutions as an instructive standard that can aid in the selection of a therapy (Eftekhar Sadat et al., 2013; Mathie et al., 2016).

Constitutions

The origins of this concept may be traced back to the ideas put forth by Dr. Nebel in the early 20th century. These ideas were later embraced by other doctors, particularly Leon Vannier. They noted that specific patients who were sensitive to the impacts of calcium carbonate displayed identical physical and psychological characteristics, as well as comparable inclinations towards sickness. An analogous finding can be drawn regarding individuals who exhibit sensitivity to other calcium salts, such as calcium phosphate and calcium fluoride (Farzaei et al., 2014). This concept originated during the 1920s and garnered both widespread acclaim and condemnation. At now, there are three main constitutional types that are widely recognized: sulfuric, carbonic, and phosphoric. In addition, there is a secondary variant (fluoric) that some experts contend is not a distinct category and can therefore be combined with the others. With the progress made in genetic research, it is crucial to recognise that the concept of constitutional types should not be regarded as a rigid categorization of patient groups. However, the homeopath's capacity to evaluate a patient's overall health allows them to choose an appropriate treatment for long-lasting illnesses, even in the absence of additional corroborating information (Bartlett et al., 2013; Frass et al., 2015).

Research Breakthrough

Extremely dilute pharmaceuticals, sometimes referred to as "ultramolecular" or "high dilutions" (HDs), are utilized in homoeopathy. This word is used to describe medicines where the source material is very unlikely to be present. The amount of water used is more than Avogadro's number, which is 6.02×10^{23}. To be precise, it exceeds 23 DH or 12 CH. Due to this paradox, there has consistently been intense controversy among critics and proponents of homoeopathy over its efficacy (Fuggle et al., 2020). 25 years have passed since Poitevin and Benveniste published their respective works on the subject of the "memory of water," and their dispute remains unresolved. In the past few years, this area has seen big steps forward in both basic research and clinical efficacy studies (Brown et al., 2006). The exact way that homoeopathic dilutions work is still not fully known, but we have learned enough about them that it seems likely that they work in the therapeutic setting. Also, homoeopathic medicines are still very popular in Europe, even though there is a lot of question about them in the academic world. People in Germany, Italy, Switzerland and Norway often use homoeopathy to help children. When standard treatments don't work very well or at all, general practitioners often suggest homoeopathic remedies Because of this, it is clear that the subject needs more research, such as an analysis of the benefits that can come from both basic and applied science studies (Ge et al., 2017).

Conclusions and Future Prospective

Homeopathy and other types of complementary and alternative medicine (CAM) can contribute to the restoration of the holistic well-being of a patient, as they focus on treating the individual as a whole rather than solely addressing their sickness. This approach aims to bring back the essential and intangible aspect of medicine, often referred to as the "soul," which is of utmost importance but difficult to define. Hormesis is a very interesting subject to study because it includes looking at the chemical and physical properties of water that support the effects of homoeopathic treatments that are very diluted. In addition, we strongly advocate for the expansion of clinical research through the production of rigorous randomized controlled trials (RCTs) and the support of often overlooked observational studies of the epidemiological kind.

Additionally, this research method has the benefit of being carried out in settings that are very similar to the ones healthcare workers actually use and the settings where these methods are used. Observational studies allow for a more accurate adherence to homeopathic methodology, and a specific type of study known as "clinical verification of homeopathic symptoms" has the potential to enhance homeopathic prescription in the future. Each therapy strategy necessitates evaluation techniques that consider its potential mechanisms of action and the treatment situation. RCTs may not always be sufficient for effectively assessing medical procedures that require specific skills, such as surgery and acupuncture. It is important to consider that identifying the appropriate homeopathic remedy relies on conducting a comprehensive medical history and establishing a trusting environment, which is not possible in a double-blind setting. Assessments regarding the effectiveness of homeopathic therapy, and therefore its potential integration with conventional medicine, should be based on a range of research approaches, including blind and open studies, randomized trials, and observational investigations. Each method yields results that enable evaluations from different perspectives.

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Chapter 53

Mastitis Healing with Homeopathy; To What End?

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ABSTRACT

Mastitis remains a major challenge to dairy producers because of its effects on animal health and productivity. It occurs in 15-20% of dairy cows annually and leads to a decrease in milk production and an increase in economic cost. Past medical therapies include the use of antibiotics but due to the growing cases of AMR, trends are shifting towards homeopathy. This chapter outlines the fundamentals of homeopathy with an emphasis on its holistic approach and its use in the management of mastitis. The effectiveness of homeopathic treatments is analyzed using various studies in contrast to the traditional antibiotic medicines. Some of the studies show that homeopathy is a viable approach, especially when used alongside antibiotics, therefore reducing the occurrence of AMR due to the decreased usage of antibiotics. However, it is also emphasized that in different studies, the efficacy of homeopathy is not consistent and its effectiveness is even lower than that of a placebo. These variations may be due to inconsistent factors such as research design, a lack of established protocols, and the personalized nature of homeopathic therapy. Lastly, it states that homeopathy may have some potential as an alternative therapy when treating mastitis but it cannot completely replace antibiotics. Future studies are recommended using well-designed cross-sectional randomized controlled trials (RCTs) to measure the effectiveness of homeopathy in real farming conditions. Mastitis management cannot only rely on a regular approach but should incorporate both conventional and complementary medicine to support animal health and farm profitability. The results indicate the need for a patient-oriented approach and the need for continuing education and study in veterinary homeopathy.

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INTRODUCTION

Mastitis is a prevalent health problem in dairy herds that impacts production, animal health, welfare, and the global economy (Ali et al., 2021). It is estimated that between 15 and 20% of dairy cows have mastitis annually, and this is strongly correlated with lower milk output (Neculai-Valeanu et al., 2021). This condition is multifactorial with several causes, including infections, udder defense systems, and environmental variables. It is described as inflammation of the mammary gland brought on by a variety of bacterial strains, fungi, including Candida spp., and algae, including Prototheca (Huilca-Ibarra et al., 2022; Krömker & Leimbach, 2017). Scientific literature data reveal that mastitis is associated with more than 140 microorganisms; the leading bacterial pathogens that cause mastitis are *Staphylococcus aureus*, *Streptococcus agalactiae*, *Escherichia coli*, and *Streptococcus uberis* (Tomanić et al., 2023). Depending on the severity of clinical signs, bovine mastitis can be subclinical or clinical mastitis with variations in severity from mild to moderate and severe. Clinical mastitis affects milk production directly and prominently and is easy to diagnose due to the changes in milk and the general clinical symptoms exhibited by the animal (Pedersen et al., 2021). In contrast, subclinical mastitis (SCM) is hard to diagnose since the cow seems normal, and the udder, as well as milk, appear normal. However, an increased number of somatic cells (>100,000 cells/ml) and the presence of the causative agent can be used to detect SCM. SCM is more prevalent and it results in higher productivity losses accordingly (Tezera & Aman Ali, 2021).

Antibiotic therapy is the primary treatment for bovine mastitis. However, its efficacy is decreasing because of the increasing drug resistance in bacteria, and is regarded as a significant global health issue (Pascu et al., 2022). Antimicrobial resistance (AMR) is thought to be the cause of approximately 30,000 fatalities annually in Europe and 700,000 deaths worldwide, with the potential to cause millions of deaths (Mestrovic et al., 2022). This indicates the rapid global spread of AMR. Therefore, there is a need to promote the integration of a multisectoral One Health approach in addressing this challenging issue. Complementary medicine, including homeopathy, is encouraged in organic and biodynamic farming as the use of antibiotics is limited by law (Zeise & Fritz, 2019). However, research studies have inconsistent findings and limited references concerning mastitis.

The purpose of this book chapter is to provide a critical analysis to evaluate the role of homeopathic remedies in controlling and treating mastitis. Furthermore, this chapter also explores the efficacy studies of homeopathic drugs in comparison to conventional treatments and discusses the potential benefits and limitations of incorporating homeopathy in bovine healthcare practices. Finally, the chapter seeks to provide a viewpoint on whether homeopathy is a viable alternative or complementary treatment for bovine mastitis.

Understanding Basics of Bovine Mastitis

Mastitis affects dairy animals worldwide, including sheep, goats, camels, and cows. It can be sporadic or pandemic, which causes significant financial losses for the dairy sector. Mastitis is one of the most serious bovine illnesses in terms of both animal welfare and economic effects. This has a negative impact on the profitability of farmers, resulting in significant output losses in the global dairy sector (Aghamohammadi et al., 2018; Das et al., 2018). A broad range of pathogens can cause mastitis, which can be epidemiologically divided into contagious and environmental types (Sharun et al., 2021). Contagious bacteria, such as *Streptococcus agalactiae* (*S. agalactiae*), *Streptococcus dysgalactiae* (*S. dysgalactiae*), *Staphylococcus aureus* (*S. aureus*), and *Mycoplasma* spp., are often transferred from an infected cow to a healthy cow during milking. The hands, towels, and/or milking equipment serve as bacterial reservoirs (Stanek et al., 2024). Environmental mastitis is caused by bacteria such as *Escherichia coli*, *Klebsiella penumoniae*, and *Streptococcus uberis* found in the cow's surroundings, including bedding, dirt, dung, excrement, and stagnant water (Pal et al., 2019). The teat canal serves as a physical barrier and source of antibacterial compounds, making it the first line of defense against pathogens. The teat canal is lined by sphincter muscles and a waxy substance i.e., keratin that prevents infections from entering (Rainard, 2024). As parturition approaches, intramammary pressure increases due to fluid accumulation. Thus, the teat canal dilates and leaks secretions, making the gland susceptible to infections. In lactation stage milking also results in keratin flushing and teat canal distention (Pal et al., 2019). The udder's humoral and cellular defensive systems must be bypassed by bacteria once they have entered the teat. They begin to proliferate in the mammary gland and infection develops due to weakened immune system. On significant alveoli damage, udder swelling and reddening can be visible. Milk undergoes several changes, such as increased conductivity, pH, water content, visible clots/flakes, and blood (Choudhary et al., 2024).

Mastitis causes economic losses due to reduced milk output, quality, and milk value, higher labor and treatment expenses, and shorter productive lives for afflicted cows. Globally, Mastitis causes around USD 33 Billion of economic loss (Pal, 2018). In Pakistan, the overall prevalence of mastitis ranges from 42-70%, and subclinical mastitis prevalence ranges from 29-57% (Shahzad et al., 2024). According to a study conducted in Pakistan by Fareed et al., mastitis is responsible for 17% of all animal disease-related economic losses. Early diagnosis of infection is crucial to effectively control mastitis. This includes understanding the etiology, developing sensitive screening tests, implementing sound management techniques, and avoiding the spread to uninfected animals (Chakraborty et al., 2019; Gurjar et al., 2012). The following factors are necessary for the successful treatment of clinical mastitis: the identification of the causative agent, the stage of lactation, the history of prior infection, parity, and other systemic disorders (Ruegg, 2017). Mastitis can be treated with traditional and cutting-edge therapeutic approaches including antimicrobial therapy, immunization, nanoparticle-based treatment, herbal therapy, and bacteriocins (Gomes & Henriques, 2016; Pinheiro Machado et al., 2019). The two most often utilized approaches for treating mastitis are immunization and antibiotic therapy. Excessive antibiotic usage and biofilm-associated resistance in mastitis have resulted in reduced responsiveness to antibiotic therapy (Panchal et al., 2024). Vaccination against bovine mastitis is inefficient due to the involvement of several bacteria. However, *S. aureus*, *S. uberis*, and *E. coli* were identified as key targets for vaccine development (Ashraf, 2020). Organic farmers in the USA use alternative therapies like as homeopathy, botanicals, vitamin supplements, and whey-based products to treat clinical mastitis. However, organic certification requirements such as no use of antimicrobials or hormones, organic feeds, and stress-free husbandry practices have resulted into limited alternatives for mastitis control in organic farms (Sharun et al., 2021).

Homeopathy as an Alternative Treatment

Homeopathy's use in food-producing animals is supported by data, despite limited scientific research on its efficacy (Keller & Sundrum, 2018). It is becoming more and more popular as an alternative treatment option for AMR, especially on organic farms (Doehring & Sundrum, 2016; Keller & Sundrum, 2018). Homeopathy is a holistic approach to immune system stimulation which is the foundation of this practice. One theory proposes that hemopathy remedies induce therapeutic effects by balancing or improving the energy of the patient. In addition to pathogen agents and clinical symptoms, homeopathy considers an animal's behavior, constitution, and surroundings (Løken, 2001).

Principles of Homeopathy

Three principles developed by German physician Samuel Hahnemann which are the foundation of homeopathy: the similia principle, drug testing with healthy persons, and dosage dilution (Aversa et al., 2016). Hahnemann observed during drug testing that the simile has the ability to start a healing process that results in symptoms in healthy individuals that are similar to the patient's symptoms (Similia similibus curentur or like cures like). Like cures like implies that a substance that can produce symptoms in a healthy person can relieve similar symptoms of an ill person (Tedesco & Cicchetti, 2001). This is a principle inherent to homeopathy, in accordance to which remedies are chosen. Traditionally, it started with Hippocrates and is a key component of homeopathy principles that defines a treatment strategy in the field of alternative medicine (Ling, 2021).

Homeopathy is a treatment approach based on the relationship between symptoms and remedies. Rather than considering the pathogen or cause of the disease, the remedy is typically selected based only on the clinical signs, traits, and behavior of the patient (Ling, 2020). A comprehensive anamnesis and an analysis of the patient's clinical signs and characteristics—such as body condition, mood, and modalities like behavior and symptom changes in response to environmental stimuli or outside factors that form the "symptom picture"—are necessary before beginning a homeopathic treatment (Weiermayer et al., 2022). A homeopathic materia medica is used to match it to a "remedy picture," which results in the "individualization" process of choosing the most likely effective homeopathic remedy including its dilutions and frequency of administration (Berna & Bagot, 2024). Table 1 depicts some of the homeopathic remedies used to treat mastitis.

Homeopathic drugs are potentiated medications derived from plants and minerals after drug trials on healthy people. Homeopathic drugs are rarely tested on animals, so these findings are transferred to veterinary medicine (Ekert, 2013). The active ingredient is diluted and shaken or triturated with a carrier substance to prepare homeopathic remedies. The homeopathic understanding of the drug is that its healing power is released through mechanical processing and becomes stronger with each step of potentiation (Esmaeili, 2022). The majority of the medicine is made up of an extract or solution that has been serially diluted, say, 1:10 or 1:100 from 10 to 100 ($10^{10\text{-}100}$, $100^{10\text{-}100}$). Stronger effects generally result from higher dilution. To improve the effectiveness of homeopathic remedies, each dilution step should be followed by vigorous shaking, known as "succussion"(Zeise & Fritz, 2019).

Table 1: Functions of Homeopathic Drugs Used to Treat Mastitis

Functions of some major homeopathic drugs used to treat mastitis Pocket Manual of Homeopathic Materia Medica (Parsani et al., 2023; William, 1981)	
Viz. Sulphur 200c, *Causticum* 30c, *Clematis flour* 200c, *Euphorbium* 200c and *Laurocerasus* 200c	Particularly helpful in treating stiffness, soreness, inflammation, redness in the teat and udder, and milk clots. It also has an antiseptic action and relaxes tissues.
Belladonna 30c, *Carbo vegetabilis* 200c, *Hepar sulfuris,* and *Bryonia alba*	Works on every area of the neurological system, causing active congestion, lowering hemorrhage from the lactogenic surface, and eventually curing mastitis
Chamomilla 30c, *Phytolacca* 30c *Arsenicum album* 30c, *Calcarea sulphurica* 30c, *Silica marina* 200c,	Traditionally a treatment for glandular swelling, it works to reduce inflammation and inflammation-induced swelling. It heals mastitis and has a potent impact on fibrous, mucous, and lactogenic tissues.

Efficacy Studies of Homeopathy Remedies for Mastitis

In medical fields, efficacy refers to measuring the desired effect of a treatment or a drug compared to no intervention or placebo in a randomized controlled trial to reduce bias from surrounding conditions. While the effectiveness of treatment refers to its use on farm or in real conditions (European Medicine Agency 2022). Homeopathy is one of the most widely used substitutes for antibiotic treatments when it comes to treating bovine mastitis (Hellec et al., 2021). The use of homeopathic remedies has many presumptive benefits in addition to lowering the use of antibiotics, such as low costs, no withdrawal period, availability over-the-counter, good customer reputation, and no role in the development of antibiotic resistance. Its unclear mechanism of action and uncertain effectiveness beyond a placebo effect, however, make homeopathy a contentious treatment option (Defiltro et al., 2020; Lees et al., 2017). Medicinal products must have proven therapeutic efficacy to ensure proper treatment for diseased animals. Randomized control trials (RCT) are considered to be gold standard tests to determine the therapeutic efficacy of homeopathic drugs (Kabisch et al., 2011). In RCT, participants are randomly assigned to one of two groups: experimental (receiving the new drug) or control (receiving a placebo).

Efficacy Studies of Homeopathy Treatment in Comparison to Allopathy and Placebo

Homeopathic remedies were used to treat various diseases. However, mastitis accounted for 60% of treatments in studies involving cattle from 1981 to 2014 (Doehring & Sundrum, 2016). A review by Dohering and Sundrum revealed heterogeneous results on the efficacy of homeopathic remedies to treat bovine mastitis. On the basis of diagnostic tests including direct detection of pathogen, California mastitis test, body parameters, and observation of clinical signs; 9 out of 20 trials on udder health and mastitis showed efficacy of homeopathy in comparison to allopathy and placebo (Doehring & Sundrum, 2016). These studies are not generalized rather than considered as single case studies because of lack of repeated trials in a comparable manner. There were twelve studies on the effectiveness of homeopathy for the treatment of mastitis that were published between 1989 and 2018 (Doehring & Sundrum, 2022). All the studies were analyzed on the specific requirement of RCT which included, randomization, control groups, individualization, blinding, exclusion, inclusion criteria, and diagnostic measures, where only 4 studies proved to be efficacious given in Table 2. Homeopathy cannot be promoted on farms due to lack of repeatable efficacy, even under controlled study conditions involving expertise and individualized treatment procedures (Mathie & Clausen, 2014).

Table 2: The Studies that Proved Efficacious in RCT from 1989 to 2018

Author	Study Design	Homeopathic Preparation	Active Ingredient	Diagnostic measure	Effect of Homeopathy
(Aubry et al., 2013)	Observational study on early subclinical mastitis treatment	Dolisovet® 10g ointment for intramammary use	(*Belladonna* 1dH, *Calendula MT*, *Dulcamara* 1 cH *Echinacea* 1 dH,	California Mastitis Test (CMT) and Body Parameters	Significant reduction of electrical conductivity and milk yield increased after 4-7 days
(Kiarazm et al., 2011)	RCT for subclinical mastitis treatment	Nosodes or Homeopathic vaccine Administered orally 5ml daily	Solution containing *Staphylococcus aureus* and *Streptococcus dysgalactia* in unknown dilution	Direct pathogen detection and CMT	Decreased bacterial detection and somatic cell count (SCC) in homeopathic treatment than placebo
(Werner et al., 2010)	RCT, Individualized mastitis treatment	Individualized homeopathic remedy identified on the principle of similium, Administered orally in sugar globule	*Phytolacca decandra*, *Hepar sulfuris, Bryonia alba, Mercurius solubilis*, *Pulsatilla pratensis*, and *Apis mellifica* all with D6 and D12 potencies	Direct pathogen detection and Clinical Signs	Effective over placebo group but no difference to antibiotic treatment
(Klocke et al., 2010)	RCT, Mastitis prevention at drying off	Individualized homeopathic remedy identified Administered orally in sugar globule	*Mercurius solubilis*, *Sulfur, Silica*, *Lachesis mutus*, *Pulsatilla pratensis*, *Calcium phosphoricum*, *Sepia, Calcium carbonicum* all at 10^6 dilution	Direct pathogen detection, CMT, and Clinical Signs	Lowered SCC and normal milk secretion

Efficacy Studies of Individualized Homeopathy in Comparison to Antibiotics

In another RCT, effectiveness of individualized homeopathy in comparison to antibiotics was determined at various levels including; bacteriological cure level and cytological cure level. 21 homeopathic remedies were chosen to treat animals with mastitis. Even though the study was meticulously planned to ensure that homeopathy was used correctly in the current RCT, the homeopathic treatment approach was noticeably less effective than the antibiotic treatment approach in curing clinical mastitis (Keller & Sundrum, 2018). Homeopathic healing effectiveness ranged from 45%, whereas antibiotics obtained an efficiency of 53% in 32 studies evaluated from 2012 to 2016 (Zeise & Fritz, 2019). There could be several causes for this. One common argument made in clinical studies about the effectiveness of homeopathy is the absence of an individualized homeopathic treatment, or repetorisation (Bez et al., 2024). The quantity, type, and strength of the treatment administered to each animal during the milking procedure in the milking parlor were the same. Some authors suggest using high potencies for acute diseases, while others use both low and high potencies (MacLeod, 2006).

Efficacy Studies of Homeopathy Preparations without Control Group

Another study focused on determining effectiveness of homeopathic preparation alone and in combination with other drug regimens to treat teat fibrosis in buffalos and dairy cattle in field conditions. Good clinical response with 50% reduction in teat fibrosis appeared in studies that used homeopathic preparation (*calacaria flour* 200C, *silicea* 200C, *Carbo-animals* 30C, *Phytolacca-Dioca* 200C, Alcohol content 91.4% and Phosphorous 30C) in combination with potassium iodide and serratiopeptidase after 6 days of treatment (Yadav et al., 2018). Furthermore, clinical effectiveness of homeopathic combination including *calacaria flour* 200C, *silicea* 200C, *Phytolacca-Dioca* 200C, *Ipecacuanha* 30C, *Belladonna* 30C, *Arnica* 30C, *Conium* 30C, and *Bryonia* 30C resulted in 96.72% effectiveness in non-fibrosed mastitis in riverine buffalo (Varshney & Naresh, 2004). Though the study proved the usefulness of homeopathic treatment but due to lack of a control group and small size (44 buffalos); homeopathic treatment can't be recognized as a generalized treatment (Varshney & Naresh, 2004).

In a case study, 6 cows of Rahi breed suffering from mastitis were treated with MESTEAT liquid containing *Belladonna*, *Mercurius Solubilis*, *Phytolacca*, *Chamomila,* and *Silicea*; given for about 2 months. This resulted into negative CMT and full recovery (Johri & Baberwal, 2024). Nevertheless, homeopathic therapy with *Silicea* 12C, *Belladonna* 12C, *Hepar Sulphur* 12C, *Phytolacca decandra* 12C, and *Phosphorus*12C in the feed of the lactating cows diagnosed to have subclinical mastitis shown to have no recovery in comparison to placebo or untreated group (Zafalon et al., 2023). In another case, biologically active substance of plant origin in homeopathic preparation (Icthyol® ointment) rubbed twice a day on udder and it showed a negative diagnostic test 2 days earlier than the control group and physiotherapy treated group. The drug has antimicrobial, anti-inflammatory, and immune modulating effects and it increased the gamma-globulins level in serum of sick animals (Kukeyeva et al., 2023).

Efficacy Studies of Homeopathy Preparation along with Antibiotics

Field trial-based research on effectiveness of homeopathic complex along with antibiotics on cattle suffering from clinical mastitis provided 90% recovery rate after 6 days of treatment. While 50% recovery rate reported for only antibiotic treated control group. The homeopathic preparation that was used in this trial included following active ingredients; *Belladona* 200, *Hepersulph* 200, *Silica* 200, *Calc flour* 200, *Conium* 200, and *Calc Carb* Q.S (as needed) (Chandel et al., 2009). A randomized controlled trial with triple blinding was planned to evaluate the effectiveness of homeopathic treatment for clinical mastitis in cows. A total of 162 dairy cows suffering from acute mastitis were randomized to receive either homeopathy (n = 70) or a placebo (n = 92). Allopathic treatments including antibiotics, anti-inflammatory drugs, and udder inflammation creams were also used in both groups to maintain animal welfare. Based on clinical symptoms, the homeopathic remedy was chosen; however, it was typically a combination of nosodes containing 200c potencies of Streptococcinum, Staphylococcinum, Escherichia coli, and Pyrogenium. These preparations undergo dilutions such that the pathogen does not remain infective but can induce humoral immunity (Kayne, 2021). The homeopathic group's cows received treatment at least once a day for 5 days. In the placebo group lactose globules were administered. The recorded data on observation of clinical signs, somatic cell count, and recovery time did not showed any additional effect of homeopathy over the placebo group (Ebert et al., 2017). Another study aimed to treat bovine clinical mastitis with homeopathic remedies Masta-forte+Actino Cure along with antibiotic therapy. A total of 160 animals suffering from clinical bovine mastitis were used for study. All the animals were diagnosed with clinical mastitis on the basis of clinical signs including udder redness, edematous, fibrosis, white flakes and blood in milk, and watery milk consistency (Steeneveld et al., 2010). All the animals were treated in two groups one with homeopathic medicine (2 ml. Masta-Forte+2 ml Actino Cure) orally twice a day for 20 days along with antibiotic therapy and the second group was only treated with antibiotic therapy. Among group one animals' recovery rate was 90.00% whereas group 2 recovery rate was 65.00% (Parsani et al., 2023). A 99.5% cure rate was achieved with homeopathy and antibiotics combined. This study indicates that homeopathic remedies cannot overrule allopathic treatments but when used in combination with fewer antibiotics, the mastitis cure rate and recovery duration improved indicating homeopathy can be used as a managemental approach rather than an alternative therapy.

Conclusion and Future Perspectives

Homeopathic remedies were found to be significantly more effective over a placebo and antibiotics treated group in various studies. In some trials, homeopathy has demonstrated that it may have a greater impact than to the placebo. The argument that homeopathy is just a placebo effect could be disproved by these studies' findings. It may be concluded that the preventative and therapeutic use of homeopathy in the chosen experiment had an impact, but the pathogen, research circumstances, and the chosen homeopathic medicine all affected the degree of cure of mastitis. Moreover, antibiotics use might be cut by as much as 75% when homeopathy and antibiotics were used together. This was accomplished by employing homeopathy, or if necessary, a mix of homeopathy and antibiotics. The phenomenon suggested that homeopathy might have a long-term impact that could support the maintenance of animals' health.

Homeopathy doesn't seem to be a universally applicable therapeutic option for mastitis. Rather, dairy practices should adopt effective preventative strategies and target-oriented therapy protocols based on bacteriological culture. Therefore, the use of individualized homeopathy is only advised in certain circumstances, such as treating mastitis caused by certain mastitis bacteria in conjunction with antibiotics (complementary therapy), scheduling timely follow-up visits, allocating adequate time for a homeopathic clinical examination, and having a working knowledge of homeopathic principles. Future research directions should be focused on Randomized control trials to prove and validate its efficacy in diverse farm practice circumstances (Bez et al., 2024). Homeopathy can be used as a complementary treatment rather than as an alternative to antibiotics.

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Chapter 54

Canine demodicosis: Herbal and Non-Herbal Treatment Strategies

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ABSTRACT

Canine demodicosis is a skin disorder caused by excessive multiplication of Demodex mites resulting in different degrees of dermatitis in dogs. Both herbal and non-herbal treatment strategies are effective. Non-herbals include topical acaricides such as amitraz and systemic anti-mite drugs like ivermectin or milbemycin oxime that target the mite populations and control inflammation. One needs to be cautious about certain basic care steps during treating this condition; these include, but are not limited to the right nutrients and cleanliness, while others involve using some herbs like neem oil and aloe vera on the dog's fur, which have been proven to reduce mite population while others may use other food supplements that enhance the immune system such as omega-3 fatty acids together with Echinacea for overall good health of the skin. Combining these two techniques would be helpful in terms of improving treatment effects. Thus, it is important to get involved with professional veterinary help in order to develop a personalized treatment plan that will carefully monitor progress made along this process. This review presents some aspects related to application and benefits of both forms of therapy for handling canine demodicosis.

KEYWORDS		
Canine demodicosis, herbal treatments, Demodex mites, acaricides, immune support, veterinary care	Received: 01-Jun-2024 Revised: 07-Jul-2024 Accepted: 06-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Demodicosis, also known as demodex, is a skin disease caused by excessive growth of Demodex mites which are normally present in small quantities in the canine skin. Dogs can become severely affected with skin sores and hair loss, to only mention a few symptoms. Management and resolution of this condition therefore require an understanding of the etiology, clinical presentation and treatment alternatives (Singh et al., 2011).

Demodex mites are commensals of the canine integument found primarily within hair follicles and sebaceous glands (Elston and Elston, 2014). Nevertheless, there are circumstances that may lead to over multiplication of these mites resulting in clinical signs associated with demodicosis such as immune-compromising conditions or genetic predisposition to the disease (Bensignor et al., 2006). Demodicosis is generally divided into two types: localized and generalized, it starts off with isolated patches of alopecia (hair loss) and mild redness referred to as localized demodicosis in puppies. However, generalized demodicosis consists of large areas covered by papules, pustules plus crusts sometimes followed by secondary bacterial infection hence difficult to treat (Hnilica, and Patterson, 2016).

The standard approach to dog demodicosis does not rely on herbal remedies, but involves the use of acaricides applied topically or administered internally. The application of topical treatments like dipping in amitraz is directed at mites that reside on the skin. On other hand, systemic treatments are by oral route or by injections using ivermectin and milbemycin oxime providing more extensive action against body mites (Marcondes et al., 2017). Such non-herbal therapies are often successful although they may have adverse effects associated with them thus requiring close surveillance and management.

Recently, there has been a growing interest in complementary herbal treatment of demodicosis. Herbal agents such as neem oil and aloe vera possess anti-parasitic and anti-inflammatory properties which make them useful (Singh et al., 2021). Neem oil obtained from the seeds of the neem tree has a broad-spectrum effect against different parasites including Demodex mites. Aloe Vera popular for its soothing and healing abilities can address skin irritations and promote growth of new skin cells. Furthermore, food supplements as omega-3 fatty acids alongside echinacea have been investigated to boost up immunity responses as well as maintain general skin health standards.

The combination of herbal and non-herbal therapies could result in a better demodicosis treatment protocol, thus enhancing drug effects while reducing overdependence on pharmacological treatments (Chakraborty and Pradhan, 2015). However, clinical studies need to be conducted to establish the drug's efficacy and safety when used together.

The following review provides a comprehensive summary of both herbal and non-herbal methods which have been employed for the management of canine demodicosis (Kebede et al., 2017). By looking into recent research and clinical practice, this review aims to provide an unbiased view on how this condition is managed highlighting advantages and disadvantages associated with each approach. The objective was therefore to enlighten veterinary practitioners as well as pet owners on effective therapeutic options thereby aiding in development of individualized treatment plans for affected dogs.

Background History

Demodicosis or demodex is a skin disorder in dogs due to over population of Demodex mites in the skin of the affected animals. This has been known in veterinary medical practice for over a hundred years and which has over the years transformed from a relatively older undiagnosed ailment into a more clinically distinct disease with relatively clearer guidelines for diagnosis and management. The approaches of treatment also transformed from non-herbal to herbal forms of remedies demonstrating the progress of the medical science and an increased focus on the use of natural therapies. The following background history gives a general information as to the evolution and appreciation of canine demodicosis explaining the shift in the approaches in handling this disease from the past practices to present practice (Kebede et al., 2017).

Prehistory and Some First Impressions

Early Veterinary Literature

Demodex mites can cause skin disease in dogs; their identification has been traced back to late-nineteenth- and early twentieth-century sources. Early findings were mostly associative, often indicating the existence of mites deep in the hair follicles of affected animal but without appreciable characterization of the role of these structures in diseases. But the first investigations were mainly devoted to the description of clinical symptoms of demodicosis and the definition of mite species (Englar, 2019).

Development of Diagnostic Methods

In the past, the approaches used for diagnosis of demodicosis were simple, basic clinical examination and simple microscopical examinations. Discoveries that marked a key shift in the knowledge of Demodex mites were made in the early part of the twentieth century, where enhancements in the techniques of microscopy revealed much about the anatomy of the parasites, as well as their complete life cycle. However, the diagnostic and therapeutic solutions, which were available even in the early years of this disease, did not evolve much (Nashat et al., 2018).

Evolution of Treatment Strategies

Traditional Non-Herbal Treatments

Early Acaricides

The management of demodicosis has since been dynamic especially after the administration of different acaricides in the mid-1900s. Chen pointed out that the practice of applying insecticides and other chemicals to control Demodex mites started to rise in the 1980s. He further stated baseline acaricides including organophosphate had higher prospects, although they were related to extra hazards like toxicity and inflammation.

Amitraz and Systemic Treatments

Considerable advancement in the management of canine demodicosis was realized with the use of Synthetic acaricide, termed as Amitraz. Although, amitraz was initiated in the 1980's as topical dip, it proved very effective in combating mites. This led the veterinary science practitioners widely use the drug, however; was also found to have adverse effects including causing the animals to be sleepy and have upset stomachs. With the development of systemic treatments, consisting in ivermectin and milbemycin oxime in the late of the 20th century there are more opportunities for treatment of more severe forms of demodicosis. These systemic therapies provided wider reach of mites control, but posed some risks towards the subject making their application needed some monitoring closely (Mueller, 2004).

Research and Development

The last decades of the twentieth century and the beginning of the twenty first century marked a great interest in herb use in veterinary dermatology. Further searches to explore the use of the various herbs to treat demodicosis were also initiated with a view of conducting experiments on the efficacy of plant extracts. This period also saw an introduction of the use of adjunctive therapies together with the main therapeutic procedures and it was catalyzed by both the practitioners and the pet owners.

Recent Developments and Synthetization of Treatment Modalities

Understanding of Demodicosis

Modern studies have helped to elaborate pathogenesis of demodicosis, and the involvement of Demodex mites in the development of the disease. Molecular biology and genetics have given detailed information on the relationships between the mites and the immune system of the host thus helping in developing better therapies without side effects. This is because there is an understanding of specific genetic linkages and factors of the immune system hence giving a better way of handling the condition.

Herbal and Non – Herbal Remedies

The combination of herbal and non-herbal treatment is new advancement in the management of canine demodicosis. In today's practice of veterinary medicine, it becomes common practice to use synthetic acaricides together with the natural herbicides (Poppenga, and Oehme, 2010). This integrative method is proactive to improve on the treatment results by attacking the direct mite burden and skin condition.

Comparative Efficacy

Research has been done in assessing the effectiveness of the herbal and non-herbal remedies to determine the strengths and weaknesses of the two. It has been found that whereas non-herbal treatments are effective for mite control through amitraz and systemic acaricides, additional benefits of herbal treatments in terms of symptom relief and, immunomodulatory effects are also useful. These methods make it possible for a more effective management program that will address the problem from different angles based on the needs of the affected dogs.

Safety and Regulatory Considerations

As can be seen in the preceding sections, questions of safety and legislation regarding herbal treatments are also significant in veterinary medicine. Despite the fact that natural products can have few side effects, they need to undergo scrutiny in terms of effectiveness and compatibility with the rest of the medication. Quality of these products must be regulated to meet the safety standards as well as the therapeutic value whenever they are to be used.

Canine Demodicosis Pathophysiology

Primarily, demodicosis is caused by demodex mites that live in the hair follicles and sebaceous glands of the skin. The two main species involved being *Demodex canis* and *Demodex injai*. Under normal circumstances, these mites do not harm the host but may overgrow due to factors like immunological defects, genetic predispositions or concurrent diseases (Veena et al., 2017). As a result of multiplication, there is inflammation causing alopecia, erythema, and secondary bacterial infections.

Clinical Presentation

Localized Demodicosis

Localized or focal demodicosis is also seen in young dogs this is a local patch of hair loss. This type of owl eye adenovirus, which is typically limited in duration and may resolve with little intervention. Common clinical signs of MG include focal alopecia and mild inflammation most frequently around the face, ears or legs. It is less severe and can be treated with specific drugs.

Generalized Demodicosis

Generalized demodicosis presents with the involvement of a large area of skin, and is more difficult to treat. In severe cases, it leads to stupendous hair loss (whole the body), enormous inflammation and even spread of secondary bacterial infections as well systemic manifestations. The classic form, usually observed in elderly dogs or those that are immunosuppressed due to a pre-existing medical disorder they have a clinical presentation of pustular lesions, thickened skin and significant discomfort.

AIN-Lowering Treatment Other Than Herbal Methods

Topical Treatments

Various topical acaricides are used for the management of demodicosis. Topical dips, like Amitraz have been the traditional treatment for years. It works by attacking the living mites on your skin. Amitraz is usually successful however, it does have the incidence of causing side effects in some dogs such as lethargy or gastrointestinal upset. Additional topical treatments consist of benzoyl peroxide or sulfur shampoos which are used to decrease mite populations and control secondary infections.

Systemic Treatments

The Systemic acaricides, they provide a wider therapeutic effect by focusing on parasites in any part of organism. Two of the most popular oral medications for treating Demodex are ivermectin and milbemycin oxime. The most popular treatment options the fact that actually work on parrot mite vs people tend to be topical antiparasitic medications similar ivermectin. Systemic therapy, meanwhile which works throughout the body but lacks precision in targeting colorectal cancer cells specifically must be carefully dosed and monitored for neurological or gastrointestinal toxicity.

Supportive Care

The most important is supportive care in preventing and managing demodicosis. This one can be managed by some basic homegrown treatment such as care of personal hygiene, usage of medicated shampoos to clean the skin and appropriate diet assistance in favoring up immune system. It will also be paramount to address secondary bacterial infections with antibiotics tailored to the flora involved.

Herbal Treatment Strategies

Topical Herbal Remedies

Dermatologists may use these products as a complement to traditional therapy for demodicosis. Neem oil comes from the seeds of neem tree and has anti-parasitic properties, meaning it can help reduce mite numbers when applied topically. Aloe vera is also a topical therapy with anti-inflammatory and skin healing properties which reduce inflammation in the region of application, as well facilitate repair of tissues damaged. Most of these remedies are safe and can be taken alongside conventional treatment.

Herbal Supplements

Herbal supplements can help in the general control of demodicosis following that they boost immunity and improve skin health. Fish oil is also a very good source of Omega-3 fatty acids which are well-known for their anti-inflammatory nature, thus can contribute to decreasing inflammation on the skin. Echinacea is recognized for its immune-boosting gains and could benefit deal with the innate immunity failings involved in demodicosis Need to be used under veterinarian guidance for the right dosage and effect.

Integrative Approaches

Herbal and non-herbal products may be effective as integrated therapeutic options, for the control of demodicosis. For example, topical herbal treatments could be used alongside systemic acaricides in order to enhance treatment efficacy and reduce dependence upon pharmacological agents. An integrative approach, treating the condition both directly by controlling mites and indirectly by bolstering immune function is also possible.

Discussion Efficacy and Safety Profile

Treatment strategies for demodicosis can differ in efficacy with the severity of disease and individual dog response. Non-herbicide treatments like systemic acaricides have been found to work well in managing mites and overcoming the symptoms. Nevertheless, these interventions are often accompanied by adverse effects and need to be monitored carefully.

This is even though herbal treatments, although promising, do not have as much scientific evidence to support them in the same way conventional therapy does. Herbal remedies are much less studied than pharmaceuticals, and because of that the efficacy is highly variable from one supplement to another. In addition, herbal treatments have a favorable safety profile, but drug interactions with other medications or treatment must be considered.

The successful management of canine demodicosis is the outcome of a combination of conventional as well as alternative treatment modalities. Currently there is no effective herbal treatment of BD; however, they can be treated with topical treatments (like acaricides), through using systemic and other products. There are topical as well ayurvedic treatments, herbal applications and a slew of medications offering additional options for all-around skin health. Combining these tactics could implement a more holistic treatment, specific to conditions seen in infected dogs. As in the case of all pediatric patients with TPLO, and especially young active dogs under 1 year old, veterinary consultation is important to help develop an effective treatment plan and monitor progress for best results while minimizing risk

Pathogenesis of Canine Demodicosis

Canine demodicosis is a multifactorial disease with immunogenetic predisposition and external stimuli playing a role in the pathogenesis of disease (Ralf Mueller et al., 2011). The primary factors contributing to the onset and progression of demodicosis include: The primary factors contributing to the onset and progression of demodicosis include:

Immunological Factors

Immune Suppression

Dogs with coexisting diseases that can affect the immune system, for instance neoplastic diseases, or dogs who have been treated with immunosuppressive compounds, are most vulnerable to demodicosis (Chudzicka-Strugała et al., 2023).

According to the present research study, the immune system fails to contain the mite population within the body hence they increase in number.

Cell-Mediated Immunity

In demodicosis, the immune response is mainly characterized by the cell mediated immunity. The inability or a decline in the function of T-cells or helper T-cells reduces the capacity of the immune system to regulate mite population density leading to disease development.

Genetic Predisposition

Breed Susceptibility

Demodicosis is more common is certain breeds of dogs such as the Bulldogs, Shar-Peis, and the Terriers. This indicates that the cause could be hereditary and maybe have something to do with the immune system and or skin's defense system.

Inherited Defects

Sometimes, demodicosis is connected with the congenital abnormalities in the immune system of a dog. Generalized demodicosis means that the disease has affected most areas in the body, and it is inherited, to some extent, by dogs with such family history (Chudzicka-Strugała et al., 2023).

Mite Biology and Behavior

Mite Proliferation

Demodex mites are ectoparasites which in general are harmless residents of the skin of their host (Kocoń, A. and Nowak-Chmura, 2017). However, in immunocompromised host the mites multiply in large numbers causing folliculitis, furunculosis and seborrhea. Localized infestation may cause pruritus, erythema and vesiculation that could be secondary to the mite's introduction of an inflammatory mediator.

Mite Antigens

Demodex mite produces antigens which trigger an immune response, which leads to manifestations of inflammation of the skin as well as further destruction of the skin. These antigenic stimulations are involved in the disease process of the above disease.

Environmental Factors

Stress and External Environment: It is noticeable that the factors that may worsen the state of health include unsuitable nutrition, simultaneous infections and environmental toxins. This may be because stress affects the immune levels of dogs, and thus allows the mite population to grow.

[Genetic Predisposition] ---> [Immunological Factors] ---> [Immune Suppression] ---> [Mite Proliferation] ---> [Inflammation and Skin Damage] ---> [Clinical Manifestation of Demodicosis
[Cell-Mediated Immunity]

Comparison of herbal and Non-Herbal Treatment

Non-herbal Treatments

Non- herbal treatments are well described in veterinary dermatology, including Amitraz is a derivative of formamidine acaricide and has been used widely since many decades. It works through the inhibition of monoamine oxidase enzyme within mites causing involvement with their paralysis and eventually death. Amitraz is often used as a dip or spot-on medication. The toxicity of amitraz–although generally effective, is associated with side effects like sedation (incoordination), bradycardia and hypothermia that may restrict its usage in some dogs.

Macrocyclic Lactones

The most widely used systemic treatment for canine demodectic mange is either ivermectin or moxidectin. Oral use of Ivermectin and spot-on formulations with Moxidectin are available. These drugs act on the glutamate-gated chloride channels of mites with resultant nerve and muscle cell hyperpolarization resulting in death. Although effective, these drugs can be especially neurotoxic and therefore should not be used in dogs with a mutation of the MDR1 gene found most commonly among Collies.

Isoxazolines

More recently, many studies fluralaner and afoxolaner were used for demodicosis treatment. Oral chewable tablets Oral chewable have demonstrated higher efficacy and lower adverse events than traditional acaricides. Isoxazolines acts by antagonizing the ligand-gated chloride channels in mites resulting to their death. This relatively benign safety profile is what makes the use of Isoxazolines appealing for ongoing prolonged management.

Herbal Medicine for Canine Demodicosis

In the past few years, there has been a sharp increase in herbal treatments which serve as alternative medicine for biomedicine and gain popularity due to its safety profile/ perceived efficacy.

Neem oil comes from the neem tree and is known for its insecticidal, anti-fungal, and anti-inflammatory activities (Uzzaman, 2020). Azadirachtin (disrupts mite development and reproduction. There are some reports that suggest topical applications containing neem oil can reduce mite density and improve the skin of dogs with demodicosis; however, further trials must be conducted on a clinical level.

Tea Tree Oil (Melaleuca alternifolia)

The acaricidal and antimicrobial efficacy of tea tree oil has been well investigated. Its major active ingredient is terpinen 4-ol that has been found to work well against wide range of ectoparasites which includes demodex mite. Tea Tree oil is TOXIC to dogs but can be used carefully (Tighe et al., 2013).

Essential Oils

Other essential oils such as lavender (Lavandula angustifolia) and eucalyptus (Eucalyptus globulus) have also been studied for their acaricidal potential. The mechanism by which these oils work may involve disruption of the mite nervous system, or it could be through actual die-off of the mites themselves. In vivo efficacy has yet to be fully established in cases of canine demodicosis, despite the initial promising results from an in vitro study.

Herbal Extracts

Different herbal extracts such as chamomile (Matricaria chamomilla) and calendula (Calendula officinalis), which have anti-inflammatory and wound-healing properties to help therapeutic the secondary skin lesions of demodicosis (Tresch et al., 2019).

Comparative Analysis

How to Compare Herbal and Non-Herbal Therapeutic Agents in the Topical Treatment of Canine Demodicosis

Effectiveness

Non-herbal treatments, specifically isoxazolines and ivermectin, have been proven effective in decreasing mite populations to cure clinical signs of demodicosis. Natural remedies, though they offer much potential are not usually sufficiently experimented to have the same strong data behind them that modern therapy (Chakraborty and Pradhan, 2015).

Safety

Herbal remedies are often considered to be safer because they come from nature. That being said, it is not always the case as some herbal substances can be very toxic to dogs and even cause allergies. Actual treatments work, but have side effects especially in certain breeds. The truth is that any treatment can only be safe if it is dosed and administered correctly.

Resistance

The development of drug-resistant mites is an important issue with prolonged use of non-herbal treatments, especially in older acaricides such as amitraz. Because of the complex composition, herbal therapies might be less prone to resistance development; however more research is needed in this regard.

Cost and Accessibility

Non-herbal treatments tend to be more expensive, and many of them are not safe for a pet owner giving their own treatment if done without veterinary advice or supervision. In this perspective; it maybe those herbal treatments, especially sourced from common plants could provide a more affordable and easily available option to dog owners, particularly in resource-limited settings as they do not require specialist extraction chemicals for their preparation.

Conclusion

Both herbal and non-herbal treatments have their respective advantages and limitations in the management of canine demodicosis. While non-herbal treatments offer well-established efficacy and quicker results, they are often accompanied by potential side effects and the risk of resistance. Herbal treatments provide a natural alternative with potential acaricidal and anti-inflammatory benefits, but they require further research to establish standardized protocols and to validate their efficacy through controlled clinical trials. The choice of treatment should be guided by the severity of the disease, the individual dog's health status, and the owner's preferences, with an emphasis on safety and the potential for long-term management of the condition. Future research should focus on integrating herbal treatments into holistic therapeutic regimens, potentially in combination with non-herbal treatments, to optimize outcomes for dogs suffering from demodicosis.

Both herbal and non-herbal treatments have their respective advantages and limitations in the management of canine demodicosis. While non-herbal treatments offer well-established efficacy and quicker results, they are often accompanied by potential side effects and the risk of resistance. Herbal treatments provide a natural alternative with potential acaricidal and anti-inflammatory benefits, but they require further research to establish standardized protocols and to validate their efficacy through controlled clinical trials. The choice of treatment should be guided by the severity of the disease, the individual dog's health status, and the owner's preferences, with an emphasis on safety and the potential for long-term management of the condition. Future research should focus on integrating herbal treatments into holistic therapeutic regimens, potentially in combination with non-herbal treatments, to optimize outcomes for dogs suffering from demodicosis.

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Chapter 55

Botanicals as an Alternate for Tick Infestation in Livestock

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ABSTRACT

In Pakistan, agriculture is the primary livelihood for many people, with livestock rearing being a key component. However, ticks, as ectoparasites, pose significant threats to these animals, potentially leading to severe health issues or even death. In underdeveloped regions like Pakistan, where proper knowledge and resources are scarce, the economic impact of tick infestations is substantial. Farmers commonly rely on acaricides to manage tick populations, but these chemical agents are not only costly but also contribute to environmental contamination, toxicity, and the development of tick resistance over time. Given these challenges, medicinal plants are emerging as a promising alternative to synthetic acaricides. Species such as *Calotropis procera, Ocimum basilicum, Allium sativum, Allium cepa, Cannabis sativa, Aegle marmelos, Carapa guianensis, Citrus maxima*, and *Withania somnifera* have demonstrated varying degrees of effectiveness in controlling tick populations and reducing the impact of tick-borne diseases.

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INTRODUCTION

Pakistan is an agricultural country predominantly, accounting for 21% of GDP. Pakistan's population lives in villages, works in fields, and depends on livestock over 70% (Mather and Abdullah, 2015). Animals such as goats, camels, cows, and buffalos are raised professionally, and 30-35 million people make a living from it. Farmers in tropical and subtropical regions have higher losses due to animal parasite disease epidemics (Batool et al., 2019). Ticks, as blood-sucking ectoparasites, pose significant harm to livestock and often cause widespread infestations. (Admassu et al., 2015). These ectoparasites, which feed on blood, affect mammals, birds and reptiles (Ali et al., 2016). Ticks feed on their hosts' blood, resulting in weight loss, decreased meat and milk production, and skin damage (Khan et al., 2022). Ticks provide a substantial health risk to animals because they can spread disease, cause miscarriage, and even death (Durrani and Kamal, 2008; Zulfiqar et al., 2012). Ticks are zoonotic, which means they can spread diseases between animals and humans (Karim et al., 2017).

Life Cycle of Ticks

Ticks live in four stages: eggs, larvae (six legs), nymphs (eight legs), and adults (eight legs) (Blouin et al., 2021). Ticks are classified into three categories according to their life cycle (Figure 1): single host, two-host, and three-host ticks (Fletcher, 2003). Throughout their post-embryonic life, one-host ticks stay on just one host; adult ticks finally detach from their host. In order to complete their life cycle, two-host ticks need two hosts: after feeding, the larvae on one host mature into nymphs, which then separate to become adults looking for another host. Ticks with three hosts go through a process whereby the larvae molt into nymphs and depart from the host to feed; one particular host is needed for each developmental stage (Ali et al., 2013). Ticks use not only their eyes, but also a sensitive hair-like peripheral structure on their legs, body, and mouth to aid in their host-seeking activities. Ticks contain olfactory sensors that allow them to locate hosts and communicate with one another (Leonovich, 2013; Carr and Salgado, 2019). Ticks also react swiftly to ammonia and carbon dioxide, indicating the presence of a host (Auffray et al., 2022).

Tick-borne Diseases

Ticks leads to many diseases as shown in (Table 1)

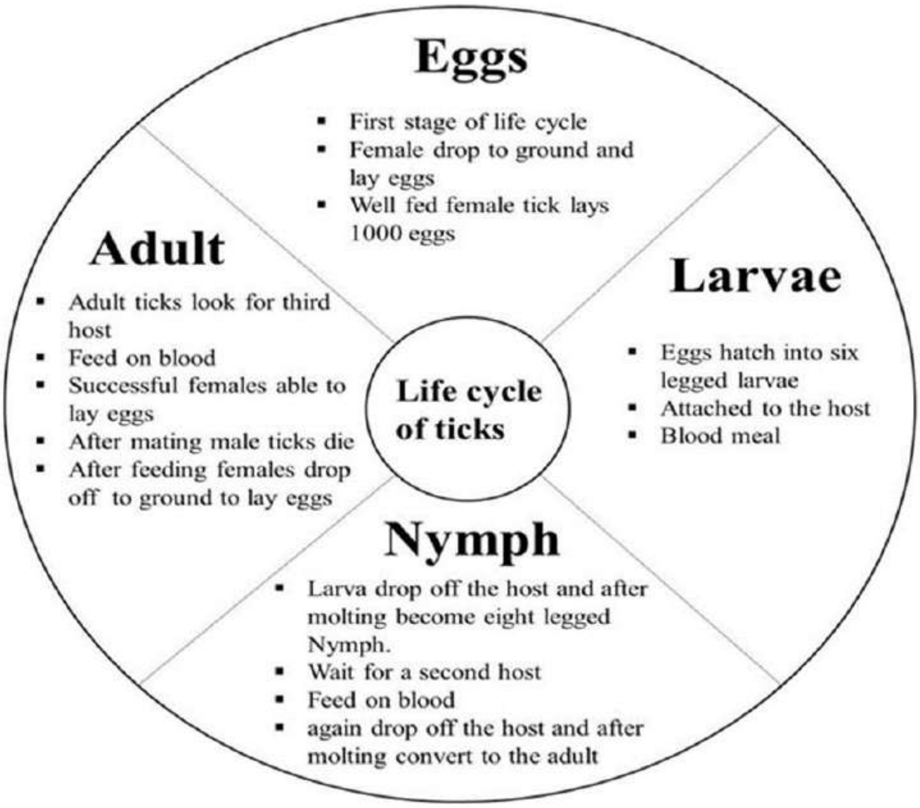

Fig. 1: Complete life cycle of tick

Table 1: Common tick borne diseases their causative agent, symptoms and mode of transmission

Sr #	Disease name	Causative agent	Mode of transmission	Symptoms	References
1	Lyme disease	*Borrelia mayonii*	*Borrelia burgdoferi*	Skin rash, fever, joint pain	https://www.cdc.gov/lyme/index.html.
2	Rocky Mountain spotted fever	*Rickettsia rickettsia*	*Dermacentor variabilis, D.andersoni, Rhipicephals sanguineus*	Headache, rash, nausea, muscle pain, vomiting abdominal pain fever	https://www.cdc.gov/rmsf/index.html.
3	Babesiosis	*Babesia microti*	Infected *Ixodes scapularis*	Sweating, chills, muscle aches, fever, hemolytic anemia , fatigue	https://www.cdc.gov/parasites/babesiosis/index.html.
4	Anaplasmosis	*Anaplasma Phagocytophilum*	*Ixodes scapularis* and *I. pacificus*	Nausea, loss of appetite, diarrhea, severe headache, fever, muscle aches	https://www.cdc.gov/anaplasmosis/index.html.
5	Ehrlichiosis	*Ehrlichia chaffeensis, E.ewingii E.muris,*	*Amblyomma americanum* and *Ixodes scapularis*	Headache, chills, upset stomach, fever, nausea, rash, muscle aches	https://www.cdc.gov/ehrlichiosis/index.html.

Application of Acaricides for Tick Control and Identification

The chemicals used to kill ticks are known as acaricides. Some of the poisons used against ticks over the last two decades include macrocyclic lactones, organophosphates, and pyrethroids (Abbas et al., 2014). Each acaricide behaves differently. Some distinct kinds of acaricides are listed below:

a) **Metabolic Acaricides**

Through attacking tick metabolic processes, metabolic acaricides eliminate the ectoparasites.These acaricides inhibit or reduce the function of enzymes required for cellular respiration in a variety of metabolic pathways. For example, 3-BrPA can inhibit the activity of hexokinase, a glycolytic enzyme, by up to 50%. Similarly, metabolic acaricides can change the response time of glycolysis and gluconeogenesis enzymes. They can also harm the mitochondrial respiratory chain, killing ticks (Braz et al., 2019).

b) Neurotoxic Acaricides

Neurotoxic acaricides are those that cause electrical or chemical reactions in tick neurological systems (Hart, 1986). Neurotoxic acaricides target tick neurological systems, causing paralysis and death (Cerqueira et al., 2022). These acaricides cause paralysis and increased nervous system activity by blocking the sodium ion channel (Wismer and Means, 2018). Pyrethrins, permethrin and pyrethroids are all neurotoxic acaricides (Abbas et al., 2014).

c) **Repellent Acaricides**

Repellent acaricides usually do not kill ticks, but instead prevent them from feeding, hatching, and molting on the host. Most repellent acaricides emit a characteristic odor that impairs ticks' olfactory senses, making it difficult for them to recognize or cling to their hosts. Certain medications have been shown to repel ticks (Kayaa, 2000).

Effects of Acaricides

The usage of these acaricides has various disadvantages, including contaminating our environment and attacking non-targeted organisms, which is harmful to human and animal health (Monteiro et al., 2018; Nath et al., 2018). Most tick species are resistant to many medications (Abbas et al., 2014). Many farmers in Pakistan claim that certain vital herbs are excellent at tick control (Zaman et al., 2012). Ticks are external parasites that can harm animals and people, either directly or indirectly. Tick-borne diseases have become a leading cause of economic losses in the global livestock industry, with nearly 10% of all ticks capable of transmitting diseases as vectors (Jongejan, Uilenberg, 2004). Ticks are a serious impediment to the development of the livestock business because ticks have a severe impact on milk and meat output, and Ticks consume the blood of the animal, causing weight loss. They also make animals prone to viral, bacterial and fungal, infections (Ahmed et al., 2007). Acaricides are chemicals used to control ticks, however there are numerous issues associated with their use.

a) Expansion of Resistance

A significant drawback with employing acaricides is that over time, ticks become resistant to the chemicals, making them ineffective for control purposes an example of this is observed in *Rhipicephalus* (Boophilus) *microplus*, a tick species infesting cattle, where resistance against acaricides has been documented (Davey et al., 2006).

b) Chemical Costs

Despite their high cost, these pesticides are not widely accessible and might be difficult for farmers to afford them, especially those countries that are developing (Dipeolu et al., 1992).

c) Environmental Contamination

There is also the problem of environmental toxicity brought by chemical acaricides because their residues contaminate the environment (Mulenga et al., 2000; Wellington et al., 2017).

Toxicity to Humans and Animals

The substance which is used for combating the acarines affects, in turn, animals and people. Any wrong handling during treatment or application of these chemicals also have toxic implications for both (Madzimure et al., 2011).

Meat and Milk Contamination

Persistence in the carcase and offal, acaricidal chemical residues may contaminate the meat and milk of the animal. People may face a lot of health problems by consuming contaminate meat and milk products infected with bacteria. As it has been noted earlier, the process of synthesizing new acaricides is challenging and demanding (Nath et al., 2018). Thus, it becomes imperative to come up with some method and strategies that are efficient as well as innovative against these ticks. People have been using plants for treatment of various diseases; but in today's world of modernization, it is mandatory to isolate these biologically active compounds to produce good drugs (Abubakar and Haque, 2020). Due to many adverse effects of acaricidal medications, it is imperative that an alternative approach for controlling ticks is sought. It is because, therefore, the opportunity of using plant extracts as an optimal approach to eliminating ticks and mites as well is equally significant as it is efficient not to mention eco-friendly.

The Importance of Medicinal Plants

In a historical evaluation of medicinal plants, the article pointed out that, traditional information that has been passed over the use of the knowledge of these plants has been through generations of observations and experiences of their efficiency in treating various diseases. Allopathic and Ayurvedic treatments as well as traditional practices have been used plant parts to cure diseases affecting the lungs, toxicity, skin diseases, stomach disorders and neurological disorders (Muthu et al., 2006; Rana et al., 2021). Traditional medicines especially those that use herbs have been considered as treatment remedies for various illnesses with the possibility to eradicate diseases like COVID-19.

However, previous studies carried out by (Polat et al., 2013) towards the documentation of traditional uses of medicinal plants in Solhan; Bingol- Turkey and Malatya- Turkey. Another research done in Nigeria is by (Bhat et al., 1985) who undertook a survey on traditional use of plants in Nigeria and ascertained that 24 species of plants were used for medical purposes in different regions of Nigeria. A similar knowledge was studied in a little more detail in the Indian Himalayan area of Chhota Bhangal western himalaya by uniyal et al 2006 and on the part of terai and central development region of Nepal among the tribal population by Joshi and Edington 1990.

Calotropis procera

The plant studied is *Calotropis procera* (figure 2) or more commonly known as aak which belongs to family Apocynaceae (Kaur et al., 2021). *Calotropis procera* is a deciduous plant which is somewhat woody, adolescent and has a high germinating growth rate in the semiarid and dry regions of the world without having regular accesses to fertilizer or irrigation water (Kaur, Verma, Nagori, and Chadha, 2021). These xerophytes can grow to be of 6m in length and prevalent in East Africa as well as Asia according to Witt, Beale, and Van Wilgen, 2018. These plants have opposite as well as alternate leaves rulings on the stems. They mostly have bronze colored dusted white sepals which are purple at the tip and have white petals which form at the terminal or axillary positions (Abeysinghe and Scharaschkin, 2022).

Fig. 2: *Calotropis procera*

Ocimum basilicum

Sweet basil is an annual herb that usually reaches a height of about two feet. It is formally known as *Ocimum basilicum* and belongs to the *Lamiaceae* family (figure 3). it is commonly found in Tropical, subtropical, and arid regions (Rubab et al., 2017 ; Egata, 2021) It is grown exclusively in Pakistan's Punjab province. This herbaceous plant throws off a powerful scent and grows branches on both sides (Rubab et al., 2017). The abundance of phenolic acid, phenolics, flavonoids, many polyphenols, and significant essential oils in the plant confers therapeutic significance. Leaves have been used traditionally to treat asthma, fever, and cough. Additionally, it has been shown to be beneficial for menstrual cycle abnormalities (Shahrajabian et al., 2020). Oil of this plant has been found very effective against muscle cramps, cold and brain fag (Naz et al., 2015) also given as a first aid for snake bite and insect sting (Adam et al., 2019; Nguyen et al., 2022). Using plants as a treatment for digestive issues, diarrhea, and dyspepsia is thought to be effective (Nazir et al., 2021; Kumar et al., 2022). The main medicinal use for this plant emerges from its anti-inflammatory and anti-cancerous properties. In addition to this, it is known as an anti-stress substance (Shahrajabian et al., 2020).

Allium sativum

Allium sativum (figure 4) commonly known as Garlic or Lehsan, belong to family *Amaryllidaceae,* has been efficaciously used for tick management (Jagadeeswary et al., 2014). Farmers in Canada, Brazil, India and Pakistan have successfully managed tick populations by using Garlic .Potential therapeutic applications with naturally occurring compounds in this herb with include, allyl methyl thiosulfnate, diallyl thiosulfnate (allicin), alliin, ajoene, diallyl disulphide, methyl allyl thiosulfnate ,diallyl trisulfde and ,deoxyalliin (Aboelhadid et al., 2013). Allicin is believed to be the most effective of these substances in reducing tick infestations (Martins et al., 2016). At a dose of 40 mg/mL on ticks, this plant demonstrated a highly deadly effect on eggs lying down, egg hatching, and overall larval death. After 96 hours following treatment, a 45% solution containing both herbal extracts substantially reduced the amount of ticks in cattle (Nasreen et al., 2020). When treated at particular dosages, garlic essential oils generated substantial mortality (90-100%) in 10-day-old *R. microplus* tick larvae (Madzimure- Nyahangare et al., 2011).

Fig. 3: *Ocimum basilicum*

Fig. 4: *Allium sativum*

Allium cepa

Allium cepa (Figure 5) is a single cotyledon bulbous plant that is harvested twice a year and is the most widely farmed among allium species. Sulphur compounds in A. cepa are responsible for its distinct taste, odor, eye irritation, and therapeutic effects (Brewster 2008). The onion (*Allium cepa*) belongs to the *Amaryllidaceae* family and is one of the most frequently farmed plants in the genus *Allium* (Koneru et al., 2016). *Allium cepa's* phytochemical screening revealed the presence of alkaloids, cardiac glycosides, flavonoids tarpenes, and resins (Gazuwa et al. 2013). *Allium cepa* has thiosulphonate and quercetin which has curative benefits (Kumar et al. 2010). A significant result was obtained that *Allium* cepa possess activity against Boophilus annulatus. The study showed that the best in vitro extract of *A. cepa* was ethanol extract of this plant (Sarwar, 2017. At acaricidal activity of methanol and aqueous extracts from the red cultivar of *Allium cepa* on female L. *Rhipicephalus* (*Boophilus*) annulatus ticks that were fully fed and engorged were tested in a study. Aqueous extract at 400 mg/ml in the red cultivar *Allium cepa L.* resulted in a tick mortality rate of 66. 66% at the same time frame that the mortality rate by cypermethrin was less at 25%. The percent inhibition of oviposition that is 80% resulting from the aqueous extract of red cultivar *Allium cepa L* was higher than that of cypermethrin.

Cannabis sativa

Marijuana or hemp or ganja belong to the Cannabaceae family of plants, and has been used in the past to repel insects (Johnson et al., 2019). This results probably from the terpenes, ketones, and ester chemical compounds present in the leaf glands rendering the variety to possess a foul smell that can scare away insects (Bonini et al. 2018). Raw cannabis leaves contains as much as 75per cent volatile compounds like; limonene and pinenes, the last a known insecticides (Elzinga et al. 2015). Methyl ketones isolated from *C. sativa* helps in reducing crop pest (Andre et al. 2016). It is as a result very likely that the combined activity of these compounds could make *C. sativa* important in controlling livestock arthropod pests. Research conducted have shown that the oils which are extracted from the industrial hemp possess important anti-tick attributes (Nasreen et al., 2020). In this study cannabis which belongs to *Cannabis sativa* (figure 6) was tested on *Rhipicephalus microplus* for its efficiency using the following methods; adult immersion and larval packet methods. It had a very high lethality score to egg laying, egg hatching and overall larval deaths at a concentration of 40 mg/mL. A 45% solution of herbal extracts caused a reduction of at least 50% ticks on the body of cattle 96 hours after treatment. The study indicates that *C. sativa* should be investigated further as a supplement or substitute for synthetic acaricides due to its the ability to manage *R. microplus* ticks (Nasreen et al., 2020).

Fig. 5: Allium cepa

Fig. 6: *Cannabis sativa*

Aegle marmelos

Aegle marmelos (Fig. 7) commonly called bilwa or bael is one of the most essential medicinal plants in the ayurveda. The only species in the Aegle genus and a part of the *Rutaceae* family, it is known in English as the 'stone apple' Aevergreen, slow growing, thorny and erect subtropical tree is native to India, Thailand ,Burma, Ceylon and Indochina (Palatty et al., 2013). In this plant, the main phytochemical group found are; steroids, aeglemarmelosine, alkaloids and coumarins. Feared species of tick such as *H. bispinosa* and R. (B.) micro plus belong to this category. In another study done for 24 hours, the study showed that 100% mortality of *H. bispinosa* caused by acaricide and 100% mortality of R. (B.) microplus by larvicide (Elango et al 2011).

Carapa guianensis Aubl.

Carapa guianensis (Fig. 8) of the *Meliaceae* family and commonly known as andiroba tree. Its origin of the name is from the indigenous language, tupi-guarani, of Brazil and it means 'bitter taste' (Parveen et al., 2021)). Local people of northern Brazil, have incorporated *L. leucocephala* in their traditional remedies as an antirheumatic, antithermic, antibacterial, anti-inflammatory, and repellent for insects using the oil derived from the seeds (Roma et al., 2013). This substance also prevents egg laying behavior in the female *Boophilus microplus* and *Anacentor nitens* ticks and at the same time functions as acaricides (Farias et al., 2007). This paper established that Andiroba seed oil treatment impacts on the oocytes morphological and physiological characteristics hence reducing the reproductive potential of female *Rhipicephalus sanguineus* ticks. Several of these changes advantage the survival of tick embryos; thus, the protein, polysaccharide, and lipid content of these cells reduces considerably.

Fig. 7: *Aegle marmelos*

Fig. 8: *Carapa guianensis Aubl.*

Citrus maxima Burm

Citrus maxima burm (Fig. 9) is also known as Shaddock, Papanus, Pummelo, and Chakotra is a perennial shrub belongs to the family *Rutaceae*. This fruit is consumed in the raw form throughout the length and breadth of India (Louzada et al., 2021). Different parts of this plant have been shown to possess medicinal properties by several researches done across the world. The chemical composition of this plant fruit consists of phenol, saponin, alkaloid, tannin and terpenoids (Chanthaphon et al., 2008).

Fig. 9: *Citrus maxima Burm.*

Fig. 10: *Withania somnifera Dunal*

Withania somnifera Dunal

Withania somnifera Donal (figure 10) is a member of *Solanaceae* Family. It is one of the most extensively utilized medicinal crops in India's late Kharif season, farmed commercially on dry ground. Other common names for this plant are Winter Cherry, Punir, Asgandh and Ashwagandha. For centuries .The underground stems and orange-to-red fruit of this plant have been used for medicinal purposes (Srivastava et al., 2018). Steroids, alkaloids, salts, flavonoids *R. (B.) microplus* are the chemical constituents. Leaves part of plant used for tick control. 50% egg hatching inhibition of *R. (B.) microplus* occurs within in 15 days (Monika et al., 2014).

Tamarindus indica L.

The tamarind tree, also called as *Tamarindus indica,* (figure 11) is a dicotyledonous plant belonging to the *Leguminosae* family, which is part of the *Caesalpiniaceae* family. Tamarind trees are distinguished by their tree-like morphology, including evergreen leaves with sturdy, malleable branches and remarkable wind resistance (El-Siddig et al., 2006). *Tamarindus indica,* a long-lived evergreen hardwood tree found in several nations and regions such as Asia (including India), Africa (tropical region), and Egypt, is also used for medicinal purposes (Aly et al., 2022) The tamarind tree contains high levels of proteins, carbohydrates, fiber, lipids, and vitamins such as thiamine, niacin, riboflavin, β-carotene and ascorbic acid. There were additional minerals such as potassium and calcium, as well as phytochemicals. This plant showed 99% acaricidal activity and cause mortality of *R. (B.) microplus* within 7 days as survey conducted in Thailand (De Caluwé et al., 2010).

Fig. 11: *Tamarindus indica L.*

Conclusion

Ticks, as blood-sucking ectoparasites, present a major threat to livestock in Pakistan, particularly in rural regions where agriculture and animal husbandry are vital for livelihoods. These parasites not only cause significant economic losses by reducing meat and milk production but also pose serious health risks to both animals and humans by transmitting zoonotic diseases. The widespread use of synthetic acaricides to manage tick infestations has led to several challenges, including the development of resistance in tick populations, environmental pollution, and toxicity, further complicating the issue.Given these drawbacks, there is growing interest in alternative, more sustainable methods for tick control. The use of medicinal plants has emerged as a promising approach within integrated pest management strategies, offering an effective and environmentally friendly alternative to synthetic acaricides. These natural solutions help reduce dependence on chemical treatments while providing a viable option for controlling tick populations.

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Chapter 56

Ethnobotanical Uses of Native Flora Through Traditional Wisdom in Punjab, Pakistan

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ABSTRACT

In this chapter, an attempt has been made to present a contribution to the ethnobotanical knowledge of punjab pakistan regarding cultural, ecological and long term benefits. The flora of Punjab, owing to millennia-long cultural depth and some historical epochs from the periphery, is as rich as to be both unique and important. How this body of knowledge has evolved from Ayurvedic, Unani, Persian to Mughal and British colonial periods speaks volumes about the resilience of Punjab traditions. Traditional healers are known as Hakims, and elders are honoured for their continued stewardship of knowledge around how to use local plants - medicinally, in foods and spiritually. The chapter looks at the implications for conservation-the loss of biodiversity, deforestation and urbanisation. This calls for community based conservation efforts and sustainable ways of managing Punjab's botanical heritage. The future prospect in the field of ethnobotanical research offer a hope to provide new drugs that is not only based on ancient-knowledge but also surprising with technology innovation or it can say injection of science. This chapter, as a whole, highlights the symbiotic nature of Punjab's flora with its people and the cultural, medical and ecological bequest left by generations past for posterity to live in harmony.

KEYWORDS		
Ethnobotany, Traditional knowledge, Biodiversity conservation, Cultural heritage, Sustainable management	Received: 30-Jun-2024 Revised: 01-Jul-2024 Accepted: 30-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Overview of Ethnobotany and Its Significance

Harmonising the cultural with ecological, historical and economic considerations to capture the broad synthesis of plants and humanity defines access in ethnobotany - a multidisciplinary field capturing aspects of plant-human relationships (Gras et al., 2021). The conversation in this paper addresses the application of plants for food, medicinal, building and religious requirements among various societies of the globe (Balick and Cox, 2020). By understanding these traditional practices and that knowledge system, ethnobotany is able to provide important insights into conservation of biodiversity, sustainable management of resources, as well as the preservation of Indigenous cultures (Kumar et al., 2021). It is essentiality stems from its capability to fill in the gap of knowledge between traditional ecological knowledge and modern science leading to a clearer understanding of the different roles played by plants both in the environment and human cultures (Balick and Cox, 2020). Additionally, through revealing potential for manufacturing sector and health that remain largely unknown about plants, ethnobotanical studies help preserve cultural heritage while also promoting environmentally friendly methods for future generations (Heywood, 2011).

Brief Introduction to Punjab, Pakistan

Pakistan has diverse ecosystems and a rich cultural mosaic particularly in Punjab making it an interesting case study for ethnobotany research (Chaturvedi and Singhal, 2020). This area is recognized as Pakistan's heartland with lots of indigenous flora that have been used over time because of traditional wisdom (Ezcurra, 2006). The ethnobotanical use of plants among people in Punjab shows their strong affinity towards nature (Amjad et al., 2020). Punjab's flora is abundant with information passed down through generations starting from culinary herbs used to enrich regional recipes to medicinal plants employed as ancient curative techniques (Shar, 2022).

Exploring the ethnobotanical landscape of Punjab helps to reveal how these interdependencies have worked and indicates that benefits can be created by combining ancient knowledge with contemporary needs for environmental well-being and global sustainability (Milbank, 2023).

Importance of Native Flora in Traditional Practices

Considering that many cultural, medical, and spiritual traditions of the world are based on the native flora, its importance in traditional practices cannot be overemphasized (Reyes-García 2010). The reality, however, is that indigenous people are strongly reliant on the great number of plants growing in the respective habitats for ceremony, medicine and subsistence (Heywood 2011).

Plants heal many health issues and disorders, which uses in traditional medicine as a main component (Muthu et al., 2006). In addition, these plants are important symbols in many types of cultural rites and spiritual practices as a result of the fact that they embody the connections with their ancestors and their natural environment (Balick and Cox, 2020). In addition to their important cultural values, native plant species play a key role in sustainable agriculture and ecosystem resilience because they are often better adapted to the local conditions (Shelef et al., 2017). It is not only important to maintain and understand the customary usage of local plants, but for protecting biodiversity and the long-term future of our planet (Willis et al. 2007).

Historical Perspectives

Footprints of talked and unspoken word exchange, needbased ecological managerial machineries, likewise the path Trodden by ancientpeople can be studied while focusing on ethnobotanical information from Punjab,since time immemorial (Sengupta et al., 2019). Punjab's fertile land and di-verse ecosystem had attracted botanists to work with it for number of years (Shukla and Behera, 2019). It reflects the many uses of local flora which have beenrecorded, tried upon by local people and handed over to generations in thepast as well (Aziz et al., 2017). Migrations, invasions, contacts with other cultures and new natural settings hasteneditin its course of history (Hoerder, 2002).

Evolution of Ethnobotanical Knowledge in Punjab

The long journey of centuries of cultural exchange, environmental adjustment, and sharing of ancient wisdom is reflected in the history of ethnobotanical knowledge in Punjab (Brush, 2008). The neighbouring cultures' association; invaders; migrants; changing ecological context over time have contributed towards its development (Davis et al., 2005). Sources contributing to ethnobotanical knowledge regarding plants of Punjab are varied. Few examples include ancient Ayurvedic-Unani plant based medicine;, Persian period;, Mughals; British colonial period and present era as well (Kizhakkeveettil et al., 2024). In contemporary era it has become a nodal body reflecting their age-old health care tradition.; eco-friendly agricultural cultural heritage ;Persian period;) people's adaptability related with environment climatic change) and interdependence interaction between human natural world (Finn et al., 2017).

Role of Traditional Healers (Hakims) and Elders

The knowledgeable seniors or traditional healers, mostly referred to as Hakims in the community are pivotal for the transmission and possession of ethnobotanical information (Gupta et al., 2014). These people hold great awareness on therapeutic properties and uses of local plants in various ethnicities (Pan et al., .2014). They are known to own a deep understanding on plants and their usage. Hence they hold respect as elderly possessing knowledge on plant use along with age old methods for healing handed down since generations (Jacob et al., 2023). They treat variety of diseases and thus play significant roles in healthcare systems where access to modern medicine is limited or not available (Bodeker and Kronenberg, 2002). Community elders serve as living libraries of indigenous knowledge as they share beliefs that are learned through years of plant work (Nicholas and, Markey, 2014) .They encourage future generation under their guide recognizing influences from the cultural identity and relationship with the natural environment following ethnobotanical activities (Hunter,, 2022). The respect exhibited by people towards these healers reveals dependency as well as respect shown referencing to an ancient practice holds much evident importance explaining logical attitude towards maintenance of health, livelihood among societies (Sorin, 2007).

Traditional Practices and Their Cultural Significance

Traditional ways of using indigenous plants are dated back to cultural significant and they are inevitable resources in many societies across the globe (Cocks, 2006). These habits which are learnt over the years are part of the society's knowledge and ethical fabric in order to depict how such civilization deals with the natural world (Griswold, 2012). These customs involve the use of native plants with individuals' social, religious, temporal, and generational associations (Balick and Cox, 2020). Such activities give an identity that is history related in the present with several people feeling they belong to a certain community (Damásio et al., 2012). Examples include preparing teas from natural herbs for such ails as cancer and ulcers, preparing ornate flower arrangements for events such as weddings and funerals and use of oratures during musical events such as festivals (Rodrigues and Spence, 2023). Therefore, by accepting and cherishing those traditions, it becomes possible to respect the natives' rooted identity as well as obtain a better insight into the relations between people and the environment (Nepal, 2024).

Influence of Historical Events on Ethnobotanical Traditions

The narrative of adaptation, survival, and cultural exchange which is revealed through the history of ethnobotanical knowledge affected by historical events is quite interesting (Lujan Escalante and Mortime, 2022). The manner or means through which mankind has interacted and utilized natural vegetation has been distorted over time by famous victories, battles among other social changes (Steinberg, 2002). For example, the exchange of plants and seeds across continents due to colonialism modified the species in numerous settings and also altered the pharmacopoeial inventory (Cook and Walker, 2013). Of the ancient Silk Road and other trade routes, the ethnobotanical practices of the civilizations were progressed by the sharing of therapeutic plants and spice (Shi et al., 2022). Also, the precluding crises encouraged people to seek novel lifestyles and occupy new territories that shaped ethnobotanical knowledge's preservation and development (Joseph et al., 2022). These events did not only determine the specific plant geographies of these regions but they also emphasized the historicity of human plants aspects, the relations between people and cultivation as well as changes in ecology (McLain et al., 2012).

Flora Diversity of Punjab

The neem tree, the mango tree, several herbs, and flowers are grown all over Punjab (Grewa, 2004). Such is the richness of plants, which forms the basis for the region's traditional ways of life, farming, and environmental equilibrium. There could be reed and lotus around the river sides, whereas, there could be woods having Mango and neem trees in Punjab (Dhammika, 2015). Creole plants cure along with the main products of the agriculture such as the cotton, sugarcane, grain or rice. These helped ministers have a diversified spread that improved Punjab's ecological and thereby sociocultural fabric and best proved how elastic Punjab's flora is, according to (Frank, 2011).

Significance of Biodiversity in Ethnobotanical Practices

As it shall be observed in ethnobotanical exercises in this work, the loss of species is a big issue as it underpins the conventional global knowledge systems (Singh, 2012). The rich source of food, medicine, shelter and other materials and the preserved culture are available with this variety of plant species. We ensure that the diverse ecosystems on which communities have relied on for many generations for plants' use are preserved (Bharucha and Pretty, 2010). Furthermore, the element of biodiversity contributes to resilience against change since it ensures that a constant supply of resources will be available for a sustainable existence in the future. Ethnobotanical methods consider all the relationships between the species within ecosystems, and each plant makes a specific contribution to equilibrium within ecosystems (Ryan, 2014). To sum up, the concept of conservation and appreciation of the biological diversity is of utmost importance if global groups' traditions, health, and welfare are to be maintained.

Traditional Medicinal Uses

Herbal Treatments for Illnesses

Punjab is the most fertile province of Pakistan rich in vegetation from where multiplicity of plants are used to treat various diseases since ancient times. Some of the plants that are used frequently to cure diseases are tulsi, or holy basil, which is supposed to boost the immune system of the human body and neem, which possess antibacterial properties. Additional herbal medications related to the enhancement of lung function, skin, and digestive diseases are in relation to these plants, and other like aloe vera and turmeric (Debjit Bhowmik et al., 2009).

Healing Herbs for Culinary Purposes

It is remarkable that a vast number of mediums used in making Punjabi dishes possess medicinal qualities. For instance, garlic has antic microbial properties apart from enhancing the taste of food (Wani et al., 2022). receive its aid in lowering blood sugar levels with the help of fenugreek seeds and improvement in digestion. These herbs when incorporated into daily meals not only enhances the taste of the food but also will have the benefits of serving the other general purposes of the body (Khalsa, 2003).

Herbal Infusions and Teas

Following the state of Punjab with reference to its flora, herbal teas are said to be used in managing various ailments (Ahmed et al., 2015). Whereas chamomile is used to induce sleep and to calm the body, mint is known for its ability to help to sooth head aches and upset the stomach. These teas are most favoured in holistic medicine and modern day pharmaceutical system in Punjab; they are normally blended with other spices like ginger or lemongrass (Kaur et al., 2018).

Incorporation into Ayurvedic Practices

The medicinal system native to the Indian subcontinent, namely Ayurveda, does not leave Punjab's wealth of plant life unnoticed. Ayurvedic doctors use herbs such as ashwagandha which has adaptogenic property, giloy that enhances the body immunity system and Brahmi that enhances a sound mind. According to Ayurvedic standards, all these herbs are useful for maintaining the body's balance and health. It has been widely used in Ayurvedic system of medicine (Chopra and Doiphode, 2002).

Therefore, it becomes clear that having embraced the western theories of the disease's causation, there is tremendous respect to the natural world evident in Punjab region's diverse plant use in traditional medicine (Rahman et al., 2019).

Culinary and Nutritional Uses of Flora in Punjab

The plant life of Punjab comprises a rich odourous and a flavourful bounty of foods that are both delicious and healthy that are well incorporated in the traditions of the Punjabies (Ahmed and Farooq, 2014). The best thing about the Punjabi food is the distinct and vivid colors, and the food is generally garnished with regional vegetables, herbs and spices.

Ritual and Cultural Significance of Flora of Punjab

Indeed, the vegetation of Punjab is very much associated to symbolism and religious rites and ceremonies that serve an important role in the manifestation of culture of the region (Michon and Bhatti, 2004). Cultural practices such as below religious festivals and rites demands flowers like marigolds and roses in the observed cultures hence are used to tap from these sources to get the flowers for house, shrines, and temples (Lehner and Lehner, 2003). The type of tree that has a lot of therapeutic properties, neem, is also widely used in cultural beliefs in security and purifying signs (Gurib-Fakim, 2006). Herbs that are believed to be sacred such as holy basil (tulsi) are often grown in the courtyards for veneration. In addition, mangoes, known as the ''king of fruits'', is a cultural symbol of health and wealth among the Punjabi people apart from being a delicious fruit. In many cases, these plants are employed in rituals, healing, and other practices that make their community connected with the nature Punjabi people have a rich connection with the earth (Anand, 2024). This link makes it possible to follow native customs and extend the supply of consolidating the cultural memory of the population.

Conservation Challenges and Efforts

Threats to Native Flora in Punjab

As identified by various studies, several factors pose a serious threat to Punjab's indigenous plant species and habitats, underlining the vulnerability of the province's bio diverse regions (Sharma et al., 2022). Problem 3 states that natural ecosystems are rapidly disappearing due to interaction with light industrialization, unplanned growth and expansion of the population base of any country pressing on vegetative cover. Tabernilla is native plants which are threatened most by the agricultural practices that always employ chemical fertilizers and pesticides, which hampers growth and subsistence.

Whether intentionally or accidentally brought, invasive species displace native plants for resources and significantly change the environment (McNeely, 2001). Increasing temperatures and unpredictable weather conditions overwhelm the region's flora beyond tolerance, which is made worse by climate change. To counter these challenges, there has to be a concentrated effort put into sustainability, environmentally friendly land employ, and raising public consciousness of the need to protect Punjab's unique biological legacy (Ghosh, 2008).

Deforestation and Urbanization

Urbanization and deforestation are mutually reinforcing issues that seriously threaten biodiversity and the environment (Kumar et al., 2022). The loss of vital habitats for many species due to forest clearing for infrastructure construction and urban growth causes a fall in biodiversity. The loss of trees also upsets water cycles, climatic patterns, and soil fertility, among other ecological balances (Kimmins, 2011). Increased resource demand brought on by urbanization causes unsustainable consumption levels and more deforestation. To reduce the negative consequences of deforestation and urbanization and ensure a sustainable future for both human populations and the natural world, it is imperative to strike a balance between the need for urban expansion and conservation initiatives (Enuoh and Bisong, 2014).

Climate Change Impacts

The impacts of the warming world are becoming increasingly horrific with increase in frequency and severity of incidences of weather related incidents (Singh and Singh, 2012). It can be severe summer like heat episodes and storms on one hand and long prolonged dry spells and melting of polar ice on the other. People in communities are affected by food and water insecurity, environments collapse and species can potentially be wiped out (Arenas-Sánchez, 2016). Emissions cuts, infrastructure improvement, and funding for renewable resources are some of the most important of those measures that need to be taken in order to minimize the negative impact and determine sustainable future.

Overharvesting of Medicinal Plants

Across the world, traditional medical methods and biodiversity are being jeopardized by the excessive agriculture of therapeutic plants (Tomlinson and Akerele, 2015). The lack of populations and extinction of important species have resulted from the unrelenting extraction of these plants for use in medicines, herbal treatments, and other applications. This inappropriate approach disturbs ecosystems and the lives of populations who rely on these resources, in addition to putting medicinal plants in jeopardy (Buhner, 2002). To guarantee that these priceless plants remain available for subsequent generations to enjoy, made to support sustainable techniques for harvesting and their protection.

Community-Based Conservation Initiatives

The measures which involve the promotion of the local people in the preservation of the natural surroundings can indeed be regarded as strategic plans that are instrumental in making the neighbouring populations take on the responsibility of the environment's protection (Berkes, 2004). Since the locals are enlisted to play an active role in the protection and proper use of the ecosystems in their immediate environment, the burden of proper usage and utilization of the consulted resources takes root and it also enhances the aspect of ownership of natural resources (Weber, 2003). These are some of the outcomes of involving the communities in the decision-making process, other than contributing to the social and economic development, and of course, the conservation of the biodiversity. Such efforts often lead to development of unique intervention strategies and practices that help people and animals working with the cooperation of specialists, authorities, and charitable foundations (Kiss et al., 2022).

Indigenous Knowledge Preservation Programs

The preservation of Indigenous Knowledge is critical in the preservation of biological diversity and latter cultural Endangered cultural assets (Ngulube, 2002). The main objectives of these programmes are to document and indeed archive the indigenous people's traditional ecological knowledge. By recognizing these people's profound insights of their ecosystems, these programmes ensure that lessons learned on sustainable resource management are not discarded. Regarding sharing of traditional knowledge, these programmes engage in establishing relationships with regional elder and leaders for passing on this knowledge to the next generation through these programmes (Kohsaka and Roge, 2021). Besides, it also helps to strengthen cultural values, including cultural individuals, as well as foster a deeper regard towards the preservation of nature, complemented by more effective and traditional conservation schemes based on thousands of years of experience (Verschuuren et al., 2021).

Sustainable Harvesting Practices

Sustainable Harvesting Practices projects that aim at ensuring that communities who depend on natural mineral endowment practice responsible mining (Hilson, 2016). opposite to that, these programs comprise sustainable harvesting techniques such as rotational harvesting and selective extraction and subsequently guarantee long-term sustainability of the forest products. People learn about proper behaviors that have positive effects on ecosystems' health and biological diversity and get most of their needs met from the obtained resources (Vandebroek et al., 2011).

Future Directions and Opportunities

A. Potential for Ethnobotanical Research and Innovation

For the future, ethnobotanical study remains as one of the most promising sources of inspiration for creating new developments in various spheres (Soejarto et al., 2005). Bioprospecting is one of the ways that could be utilized to look for new medicines and products without undermining Indigenous peoples' traditional knowledge. Some of the modern methodological approaches can be combined with centuries-old practices that would help researchers find new therapeutic substances and learn more about the scientific basis of traditional therapies (Chao et al., 2017). Pharmacological studies are particularly highly rated as these appraisal researches explore biochemical basis of existing treatments and may open the search for new treatments. This use of combining conventional knowledge with the biological research is beneficial for health care and also guards and asserts the credibility of diverse indigenous people's history (Finn et al., 2017).

B. Revitalizing Traditional Practices

With regards to the goal of sustainable development, reviving old ethnobotanical practices seems to become a somewhat significant task (Prūse, 2020). Information advocacy moves are also crucial in this approach since they teach indigenous people and other society members the value of ancestral data. By instilling pride and awareness in these practices, we can secure their continued existence and significance (Phipps and Ozanne, 2017). Furthermore, incorporating traditional ethnobotanical knowledge into modern healthcare systems provides a double benefit (Vandebroek, 2013). It not only improves medical procedures by incorporating holistic and time-tested cures, but it also gives communities access to indigenous treatments. This combination fosters equitable medical care while preserving the important heritage of ethnobotanical practices.

C. Collaboration among Scientists and Indigenous Communities

To establish a sustainable route ahead, scientists and indigenous populations must work together (Snively and Corsiglia, 2001). Respecting indigenous knowledge systems and including community people in investigations promotes collaboration and confidence. Scientists can learn from generations of traditional knowledge holders, acquiring knowledge that textbooks and laboratories may not provide (Snively and Corsiglia, 2001). Indigenous communities benefit from scientific understanding, resources, and technology that may help them with conservation and sustainable practices (Rist and Dahdouh-Guebas, 2006). These collaborations foster creative conservation solutions based on cultural legacy and ecological expertise. We are paving the road for a future in which ethnobotanical traditions coexist with contemporary breakthroughs, benefiting both civilization and wildlife (Anand et al., 2023).

Conclusion

Cultural-use information on plant resources of Punjab province of Pakistan highlights and depicts one more aspect of people and plants. This chapter underlines the necessity of this knowledge's preservation, as it is valuable from both a cultural history and historical-humanitarian perspective as well as the application it may have towards sustainable development goals, the protection of global bio-diversity, and the advancement of human health. Looking to the future it is imperative, therefore, to understand that there is much which can be learned from tradition and that it is vital to defend and promote those activities which safeguard this legacy for the future. By joining our efforts together with the enhanced sense on the preservation of the nature, it will be possible to preserve the unique ethnobotanical experience of Punjab for years to come.

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Chapter 57

Diabetes Mellitus: An Overview and Current Phytotherapeutic Agents

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ABSTRACT

Diabetes is a long-term health problem that causes high blood sugar levels because the body doesn't make enough insulin or the insulin doesn't work properly. While oral hypoglycemic drugs and insulin therapy work well, they can also cause problems and side effects. It is important to consider other ways to treat the problem. Over time, plants that can help treat diabetes have been important. They provide safer and more natural ways to manage the condition, and they can also save money. These plants have many different healing powers. These can help control diabetes by making more insulin, helping the body use insulin better, stopping the body from absorbing too many carbohydrates, and giving antioxidants and anti-inflammatory benefits. Studies have found that medicinal plants can help control blood sugar and improve overall health. These studies include clinical trials and case studies. It's really important to think about safety and rules because we need to carefully check for any possible bad effects, how the medicine might interact with other medicines, and make sure the medicine is of good quality. It's important to make sure that herbal medicines are safe and effective. This makes sure they are good to use. In the future, scientists should explore new plants for treating diabetes, understanding their effects, and testing them on large populations. Integrating these plants into standard medical care could enhance diabetes management. Patients can improve their condition by combining these plants with conventional treatments and lifestyle changes. Collaboration among healthcare professionals, patients, and researchers is essential to fully benefit from the use of medicinal plants in diabetes care.

KEYWORDS
Diabetes Mellitus; Medicinal Plants; Glycemic Control; Insulin Sensitivity; Alternative Therapies; Antioxidant Properties; Clinical Trials

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INTRODUCTION

Diabetes mellitus (DM) is a long-term health problem that causes high blood sugar levels. This occurs when the body cannot produce enough insulin or cannot use it properly. There are two main types of diabetes: type 1, which occurs when the body cannot produce insulin, and type 2, which occurs when the body cannot use insulin well and cannot produce enough insulin. Diabetes is a big problem that many people around the world face and it affects their health (Mughal et al., 2020).

According to the International Diabetes Federation, around 537 million adults between the ages of 20 and 79 had diabetes in 2021. Data shows that there may be 643 million people in 2030 and 783 million people in 2045. Diabetes is becoming increasingly common in poor and middle-income countries. Diabetes can lead to serious health problems, including blindness, kidney failure, heart disease, and loss of a foot or leg. The above problems have a great impact on the lives of patients and also impose a great cost on the healthcare system (Soomro and Jabbar, 2024).

Traditional diabetes treatments, such as insulin injections and oral medications, have been shown to be effective. However, these treatments have disadvantages such as side effects, financial burden, and patients not following instructions. The challenges discussed demonstrate, why we need to use different treatments that are safer, more accessible and less expensive. Some natural treatments, like herbal ones, may help improve diabetes treatment. These treatments offer extra ways to help patients and can make them feel better while reducing side effects and making it easier for patients to follow their treatment plan. People around the world have long used plants as medicine to treat a variety of health problems, such as diabetes. Plants contain substances that can help lower blood sugar, make insulin work better, absorb glucose, and protect pancreatic cells. A growing body of scientific research shows that using plants as medicine can help people with diabetes. Studies have found these plants to be effective and safe. Using herbal remedies alongside regular treatment for diabetes helps to manage the condition as a whole. This includes controlling blood sugar levels and preventing related problems (Kumar et al., 2021).

Types of Diabetes Mellitus

Type 1 Diabetes

Type 1 diabetes happens when the immune system attacks and destroys the β cells in the pancreas that make insulin. This means that the body doesn't make enough insulin, so people need to take insulin for the rest of their lives to stay healthy. The condition usually starts when a person is young, but it can happen at any time in their life (Roep et al., 2021).

Type 2 Diabetes

Type 2 diabetes is the most common kind of diabetes, making up about 90-95% of all cases. This condition happens when the body's cells don't respond well to insulin and the body gradually makes less insulin. Many things can cause certain medical conditions to start, like being overweight, not moving much, eating unhealthy food, getting older, having family members who also have the condition, and your ethnic background. Controlling diabetes often means making changes to how you live and taking pills to lower your blood sugar. As the sickness gets worse, more people need insulin therapy (Kumar et al., 2020).

Gestational Diabetes

Pregnant women can get gestational diabetes when their body has trouble in processing sugar, especially during pregnancy. This condition is usually found during tests done between the 24th and 28th weeks of pregnancy. Women who had diabetes during their pregnancy are more likely to have diabetes after they have their baby. These problems can be really bad for the mother and the baby. They might be born too early, be too big, or cause high blood pressure for the mother (Poblete and Olmos, 2021).

Pathophysiology of Diabetes Mellitus

Diabetes is caused by a mix of genes, environment, and how a person lives. Type 1 diabetes happens when the body's immune system destroys the cells in the pancreas that make insulin, so the body can't produce insulin anymore. Type 2 diabetes happens when your body has trouble using insulin and making enough of it to control your blood sugar levels for a long time. Many people with Type 2 diabetes who are obese have trouble using insulin, especially around their belly fat. This affects how the body processes insulin. Continuously having high blood sugar levels for a long time can harm your organs and tissues, causing diabetes-related problems (Cole and Florez, 2020)

Common Symptoms and Complications

Signs like peeing a lot, feeling very thirsty, losing weight without trying, being hungry, feeling tired, having blurry vision, cuts that heal slowly, getting sick often, and tingling in hands or feet may mean there's a medical issue (Taware, 2023).

Complications

A higher chance of having a heart attack, stroke, and clogged arteries getting worse. Also, there is a greater possibility of nerve damage causing symptoms such as pain, tingling, and less feeling, especially in the arms and legs. Harm to the kidneys can cause long-term kidney disease and complete kidney failure. When the blood vessels in the eye are damaged, it can make it hard to see and might even cause blindness. Poor blood flow and nerve damage can cause foot sores, infections, and sometimes even the need for amputation. Other problems people with diabetes might have include infections, skin changes, and skin conditions. Additionally, individuals with diabetes may be at higher risk of developing mental health problems such as depression and anxiety. To keep diabetes in control, it's important to check blood sugar levels, follow doctor's advice, stay healthy, and watch out for problems (Caplan, 2024)

Conventional Treatments for Diabetes Mellitus

Oral Hypoglycemic Agents

Oral hypoglycemic agents, or OHAs, are pills that you take to lower your blood sugar. These medications help people with Type 2 diabetes by making insulin work better, increasing insulin release, or lowering glucose levels in the body. The most common oral drugs are Metformin, which reduces liver glucose production and improves insulin sensitivity. Glipizide and Glyburide help the pancreas make more insulin. Thiazolidinediones such as Pioglitazone and Rosiglitazone can help the body's peripheral tissues respond better to insulin. Medicines like Sitagliptin and Saxagliptin can help the body make more insulin and lower glucagon levels by stopping the DPP-4 enzyme. SGLT2 inhibitors like Canagliflozin and Empagliflozin help the kidneys get rid of more sugar in the urine. Alpha-glucosidase inhibitors like Acarbose and Miglitol can slow down the digestion and absorption of carbohydrates in the intestines (Chakravarti and Nag, 2021).

Insulin Therapy

People with Type 1 diabetes need insulin to manage their condition. Some people with advanced Type 2 diabetes also need insulin when pills are not enough. Giving insulin usually involves using either shots or insulin pumps. Many types of insulin come in different forms. They work at different speeds, have different peak effects, and last for different amounts of time. This chapter of the book talks about how different insulins work, like how fast they start working, how strong they are, and how long they last. It looks at rapid, short, intermediate, long, and ultra-long-acting insulins. Insulin-like Lispro and Aspart start working quickly in 15 minutes, work best in 1-2 hours, and lasts for 3-4 hours. Regular insulin starts working in 30 minutes, peaks in 2-3 hours, and lasts for 3-6 hours. Intermediate-acting insulin, like NPH insulin, takes 2-4 hours to start working, has its strongest effect in 4-12 hours, and stays in the body for 12-18 hours. Long-acting insulin-like Glargine and Detemir start working in a few hours, don't have a big peak, and keep working for up to 24 hours. Finally, Degludec is a type of insulin that lasts for a very long time and keeps insulin levels steady for more than 24 hours (Syed, 2022).

Lifestyle Modifications

Making changes to how you live is very important in managing diabetes well, no matter what type of diabetes you have. Eating various healthy foods like fruits, vegetables, whole grains, lean meats, and good fats is important for staying healthy. We should watch how many carbs you eat and avoid foods with a lot of added sugar. Exercising for 150 minutes each week can help your body use insulin better. Maintaining a healthy weight is important by eating balanced meals and exercising regularly. It's best not to smoke if you have diabetes to decrease the risks. We should drink less alcohol to keep our blood sugar levels stable and avoid having any problems with our medications. Traditional diabetes treatments work well but have some drawbacks and may cause side effects (American Diabetes Association, 2021). Table 1 shows various plants used for the treatment and management of diabetes.

Table 1: Plants used for the treatment of diabetes and their management

Sr.	Plant Name	Constituents	Diabetes Effect	Management	References
1	Bitter Melon	Charantin, Vicine, Polypeptide-p	Lowers blood glucose levels, improves insulin sensitivity	Consumed as juice, extracts, or in cooked dishes	(Gao et al., 2023)
2	Fenugreek	Soluble fiber, 4-hydroxyisoleucine	Reduces fasting blood sugar, improves glucose tolerance	Seeds soaked in water, powdered form, or supplements	(Cortez et al., 2023)
3	Cinnamon	Cinnamaldehyde, Polyphenols	Enhances insulin sensitivity, lowers blood sugar levels	Used as spice, in tea, or as supplements	Silva et al., 2022)
4	Aloe Vera	Anthraquinones, Glucomannan	Lowers fasting blood glucose, improves HbA1c levels	Consumed as juice or supplements	Haghani et al., 2022)
5	Gymnema Sylvestre	Gymnemic acids	Reduces glucose absorption, stimulates insulin secretion	Consumed as tea, extracts, or supplements	(Dvangan et al., 2021)
6	Berberine	Berberine	Lowers blood glucose, improves insulin sensitivity	Extracts, capsules, or tablets	(Hang et al., 2021)
7	Turmeric	Curcumin	Lowers blood glucose, anti-inflammatory properties	Used as spice, in milk (golden milk), or supplements	(Bozkurt et al., 2022)
8	Ginseng	Ginsenosides	Improves insulin sensitivity, reduces blood glucose levels	Consumed as tea, extracts, or supplements	(Naseri et al., 2022).
9	Neem	Azadirachtin, Nimbin	Lowers blood glucose levels	Leaves, powder, or extracts	(Patil et al., 2022).
10	Holy Basil	Eugenol, Cinnamic acid	Lowers blood glucose levels, enhances insulin secretion	Consumed as tea, extracts, or supplements	(Ganguly, 2021).

Role of Medicinal Plants in Diabetes Management

Historical Perspective

People have been using plants to treat diabetes for a long time. It's a common practice in many traditional healing methods around the world. Olden cultures like Egypt, India, China, and Greece used herbs and plant parts to help with diabetes symptoms. Traditional Chinese Medicine uses herbs like ginseng, bitter melon, and berberine to lower blood sugar. Ayurveda, the traditional Indian medicine, uses plants like fenugreek, turmeric, and neem to manage "Madhumeha," which is diabetes. Native American Medicine used blueberries and Jerusalem artjson to help with diabetes, and Middle Eastern Medicine used fenugreek and garlic for the same reason. In the past, medicinal plants have been important in helping us learn how they can help treat diabetes. This has paved the way for modern scientific research (Andrade et al., 2020). Table one shown the plants used for the treatment of diabetes and their management.

Advantages of Using Medicinal Plants

Natural and Less Toxic

Many people think that using plants for medicine is a natural option instead of using drugs made in a factory. They believe that plant medicine has fewer and milder side effects. Plants have natural chemicals that work together to make them heal better and reduce the chance of causing problems. Bitter melon has charantin, vicine, and polypeptide-p that help to lower blood sugar with few side effects (Balick and Cox, 2020).

Cost-effective

Many people in poor countries can't afford expensive diabetes treatments. They might find it helpful to use plants for medicine because it's cheaper. Growing medicinal plants is a good and economical way to benefit people's health, especially those who do not have much money. It can help treat diabetes and is easily accessible (Adler et al., 2021).

Multifunctional Therapeutic Effects

Many natural plants contain substances that can help treat diabetes and related problems. Many plants can help the body use insulin better and control blood sugar levels. For example, cinnamon contains cinnamaldehyde, which helps insulin work better, while fenugreek seeds contain 4-hydroxyisoleucine, which causes the body to release more insulin. Berberine, found in different plants, can activate AMP-activated protein kinase (AMPK). This helps reduce blood sugar levels. The curcumin contained in turmeric helps protect pancreatic cells from damage. Green tea and blueberries also contain antioxidants that may reduce stress and inflammation in diabetes (Blahova et al., 2021).

Mechanisms of Action of Medicinal Plants in Diabetes Management

Enhancement of Insulin Secretion

Some plants can help the pancreas produce more insulin. This is important for people with type 1 and type 2 diabetes. This plant contains substances that can help pancreatic cells work better and produce more insulin. The fenugreek plant contains an amino acid called 4-hydroxyisoleucine, which helps the body produce more insulin. Bitter melon, also known as bitter gourd, contains substances such as p-polypeptide and momordica charantia that act similarly to insulin and can help improve insulin production in the body (Blahova et al., 2021)

Improvement of Insulin Sensitivity

To control type 2 diabetes, it is important to get the body to use insulin better. This is because insulin resistance plays an important role in causing this disease. Using plants as medicine can help the body use insulin better and lower blood sugar levels. Cinnamon, a type of plant, contains a substance called cinnamaldehyde that helps the body to respond better to insulin. Cinnamaldehyde makes insulin work better and helps cells use sugar more. This is good for the body. Berberine, found in certain plants, makes a protein in the body work better and helps muscles take in more sugar (Rachdaoui, 2020).

Inhibition of Carbohydrate Absorption

Certain plant-based treatments can stop the body from breaking down and using carbohydrates from food, which helps lower blood sugar levels after eating. Acarbose and Miglitol are natural substances that can slow down quickly your body breaks down carbs. Gymnema Sylvestre is a plant with gymnemic acids that stop sugar from being absorbed in the intestines (Greger, 2020).

Antioxidant Properties

Oxidative stress can affect diabetes and its complications a lot. Plants with health benefits and lots of antioxidants can help protect cells from getting damaged by harmful substances called free radicals. Green tea is made from a plant called *Camellia sinensis* and has a lot of antioxidants that help reduce stress in the body. Turmeric has a compound called curcumin that can protect cells in the pancreas and other tissues from damage caused by stress. Turmeric is another name for the plant called Curcuma longa (Sharifi et al., 2020)

Anti-inflammatory Effects

Long-lasting inflammation is connected to trouble using insulin and the development of problems related to diabetes. Certain plants have special properties that can help reduce swelling in the body and improve the body works. The substance called curcumin, found in turmeric, can lower inflammation by reducing certain chemicals in the body that cause swelling. Ginger is a common plant with a bioactive substance called gingerol. This substance helps reduce swelling and pain by stopping the body's inflammation process (Forrester et al., 2020).

Common Medicinal Plants Used in Diabetes Management

Aloe Vera

A study found that people with Type 2 diabetes who added aloe vera gel to their diet had lower blood sugar levels compared to those who didn't. Many people have said that aloe vera gel can lower blood sugar and help people with diabetes. Additionally, using aloe vera gel may cause less side effects than regular medical treatments. Also, there is evidence showing that the good results come from the active ingredients in aloe vera gel. Aloe vera contains many helpful ingredients that work together to treat diabetes. These things help with diabetes in different ways and have many good effects on health. These things help the body use insulin better, make more insulin, and protect cells in the pancreas. This can help lower blood sugar levels. Improving insulin sensitivity helps the body use glucose better. Also, the substance can help protect cells from damage by fighting against oxidative stress and inflammation as an antioxidant. Also, the enzymes that help process glucose affect the amount of sugar in the blood, making it lower. So, this stuff helps lower blood sugar levels, improve cholesterol levels, and reduce a measure of long-term glucose control (Deora and Venkatraman, 2022).

Bitter Melon

A research study found that bitter melon extract helped lower blood sugar in people with Type 2 diabetes. It worked just as well as metformin. Many research studies have shown that adding bitter melon to the diet can help people with Type 2 diabetes. These studies found that patients were able to better control their blood sugar levels and relied less on artificial medications. Bitter melon has good effects because it contains charantin, vicine, polypeptide-p, momordicin, and momordin. The bitter melon plant has a lot of helpful compounds that can lower blood sugar levels. These chemicals act like insulin, help release insulin, and improve how cells take in glucose. Polypeptide-p works like insulin to bring down blood sugar levels. Furthermore, charantin and vicine help the pancreas produce more insulin and also help the body absorb glucose better. These things are good for you because they help lower your blood sugar levels and make our body more sensitive to insulin. They also protect our cells from damage (Hsu et al., 2020).

Fenugreek (*Trigonella foenum-graecum*)

Adding fenugreek seed powder helped people with diabetes to lower their blood sugar levels when they haven't eaten and also improved their overall blood sugar control. The research found that fenugreek can help people with diabetes control their blood sugar and lipid levels. Some people with diabetes have seen better control of their blood sugar and insulin levels when they add fenugreek seeds to their diet or treatment, as reported in informal studies and clinical cases. Active compounds are tiny parts in something that cause a certain reaction in living things or chemicals. These things can interact with cells in the body and cause reactions. Many scientists study these natural substances to see if they can be used to make new drugs. Some of these substances, like 4-Hydroxyisoleucine, Trigonelline, Galactomannan, and Diosgenin, may have good effects on health. A lot of studies have been done on these compounds because they affect how the human body works. Fenugreek seeds contain compounds that help with insulin release, the body's response to insulin, and the breakdown of carbohydrates. These compounds have positive effects. These things contain 4-Hydroxyisoleucine, which helps release insulin from the pancreas, and galactomannan, a type of fiber that slows down digestion and the absorption of carbs. In addition, trigonelline helps the body use insulin better and take in glucose (Yako, 2020).

Gymnema Sylvestre

Gymnema supplements help reduce blood sugar levels and improve insulin levels in patients. Studies have found that actively working parties have the greatest impact on this system. Gurmar contains gymnemic acids, gymnemycins, saponins and flavonoids. The Gymnema plant contains a substance called gymnemic acids that can help treat diabetes. Studies have found that these substances can block the absorption of sugar, help the body produce more insulin, and help regenerate pancreatic cells. Gymnemic acids prevent the body from absorbing sugar by blocking sugar receptors in the intestines. Additionally, these substances help the body release insulin and help repair the beta cells of the pancreas. Additionally, gymnemycins help reduce sugar cravings by making sweet foods taste less sweet. This combination of effects has good benefits, such as reducing blood sugar levels before and after meals, improving insulin production and the working capacity of beta cells (Girgis et al., 2022).

Cinnamon

Using cinnamon as a supplement may help lower blood sugar and improve cholesterol levels in people with type 2 diabetes. Research from multiple clinical trials has shown that cinnamon can lower blood sugar, A1C, and cholesterol levels in people with type 2 diabetes. This means that cinnamon may contain substances that can help control a person's diabetes symptoms. In this research, substances such as cinnamaldehyde, cinnamic acid and cinnamate were mainly used, but also polyphenols. Cinnamon has many benefits for the body, such as helping insulin work better, controlling blood sugar levels and acting as an antioxidant. Cinnamon contains cinnamaldehyde and polyphenols, which help insulin work better, improve the way glucose is used in the body, and have antioxidant effects. Cinnamaldehyde helps insulin work better and improves the way the body uses glucose. Polyphenols can also reduce stress and inflammation in the body. These effects keep the body healthier by lowering blood sugar levels, improving long-term blood sugar control, and preventing damage caused by diabetes. This can help reduce the problems that come with diabetes (Jamali et al., 2020).

Berberine

Research shows that berberine works as well as metformin in lowering blood sugar levels and improving insulin sensitivity in people with type 2 diabetes. Research shows that berberine may help lower blood sugar and improve the body's response to insulin. These findings suggest that berberine may have the same benefits as traditional medications in lowering blood sugar levels.

The properties of berberine, berbamine and palmatine make these compounds very interesting. Berberine, a chemical found in different plants in the Berberidaceae family, has been studied extensively to see if it can help treat diabetes. AMP-activated protein kinase (AMPK) is important in controlling how our body uses sugar and fat. Activating AMPK helps the body better absorb glucose and improves the body's response to insulin. Additionally, AMPK prevents the liver from making glucose by blocking a process called hepatic gluconeogenesis. Additionally, AMPK activation is important for improving fat levels by controlling how the body handles fat. Activating AMPK has benefits such as reducing fasting and post-meal blood sugar levels, reducing glycated hemoglobin (HbA1c), and improving blood sugar control. Additionally, it has been found to improve blood fat levels, which can reduce the chances of heart disease (Xie et al., 2022)

Scientific Evidence Supporting the Use of Medicinal Plants

Clinical Studies and Trials

Research and trials have shown that the use of medicinal plants can help control diabetes. The research usually involves people and tries to test if different plant extracts and compounds are safe, how much to use, and how well they work. Case studies and anecdotal evidence are commonly used in academic research. Using stories and case studies helps show how well medicinal plants can help treat diabetes. While not as strict as clinical trials, these reports give important insights into how things are used and their potential benefits in real life (Salleh et al., 2021).

Safety and Regulatory Considerations

Potential Side Effects and Toxicity

Using medicinal plants to manage diabetes can be helpful, but we need to be careful about possible side effects and toxic effects if we use them the wrong way or too much. Aloe vera is a type of plant that can be used for medicine. This stuff has good effects on health and is used in many industries like medicine, beauty, and wellness products. This plant has special substances that scientists are interested in because they can help with skin health, healing wounds, and reducing inflammation. More people are interested in using it as a natural treatment so researchers are studying how well it works and if it's safe to use on the skin or in the mouth (Msanda and Cherifi, 2020).

Potential negative effects: Consuming too much may lead to stomach pain and loose stools. Using this substance too much or for a long time can mess up the balance of important minerals in your body and hurt your kidneys. Bitter melon is a type of tropical plant that grows on a vine. It is part of the gourd family (Drewes et al., 2020).

Side effects may include low blood sugar, stomach pain, and headaches. Too much eating or drinking can hurt your liver and make it hard to have babies. Fenugreek is also known as Trigonella foenum-graecum. Some people may have stomach problems like bloating, gas, or diarrhea, as well as allergic reactions after taking it (Buse et al., 2020).

Overdosing can make your blood sugar go down and affect how your blood clots. Gymnema Sylvestre is a plant that has been used in traditional medicine for a long time and is known for its good healing abilities. It can make you healthier by preventing diabetes, helping you stay at a healthy weight, and lowering cholesterol. Many studies have shown that it can help treat diabetes and obesity. We need to study it more to understand how it works and what harm it could cause. Possible bad effects: belly ache and low sugar in your blood (Mason et al., 2022).

Limited research has been done on the possible long-term effects of this substance, but it is thought to be safe when used as directed. Cinnamomum verum, also known as cinnamon, is a spice made from the inner bark of trees in the Cinnamomum genus. Potential negative effects of eating cinnamon can include allergic reactions and sores in the mouth. Eating a lot of a type of cinnamon called Cinnamomum cassia with coumarin can damage the liver. Eating too much coumarin can damage your liver. Berberine is a substance found in different plants like Berberis, Hydrastis canadensis, and Coptis chinensis. Chemical compound from plants. A lot of studies have been done on it because it could have medical benefits and be used as a treatment. Potential side effects: This medicine might make your stomach feel bad, like making it hard to poop, giving you diarrhea, or making your belly hurt. If you use it for a long time or take a lot of it, it might make your blood pressure go down and could cause problems with our heart (Pathak and Sharma, 2021).

Interactions with Conventional Medications

Using natural plants with diabetes medication can make it harder to control diabetes. Plants like Aloe Vera, Bitter Melon, Fenugreek, Gymnema Sylvestre, Cinnamon, and Berberine can make some medications work stronger, which can be risky for low blood sugar. Also, some of these plants could react with blood thinning and clot prevention drugs, increasing the chance of bleeding, or changing the levels and effects of medications that are processed by the liver. It's important to keep a close eye on your blood sugar levels and think carefully about how these herbs might interact with our other medications (Ansari et al., 2022).

Quality Control and Standardization

It's really important to make sure that herbal medicines are safe and work well. This means checking that they are good quality, pure, and strong. Following good manufacturing practices (GMP) helps to make sure that herbal products are always made and controlled in the right way to meet high standards of quality. Testing for contaminants such as heavy metals, pesticides, and microorganisms is critical to product safety. It is also important to ensure that each batch of a product contains the same amount of active ingredients. Taking the right amount of medication at the right time is essential to staying safe and regaining your health (Gil et al., 2021).

Different rules and guidelines control how medicines are made and used. These rules may be different in each country and even in different regions within the same country. This can affect the ease of obtaining a medication, its effectiveness, and its safety for the person using it. The DSHEA makes sure that herbal medicines are safe and labeled correctly, but it doesn't require them to be approved before being sold. The European Union's Herbal Directive lets medicinal plants be registered as traditional herbal medicines if there is proof that they have been used traditionally and are safe, even if there is no evidence from clinical trials that they are effective. In India, Ayurvedic, Siddha, and Unani Drugs are controlled by the Drugs and Cosmetics Act. This law requires that these drugs meet traditional medicine standards and undergo safety checks. China's government watches over Traditional Chinese Medicine to make sure it's safe, works well, and is high quality

(Brinckmann et al., 2020).

Practical Considerations for Using Medicinal Plants

Dosage Forms (Extracts, Teas, Capsules, etc.)

Many kinds of plants can be used to help with diabetes. Each one has its benefits and things to consider when using it. Liquid extracts are strong forms that can be mixed with water or taken straight. Quickly taken into the body and easy to consume in precise amounts, standardized extracts ensure that the levels of active ingredients are always the same, leading to dependable health benefits. Herbal teas are made by soaking parts of plants that can help with medicine in hot water. They are easy to make and eat, but their strength can change depending on how they are made. Infusions are a strong tea that is brewed longer to make it more powerful. Capsules and tablets have crushed plants that can heal you. They make it easy to measure and take the right amount. Tablets and capsules give you the right amount of medicine easily, but tablets might have extra ingredients. Ground medicinal plant material can be mixed with food or drinks as loose powders. Tinctures are strong extracts kept in alcohol. They can be easier to measure for the right amount, but they may not be as handy as capsules or tablets because they last longer and work faster. Not suitable for people who don't drink alcohol. Creams and ointments are good for treating specific problems like diabetic nerve pain or skin issues (Blahova et al., 2021).

Dosage and Administration

The right way to use medicinal plants depends on the specific plant, its form, and the person using it. Here are some tips for using common medicinal plants, take 1-3 tablespoons of Aloe Vera gel every day, either on its own or mixed with water or juice. We can have Bitter Melon by drinking 50-100 ml of fresh juice every day or taking 1-2 capsules with 500 mg of dried extract twice a day. It works best if you take it on an empty stomach. You can eat fenugreek by taking 5-10 grams of seeds every day, or 500-1000 mg of standardized extract two times a day. the seeds in water overnight or add the powder to your food or drinks. Gymnema Sylvestre is a plant extract that you can take as a pill. Take 200-400 mg twice a day before meals to help lower your blood sugar after eating (Pengelly, 2020)

Sourcing and Authenticity

We need to ensure that the medicinal plants are of good quality and authentic so that they work well and are safe and harmless. When purchasing medicinal plants, it is best to buy them from trusted sellers who follow strict regulations and have them tested by third-party companies. This ensures that the plants are pure and strong. It's a good idea to check the label to see if it indicates that the product is organic, non-GMO, and contains standardized extracts. Make sure the label has detailed information about the product's ingredients and the dosage to take. Also, choose products that have been checked for harmful metals, chemicals, and bacteria to avoid impurities. Choose products that don't have anything extra or unnecessary added. When purchasing plants, choose plants that have been harvested in a way that is good for the environment and treats humans fairly (Dasilva et al., 2022).

Integrating Medicinal Plants into Diabetes Management Plans

Using herbs as part of a whole-body approach to treating diabetes requires collaboration with your doctor and other health professionals. Always check with your doctor before using any plants as medicine to make sure they won't cause any problems with your other treatments and that you are taking them in the correct amounts. Personalized care is important for good diabetes control. Tailor your use of herbs to your body's needs, your preferences, and how your body responds to the treatment. Monitor your blood sugar levels carefully and adjust your medications as necessary. Be aware of any side effects or problems when using conventional medications and complementary treatments at the same time. It's good to make changes to our daily habits, such as eating healthy, staying active, and managing stress, to help manage diabetes. It can also be useful to add natural plants that can help treat diabetes. Be sure to tell patients how to use medicinal plants correctly, what benefits they have, and any problems they may have. Encourage your child to make smart decisions and stick to a treatment plan (Yako, 2020).

Future Directions and Research Needs

Emerging Medicinal Plants with Potential Anti-diabetic Properties

Scientists have been discovering new plants that can help treat diabetes. These new plants could further help control diabetes. Moringa contains several nutrients that can help lower blood sugar levels and make insulin work better. Nigella sativa, also known as black seed, contains a substance called thymoquinone, which in studies has been found to help lower blood sugar levels in animals and make insulin work better. Ayurvedic medicine uses Salacia reticulata to help treat diabetes. Studies show that it can make it harder for the body to absorb carbohydrates and help control blood sugar levels. Viola macrophylla contains corosolic acid, which may help lower blood sugar levels by making insulin work better. Ginseng contains ginsenosides, which can help the body produce more insulin and respond better to it. This can be helpful for people with diabetes (Tran et al., 2020).

Integration with Conventional Medicine

This means making rules for using plants as medicine for diabetes, getting doctors and herbalists to work together, teaching patients about the good and bad parts of using plants, making sure plant products are safe and good quality, and making it easier for people to get insurance to cover plant treatments for diabetes (Allen et al., 2023).

Conclusion

Diabetes is a chronic condition in which high blood sugar results from insufficient insulin. Globally, it's rising and impacting health and finances. While treatments include medication and lifestyle changes, medicinal plants offer a cost-effective option with benefits like increasing insulin levels and protecting against damage. However, it's crucial to be aware of potential side effects and quality concerns. Regulating and ensuring the safety of herbal products can enhance their effectiveness in managing diabetes.

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Chapter 58

Herbal Harmony

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ABSTRACT

Herbal medicine, an ancient and global practice, continues to be a key element in healthcare, integrating traditional knowledge with modern science. Systems such as Traditional Chinese Medicine, Ayurveda, and indigenous healing practices utilize herbs to promote balance and health. The bioactive compounds found in various herbs, including phytochemicals like flavonoids and alkaloids, exhibit a range of therapeutic effects, such as antimicrobial, anti-inflammatory, and neuroprotective properties. Modern research emphasizes enhancing the bioavailability of these compounds through advanced delivery systems like nanoencapsulation. Furthermore, synergistic effects between multiple herbs are being explored for their potential in treating complex conditions, such as cancer and neurodegenerative diseases. The scientific validation of herbal remedies, combined with an evidence-based approach, offers promising prospects for integrating botanical medicine into mainstream healthcare, supporting physical, emotional, and mental well-being through natural, holistic methods.

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INTRODUCTION

From the start of time, herbal medicines and alternatives have been a significant part of healthcare techniques. To balance and improve their health, people now a day prefer herbal solutions. Another name for herbal medicine is botanical medicine because it use plant products and plant based compounds for ameliorative purposes. Ayurveda, traditional Chinese medicine and indigenous healing traditions use herbal remedies for therapeutic purposes (Kahkashan et al., 2023) Herbal medicine, also known as plant medicine, relies on plants or plant substances for healing purposes. It's an ancient practice found in systems like Traditional Chinese Medicine, Ayurveda, and indigenous healing traditions. These traditions have used herbal remedies for centuries across diverse cultures (Parvin et al., 2023). In these traditional systems, the belief is that good health results from balance and harmony within the body. Herbs are thought to possess specific properties that can restore and maintain this balance. In the modern medical context, herbal medicine is often considered part of alternative medicine. This category includes various unconventional treatment approaches (Marques da Fonseca et al., 2020).

The Science of Herbal Harmony

Active Compound

Exploration of Bioactive Compounds in Herbs (Phytochemicals)

Numerous herbs have been studied to identify their bioactive compounds that exhibit antimicrobial properties. Garlic (*Allium sativum*) and Thyme (*Thymus vulgaris*) are two herbs that contain phytochemicals such as alkaloids, flavonoids and essential oils, which have been found to possess antibacterial, antiviral and antifungal activities as shown in fig1 (Orhan et al., 2010). However, the therapeutical efficacy of these bioactive compounds is largely influenced by their bioavailability, which is often hindered by poor solubility, stability and absorption. Therefore, researchers are actively exploring innovative delivery systems, such as nanoencapsulation, to improve the bioavailability of these compounds by enhancing their solubility and stability (Singh et al., 2022). Additionally, the flavonoids found in herbs like *Ginkgo biloba* have been demonstrated to have antioxidant and neuroprotective effects (Woodfin et al., 2024).

Many herbs contain bioactive compounds that possess anti-inflammatory properties, making them potential candidates for managing inflammatory conditions. Some of these compounds, such as resveratrol in grapes and curcumin in turmeric, have been thoroughly studied for their ability to modulate inflammatory pathways (Sarkar et al., 2021). Understanding how these compounds interact with the immune system can provide valuable insights into their potential use in the treatment of inflammatory disorders. Additionally, herbs are being investigated for their immunomodulatory effects. For example, compounds found in *Astragalus membranaceus* have been shown to have immunostimulatory properties, which enhance the activity of immune cells (Chen et al., 2019) (Fig. 1).

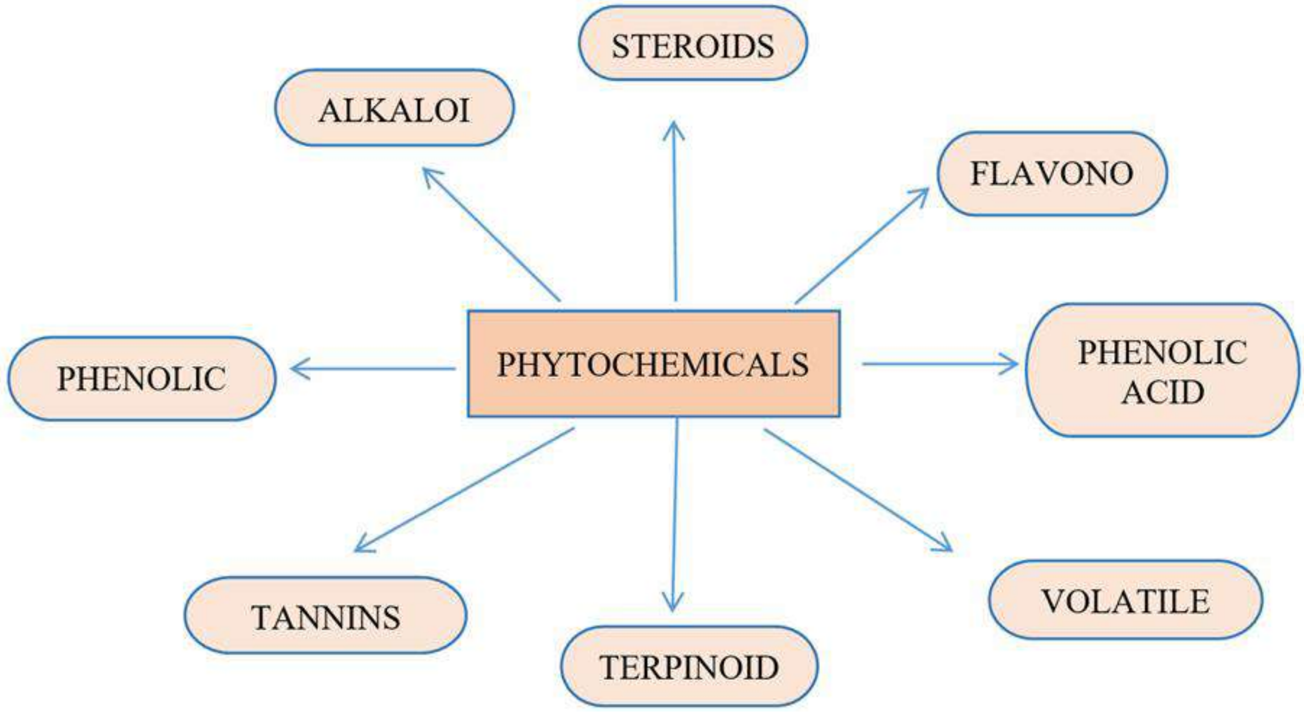

Fig. 1: Phytochemicals and their compounds

Understanding the Synergistic Effect of Multiple Compound

Herbs have recently gained attention for their potential neuroprotective effects, with phytochemicals playing a crucial role in these properties. Various compounds like curcumin from turmeric, ginsenosides from ginseng, and quercetin from onions have demonstrated neuroprotective effects in several preclinical studies (Najafi et al., 2023). To develop potential therapeutic applications, it is essential to understand the mechanisms underlying these effects. For example, curcumin has been shown to modulate multiple signaling pathways involved in neuroinflammation and oxidative stress (Bhatia et al., 2019). Understanding the mechanisms by which these compounds interfere with cancer development and progression is also critical for developing targeted interventions. Furthermore, current research is focusing on the synergistic effects of combining multiple herbs or their bioactive compounds for enhanced anticancer activity. Traditional herbal formulations, such as those in traditional Chinese medicine, often involve a mix of herbs to achieve a holistic approach in cancer management (Wang et al., 2019).

Synergistic interactions between the compounds found in individual plants, mixtures, or medicinal plant extracts are crucial factors that contribute to their therapeutic efficacy. Therefore, it is important to thoroughly evaluate the synergy of medicinal plant extracts using rigorous analysis methods and validate them through clinical trials. However, we still have an incomplete understanding of the specific bioactive compounds that are responsible for these effects and the mechanisms by which they interact (Vaou et al., 2022).

Milk thistle and dandelion are two commonly used herbs for supporting liver health and detoxification. These herbs have individual properties that protect the liver. When combined, preclinical and clinical studies have shown that the two herbs work synergistically to improve liver health. The combination is believed to enhance liver detoxification pathways, reduce inflammation, and protect liver cells from oxidative damage (Younossi et al., 2019).

Evidence- Based Medicine

Scientific Studies Supporting the Efficacy of Herbal Remedies

The integration of traditional medicine with modern science can be promoted by scientific researchers working together. This collaboration can help combine the knowledge of traditional medicine systems with evidence-based approaches. The use of rigorous scientific methodologies can further enhance the development and utilization of medicinal plant bioactive compounds (Dar et al., 2023). Although herbal remedies have a long history of use in traditional medicine, it's important to note that evidence-based medicine places a strong emphasis on scientific studies and rigorous research to establish the efficacy and safety of treatments. It's worth mentioning that not all herbal remedies have been extensively studied, as the scientific literature varies. However, there are some instances where scientific studies have explored the effectiveness of certain herbal remedies.

Echinacea spp. for the Prevention of COVID-19 and other Respiratory Tract Infections in Humans

Native Americans have been using echinacea plants, which are native to North America, for generations to treat a variety of ailments. Over the past century, a lot of research has been done on echinacea, especially in regards to how well it works to cure and prevent respiratory ailments. With the bulk of commercially accessible products containing E. purpurea and/or E. angustifolia, it is one of the most widely purchased natural health supplements globally (Kembuan et al., 2020). The hydroethanolic extract (65% v/v) of freshly harvested *Echinacea purpurea* (L.) Moench (95% aerial parts and 5% root) in pharmaceutical quality, adhering to good manufacturing practices (GMP)) was found to have broad virucidal activity against a wide range of coronaviruses, according to data published in vitro by Signer et al., (2020).

Peppermint Oil for Irritable Bowel Syndrome (IBS)

IBS is a chronic disorder that involves the gastrointestinal tract and the brain's communication with it. Common symptoms of irritable bowel syndrome include abdominal pain for at least one day per week and alteration in bowel habit. IBS has a profound effect on an individual's quality of life and is often costly more for patients, healthcare systems and societies. Peppermint oil is one of the most popular remedies used in IBS (Table 1). Recently, the largest randomized clinical trial to date on the effectiveness of peppermint oil for IBS was conducted and its results were reported (Weerts et al., 2021).

Turmeric for Inflammation and Joint Pain

Curcumin is a natural ingredient found in Curcuma longa L which is commonly referred to as turmeric and its extract known as Turmeric extracts (TEs) have been reported to have many biological activities. Some of these activities include antioxidant, anti-inflammatory, anticancer, antigrowth, antiarthritic, antiatherosclerotic, antidepressant, antiaging, antidiabetic, antimicrobial, wound healing, memory-enhancing activities of these plant sources as mentioned by Calderon-Perez and al. in 2021 (Table 1). Curcumin is used in the form of a nutritional supplement that should help the body to experience anti-inflammatory properties of turmeric extract; nevertheless, this substance has low bioavailability, which hampers its efficiency. Singhal et al., (2021) conducted a study in which the researchers compared the safety and efficacy of bioavailable turmeric extract with that of paracetamol in knee osteoarthritis sufferers.

Valerian Root for Insomnia

There are above 200 varieties of valerian all over the world among which *V. wallichii DC* is one. *V. edulis Nutt.* and *V. fauriei Briq*. Nonetheless, *Valeriana officinalis L.* is the most widely recognized species in Europe and North America; it is referred to as "valerian." Currently, valerian in the United States is considered by the FDA as a dietary supplement. As estimated by the European Medicine Agency (EMA), the root of *Valeriana officinalis* helps to reduce the features of mild nervous tension and sleeplessness (Shinjyo et al., 2020).

Table 1: Different herbs and their uses

Herbs	Treatment
Echinacea spp.	Covid-19, Respiratory illness
Ginkgo Biloba	Cognnitive disorder; hypertension, alzheimer's
St. John's wort	Depression, insomnia, ADHD, Anxiety disorder
Peppermint oil	Irritable Bowel syndrome
Turmeric	Inflammation and joint pain

Achieving Physical Harmony

Herbal Nutrition

The taste and flavour of food products in meat processing industry is improved by the wide use of spices and herbs. There is a wide amount of essential oils and biologically active compounds in herbs and spices. There are many spicy herbs like dill, anise, mint, coriander, parsley, fennel, lemon balm mint, rue, hyssop, sweet clover, basil, thyme, oregano, wormwood, lovage, marjoram etc. Majority of the aerial portion of these spicy herbs is edible while the use of the roots is comparatively negligible (only in angelica, coluria, calamus etc). Spicy herbs are found to have many immensely potent bio-active principles. Carvone, limonene and tepherrone: these are other compounds found in Dill oil which are known to possess cancer preventing qualities. Some diseases include Parkinson's disease, diabetes, arthrosclerosis, and diseases of liver are prevented by dill antioxidants. Preservation in spices and herbs market is continuously increasing over last few years on the global level. India contributes to the production of the 50 out of the 86 items, global production of these items (Pchelkina and Kupaeva, 2024).

Incorporating Herbs into Daily Diet for Optimal Nutrition

Taking a look into WHO's opinions, consumption of red meat is "probably carcinogenic to humans". Also, more episodes of chronic illnesses result from intake of red meats. Therefore, it became an array of newly invented techniques like addition of herbal plants as an antioxidant that offers benefits to the health of consumers. Therefore, for altering and enhancing the fatty acids profile in meat of animal to meet the customer requirements various natural antioxidants such as curcuma, oregano, rosemary, and thyme are applied (Odhaib et al., 2021).

Herbs and spices being used at the current moment as food preservatives are natural compounds and they contain a number of compounds of antimicrobial as well as antioxidant activity. Herbs belonging to *Labiatae* family are among the most explored species with regard to their abilities to exert preservative effects. Quite a lot of work has been carried out on the thyme duo to its antimicrobial and antioxidant properties with the aim of enhancing the quality of foods. Mostly thyme is used in entire meat product for technological purpose, mainly antioxidant and preservative. Extending the shelf life is the main objective of using thyme, however the limiting aspect of using thyme's oil and extract is its unpleasant odor and taste. To prevent this othermethods can be used like natural compounds inclusion encapsulated in nanocarriers (Nieto, 2020).

Role of Herbal Supplements in Supporting Overall Health

The use of dietry additives and botanical medicines has increased globally due to enhanced quality of life and their advantages. Although, herbal medicines present for centuries but their use regulates and varies across countries. Some countries started using them recently while some are using for a long time. The knoweldge of using these dietry additives and botanical medicines could be based on traditional practice (Thakkar et al., 2020).

Tea has various potential health benefits and is one of the most popular and largely consumed items. There are many polyphenol antioxidants in herbal teas which are useful in protection and treatment of various ailments and maintain overall health. The maintaining of basal cellular homeostasis in organism is called autophagy which is essential against various diseases like cancer, obesity, type II diabetes and Alzheimer's disease. Natural medicines are safe, effective and cheap alternative for balancing autophagy and homeostasis. Tea can mediate autophagy as it is part of many people's diet (Brimson et al., 2021).

In today,s world obesity has been treated with many conventional medications. But their dangerous side effects and availability of these medicines limits their use. So, formation of easily accessible, safe, effective and cost-effective entities is critical. Plant-derived medicines are first choice in defense to prevent humans from diseases and to keep them healthy. Synergistic polyherbal compositions will operate on many targets, increasing their anti-obesity impact. These herbs offer many other health advantages in addition to their ability to prevent obesity. Certain plants and the parts of them can be used to treat obesity and diseases associated with it (Rahman et al., 2022).

Herbal Remedies for Common Ailments

Due to their remarkable medicinal and biological features, Indian condiments and spices are known for ages. Spices have many forms such as fruits, seeds, leaves and buds or flowers. The dry seeds of Bishop's weeds also known as "Ajwain seed". These seeds have always been an important part of Unini medicine. In Indian Ajwain oil is used as aromatic and antiseptic carminative. Eating few seeds with betel leaves can relieved indigestion and flatulence. Taking a teaspoon of these seeds is an instant household remedy for indigestion and gastric problems. Taking Ajwain with little jiggery cures gastrointestinal infections after the birth of child. They also work as mucus clearing spice so they are used for respiratory diseases. Cumin is known as one of the oldest species and belongs to coriader family. Its seeds are yellowish-brown in colour and are long and oval in shape. They have aromatic smell and bitterish taste due to volatile in seeds. They are effective against many diseases like morning sickness, indigestion, disorders of digestive systems, diarrhoea etc. If we chew some seeds for half an hour before food they will help to increase hunger and digestion. Cumin is a sedative food so they are also called brain food. Black cumin seed powder mixed with honey can help in relieving slow learning, forget fullness and dullness (Husain, 2021).

Emotional and Mental Harmony

In Indonesia anxiety is more likely to be experienced among teenagers in contrast with the adults by half and commonly affects women by 32%. Financial variables of family, climate, companions and family brokenness are outer elements connected with pressure, uneasiness and misery. Where financial status is connected with in general wellbeing conditions including life fulfillment and bliss. Additionally, device dependence and tormenting are outside variables of stress, uneasiness and despondency since tormenting causes mental misery, forceful way of behaving, antagonism and psychosomatic side effects. Teens that have stepfamilies are more likely to experience bullying. As a result of have been bullied and not having a loving parent. Each teen countenances stressors from family, school climate, friends, educators and examples, however not every one of them have great adapting to adjusting. Guardians who are not agreeable, family brokenness and struggle in the relationship among kids and guardians are critical stressors in the mental advancement of Teenager. Family is an agreeable spot to develop and create for teens separated from school and companion gatherings. Troubled mental encounters in the family during youth lead to gloom, low self-idea and maladaptive adapting in young people. Great adapting and family backing can increment confidence, a more hopeful view, and diminish pressure, nervousness and misery in teenagers (Windarwati et al., 2020).

Adaptogens Herbs

Adaptogens represent a group of compounds which are found in nature and are produced synthetically from various species of plants. These plant based chemicals can help to raise the stress threshold of the body and the level of its productivity by triggering non-specific response (physical, chemical and biological). These adapt gens are involved in routine metabolic activities in the body, enhance mental and physical wellbeing besides enhancing the body's ability to cope with stress. The majority of plant adaptogens were extracted from several plant kingdom classes, such as plant adaptogens include members of the *Araliaceae* family (*Panax ginseng*), *Asteraceae* family (*Rhaponticumcarthamoides*), *Cracuseae* family (*Rhodiola rosea*), *Schisandraceae* family (*Schisandra chinensis*), and *Eleutherococcussenticosus* family. Few artificial adaptogens are currently introduced in addition to the natural compounds known as adaptogens increase the body's resistance to biological, physical, environmental and emotional pressure in order to restore metabolic functions. The body is able to maintain its optimal stability as a result of this restoration of hormones, the immune system and other signal molecules, which prompts the activation of the defense mechanism against severe and incurable diseases. As of late researchers investigated the more advantages of these compounds and their part in protective system in forestalling the illnesses, upkeep of ideal homeostasis and rebuilding of body strength.

Cognitive Enhancer

Nootropics are made from plants and neurotransmitters, and they work by modulating glutamate receptors, increasing acetylcholine levels, and inhibiting monoamine oxidases. Nootropics are also known as cognitive enhancers, a drug to cure cognitive issues in patients suffering from Alzheimer's disease, stroke, schizophrenia, attention deficit hyperactivity disorder and aging. They are used to treat psychological conditions such as moderate cognitive impairment and Alzheimer's dementia. On the other hand, adverse reactions like anxiety, nausea, dependency, and insomnia are possible. These drugs should be taken into account by doctors, because certain patients may benefit from them (Patel et al., 2024).

Herbs Supporting Cognitive Functions and Memory

Short-term memory loss and poor memory are two of the main issues in today's fast-paced world. A condition known as memory loss or amnesia is characterized by an individual's inability to recall past events or recollections. The hectic nature of modern life, inability to focus, emotions, ageing, anxiety, and other brain illnesses are some of the variables that affect memory. Memory impairment is caused by multiple factors, such as oxidative stress, senile plaque formation in the brain, and acetylcholine breakdown. In recent years, there has been an increase in the use of herbal treatments to improve memory. Food and herbal products can slow down the deterioration of brain tissue and other physiological alterations that lead to memory loss. Many traditional medical systems, including the Chinese, Indian, and Persian systems, have long reported the use of different herbs and food items to improve memory deficits. The author covers a number of conventional herbal memory-enhancing systems in this chapter, along with potential mechanisms, in vivo research, and clinical trial results (Arya et al*.,* 2024).

According to Neto et al., (2024), due to ageing, there has been rise in neurodegenerative diseases and there is evidence of Bacopa monnieri (BM) on brain health. BM has established effects like anti-apoptotic and antioxidant, neuro protective, neuro repairing, kinase activating ability for synaptic restorative effect in nerve transmission socio-economic improvement. Studies have also revealed that for BM, Nuclear Factor-κB phosphorylation and marker can be decreased, whereas its effects on such aspects as emotion and cognition are enhanced.

Incorporating Herbs into Lifestyle for Mental Well-being

According to Soni et al., (2024), The Indian medicine system that is Ayurveda has always been based on the triad of body, spirit, and the mind. Some of the body aspects are important in health and they are energy channels such as Prana, Chakra, Kosha, and Oja. There is evidence that combine work with minor somatic structures and conventional medicine may help to regain pathologies of an individual's psyche and physique. To grasp the concept of Ayurveda in its purest state, one has to understand the different anatomic aspects that are not directly tied to the body but provides information on the entire spectrum of Ayurveda from physiology, psyche, soul, and the spirit.

Millions of people worldwide suffer from constipation, a common digestive ailment that will be discussed in this chapter from an Ayurvedic perspective. The inability to pass firm stools or empty the intestines is referred to as constipation. An imbalance in the vata dosha, which controls the flow and removal of waste products from the body, results in constipation. The vata dosha's cold, dry, and harsh characteristics interfere with and affect intestine function. Ayurvedic constipation remedies, including natural laxatives, dietary modifications, exercise, massage, and lifestyle adjustments, will be covered in this chapter. Among the natural laxatives are flax seeds, psyllium husk, raisins, castor oil, and triphala. Dietary adjustments include consuming more whole grains, fruits and vegetables as well as warm beverages (cold, dry and heavy) (Parwe et al*.,* 2024)

Herbal Harmony in Beauty and Skincare

Skincare and treatment use natural herbal compounds from ages now. Plants are safe and applicable in cosmetics formation. Inflammatory, carcinogenic and mutagnic impacts are results of ultraviolet radiation. Some plants contain photoprotective properties. Phytochemicals present in plants are potential ingrediants of sunscreen (Michalak, 2023). Soy is used in cosmetic industry for lubrication and moisturizing impact in skin products. Soybean is used as anti-againg compound. Sunflower contain polyphenol and are used for its moisturizing and anti-aging properties. Marigold show anti-microbial and anti-oxidant effects, therefore, used in anti-aging products (Ferreira et al., 2021)

Conclusion

Herbal medicine, deeply rooted in ancient traditions, continues to gain modern relevance. Its bioactive compounds offer therapeutic benefits for various ailments, though challenges like bioavailability and the need for rigorous scientific validation remain. Integrating traditional and evidence-based approaches can further enhance its efficacy, supporting both physical and mental well-being.

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Chapter 59

Plant as Anthelmintic Allies in the Fight against Fasciolosis: A Review

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ABSTRACT

Plants are the primary food source for ruminating mammals; therefore, using different medicinal plants (extracts, oils, and bioactive compounds) could be effective fasciolicides to prevent economic losses due to fasciolosis. The problem of anthelmintic resistance in flukes due to the excessive and inappropriate use of fasciolicides poses an alarming threat and urges the development of new and alternative fasciolicides. Now, the focus is diverging towards plant-based fasciolicides because of their safe and environment-friendly nature. Different plants' essential oils and active compounds are effective in controlling egg hatching and causing the mortality of adult flukes. The *Artemisia* and *Etlingera* extracts exhibited significant efficacy against eggs and adults of *Fasciola spp.* The plants (*Zingebar officinalle* and *Potentilla fulgens*) also showed considerable efficacy against miracidia, sporocyst, rediae, and cercarial stages. The use of plant oils in controlling parasitism has been practiced all over the world. Oils from (*Pelargonium graveolens*, *Citrus aurantium*, *Helianthus annuus*, and *Cuminum cyminum*) plants actively inhibit egg development. Moreover, plants' active compounds, diterpenoids, thymoquinone, curcumin, flavonoids, acids, artemisinin, and saponins also show promising effects on egg development and adult fluke productivity.

KEYWORDS		
Fasciola, Fasciolosis, Anthelmintics, Phytotherapy, Medicinal Plants	Received: 06-Jun-2024 Revised: 22-Jul-2024 Accepted: 21-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Fasciolosis (Fascioliasis) is a zoonotic disease that affects animals and humans worldwide. A trematode parasite, *Fasciola hepatica* (liver fluke), causes the disease and can be transmitted to animals and humans through its infective stage (metacercariae). The life cycle of this parasite consists of two hosts. The eggs are shed in the faeces of ruminants as sheep, cattle, and goat, and are hatched into the miracidia that infect the first host snail (Lymnid). There, it progresses asexually into its two stages, sporocysts and rediae, after which snail starts shedding cercariae in the water. These cercariae swim randomly, and after a few hours, they lose their tail, get enclosed in a wall and become metacercariae (infective stage) and attached to the watercress or leaves. When the final host mammals (sheep, cattle, and goat), ingest watercress, undercooked vegetables or leaves, the infective metacercariae become converted into immature flukes which excyst in the duodenum, penetrate the intestinal wall and migrate through liver parenchyma to biliary ducts (FAO, 2020; Mia et al., 2021).

Prevalence of Fasciolosis

Fasciola hepatica is prevalent worldwide, while *Fasciola gigantica* is distributed in the tropics (Urquhart et al., 1996). The overall infection rate is increasing due to climate change, drug resistance, and its ability to intrude new areas. It infects more than 2.4 million people worldwide, with 180 million at risk of infection in 66 countries. In livestock, it is hard to quantify, but according to an estimate, it infects over 600 million domestic ruminants annually, which causes heavy economic losses (Collado et al., 2019). The global prevalence of fasciolosis in livestock ranges from 0.72 to 94% (Khan et al., 2013). Humans are accidental hosts which may be due to the ingestion of raw or undercooked vegetables. The infection rate in humans is low with an estimated 4.5% of people worldwide are thought to have fasciolosis (Infantes et al., 2023).

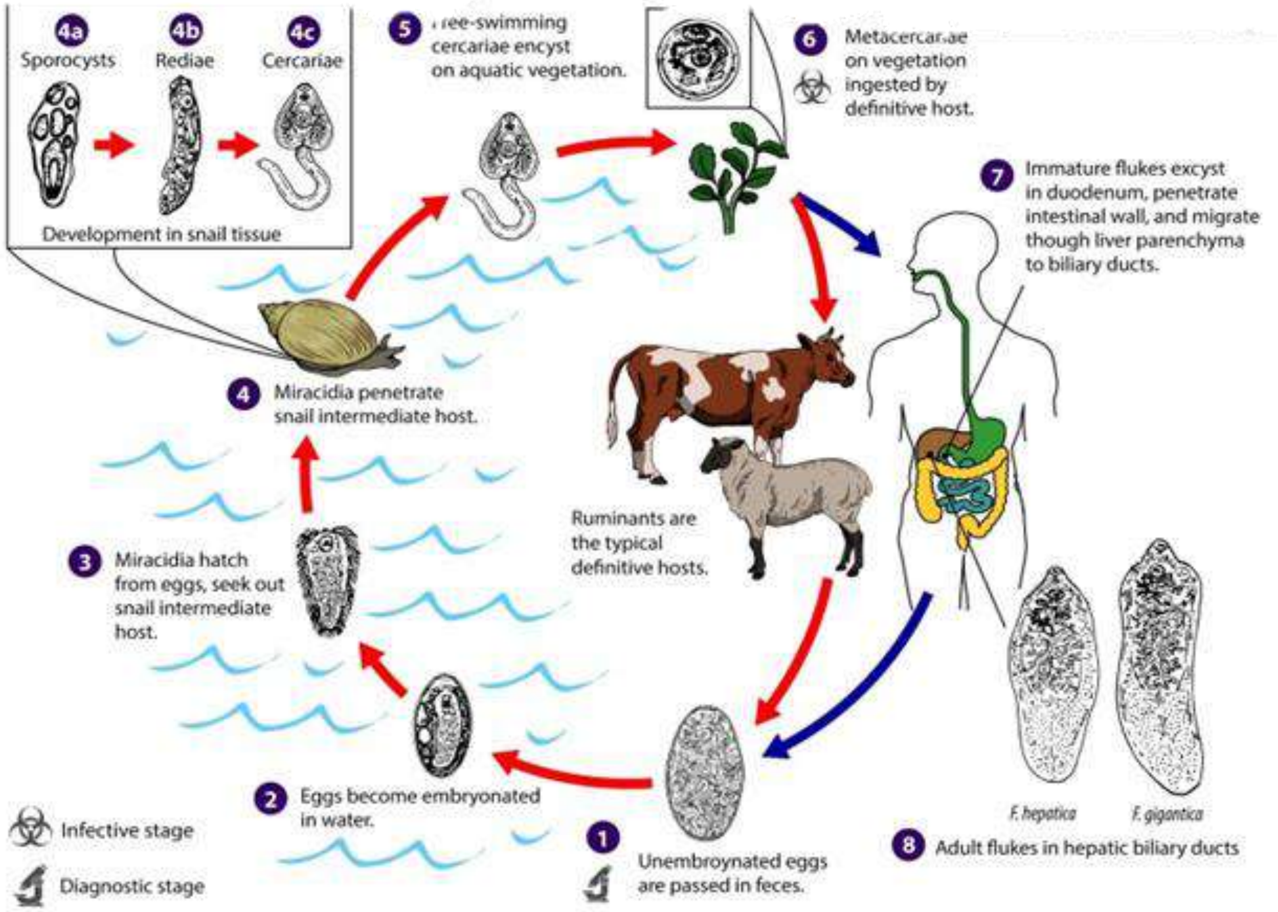

Fig: Life cycle of *Fasciola* spp.

The prevalence of fasciolosis in Pakistan from 2000-2020 was reported in a study. It was 42.70% in Sindh, 25.20% in Baluchistan, 17.70% in Punjab, 10.70% in KPK, and 1.50% in Islamabad. The prevalence was highest among sheep in Punjab at 65.7%, in Baluchistan cows at 28.5%, and in KPK buffalo at 15.9% (Rizwan et al., 2022).

Economic Impact

Helminthes infection costs the agriculture sector an annual loss of $20,000 million towards animal productivity, out of which, the liver fluke infection was predicted to cause annual losses of about US$3.20 billion worldwide (Mehmood et al., 2017; FAO, 2020). The following Table 1 summarizes the economic losses throughout the world due to *Fasciola* infection.

Table 1: Economic Losses in Different Regions of the World

Regions	Countries	Economic Loss through	Economic Loss	Reference
Asia	Iraq	Liver condemnation	US$ 8801.69	Kadir et al. (2012)
	Saudi Arabia		US$ 0.2 M	Degheidy and Al-Malki (2012)
	Sudan		US$ 1.94 M	Abebe et al. (2010)
Africa	Uganda	Liver condemnation	US$ 92 M	Joan et al. (2015)
America	Brazil	Weight loss	35 US$ PH	Dutra et al. (2010)
	Mexico	Productivity loss through reduced milk and meat yield	US$ 4.2 M	Rodriguez et al. (2017)
Australia	Australia	Productivity loss through meat and milk, liver condemination	60–90 M A$	Toet et al. (2014)
Europe	Switzerland	Reduced milk yield, fertility and meat	52$ M	Schweizer et al. (2005)

Control of Fasciolosis

Chemotherapy

Chemotherapy has a primary role in controlling parasitic diseases as it is affordable and effective (Khan et al., 2017). The control of fascioliasis is mainly achieved using synthetic anthelmintics such as albendazole, triclabendazole, and nitroxynil (Nixon et al., 2020; Kouadio et al., 2021). Among the benzimidazole derivatives, triclabendazole (TCBZ) is the most important and widely used drug of choice that can effectively control fasciolosis (Castro Hermida et al., 2021). It is the only drug that has an efficacy of >98% against adults and especially immature flukes as compared to other flukicides that target only adult flukes (Kahl et al., 2023).

Resistance against Anthelmintics

The liver fluke infection is increasing due to climate change, changes in the land use, increased movement of livestock, and its ability to intrude into new areas, which is compounded by the rising issue of anthelmintic resistance in *Fasciola* spp. (Beesley et al., 2023). The problem with the triclabendazole (TCBZ) resistance may be due to the farmers using less effective substitutes or even administering the dose inadvertently (Fairweather et al., 2012). In the recent years, many studies have shown that TCBZ is ineffective against *F. hepatica* in ruminants all over the world. The threat of drug resistance requires serious attention, as many reports have demonstrated drug resistance worldwide, including Scotland **(**Sargison and Scott, 2011), Spain (Martinez Valladares et al., 2014), and New Zealand (Hassell and Chapman, 2012), Wales (Gordon et al., 2012), Peru (Ortiz et al., 2013), Australia (Brockwell et al., 2014), Ireland (Hanna et al., 2015), and Argentina (Larroza et al., 2023).

Besides the issue of anthelmintic resistance, chemical residues found in derived products like milk and meat and their environmental effects are additional crucial factors to be aware of (Da Silva et al., 2020). Thus, for sustainable livestock production, the management of fasciolosis towards TCBZ resistance and the development of new alternatives as flukicides are necessary.

Plants as Anthelmintic Allies

Currently, the livestock sector is under threat due to the problem of increasing resistance to anthelmintics, which is because of factors including inappropriate dosage and repeated exposure of anthelmintics for deworming. Hence, search for alternative anthelmintics is necessary. For this, plant-based anthelmintics could be a preference for coping with this problem. Plant-based anthelmintic are becoming a growing trend because they are safer than the synthetic ones. Moreover, plants provide cost-effective substitutes that are more effective than synthetic anthelmintics (Zirintunda et al., 2022).

Around 80% of people use traditional medicine all over the world, and out of them, about 85% depends on medicinal plants (Nascimento et al., 2000; Oyebode et al., 2016; Romero-Benavides et al., 2017; Sanchez et al., 2020). Plants have been used as medicinal agents from millennia and become the integral part of animal's life. Moreover, plants are also immune boosters that protects against many diseases and also provide many vital nutrients to animal's body. Plants have some of the nature's most effective medicinal compounds. Their extracts and bioactive substances have the potential to become new medicinal agents because of their diversity and environment friendly nature (Abbas et al., 2020; Nurlaelasari et al., 2023). Many medicinal plants can be used as antibacterial agents (Chassagne et al., 2021), antiparasitic (Benlarbi et al., 2023), and antifungal agents (Nigussie et al., 2021). Hence identifying and validating different compounds and their extracts as effective fasciolicide is also necessary. For this, during the recent decades, many plants and their extracts have been evaluated for their anthelmintic activity worldwide (Pessoa et al., 2002; Kozan et al., 2006; Eguale et al., 2011; Ahmed et al., 2013; Payne et al., 2013; Acharya et al., 2014; Esteban Ballesteros et al., 2019).

Plant Extracts

Use of plants as a whole requires a lot of plant mass moreover these are not as much effective. Instead, plant extracts and purified fractions must be used which can provide effective alternative to fasciolicides. The efficacy of plant extract depends on the solvent (water, methanol, ethanol, etc.) used for the extraction and also the mechanism of extraction (hot or cold maceration, proclation, soxhlet extraction, etc.). The solvents provide a medium for the extraction of active phytochemicals like phenols, alkalines, tannins, saponins, etc., and these should be extracted in a preferred medium. Plant extracts provide a combination of different phytochemicals that collectively act as fasciolicide. There are many studies that use different plant extracts to validate their efficacy against *Fasciola spp*. Nurlaelasari et al. (2023) conducted an experiment to evaluate the antifasciolic activity of Mugwort (*Artemisia vulgaris)* extract on the both adult and eggs stages of *Fasciola gigantica.* They assessed the ovicidal efficacy by incubating the eggs with the *A. vulgaris* extract at 5%, 2.5%, and 1.25% for 5, 9, 11, 14, and 16 days. The adult mortality assays were performed after incubating with the extract for 5, 10, 20, 40, 80, 160, 320, and 640 min. All the extract concentrations show significant anti-fasciolic activities. Among these, a 5% concentration of extract showed high level of ovicidal activity, whereas a concentration of 20% extract inhibits 66.67% of eggs hatching after 40 min of exposure. The extract also had high flukicidal efficacy, causing disintegration of different physiological structures (vitelline follicles, intestine, acetabulum, tegument, and spine) of adult fluke. This study has indicated that *A. vulgaris* extract exhibits potential antifasciolic properties. In another study conducted by Wulandari et al. (2023), Torch ginger (*Etlingera elatior)* ethanolic extract was evaluated on eggs and adults of *Fasciola gigantica*. The egg-hatching assay was performed at different concentrations. The ova development was reduced by 56.67%, 56.67%, and 36.67%, at 5%, 2.5%, and 1.25% concentrations, respectively, on day 11 post-incubation, and after 14 days, these developed eggs were decreased by 70%, 50%, and 13.33%, respectively. The flukicidal efficacy was recorded at 10% and 20% of the extract concentration, and the death of flukes was noted after 640 min and 80 min, respectively. The skin was damaged, the inner membrane of spina has erosions and syncytium was detached from the tegument. The study showed that *E. elatior* extract has antifasciolic activity against different stages of flukes. The ginger (*Zingebar officinalle*) hydroalcoholic extract was evaluated on the miracicidal stage of *Fasciola hepatica* by Ghafari et al. (2021). The hatched miracidia was incubated at 2, 5, and 10 ug/mL concentrations. The extract concentrations of 10, 5, and 2 ug/ml cause the fatality of miracidia within 105, 275, and 520 sec. and reduce the speed of miracidia movement to 0.08, 0.77, and 0.82 mm/s, respectively. The comparative efficacy with triclabendazole shows that the extract has antimiracidial efficacy. Kumar et al. (2020) performed the *in-vitro* larvicidal assay on sporocyst, redia, and cercaria stages of *Fasciola*. The Lined Cinquefoil (*Potentilla fulgens*) organic extracts and column-purified fractions larval motility was time and concentration-dependent. The highest toxicity against sporocyst, redia, and cercaria after 2h (LC50) of exposure was column purified fraction 62.4, 59.5, and 45.1 mg/L, respectively. In contrast, the lowest toxicity at this time was of ethanol extract 66.2, 64.7, and 51.3 mg/L, respectively. The same trend was found after 8h (LC50) of exposure, where column purified fraction has the highest toxicity while ethanol extract has the lowest toxicity.

Plant Oils

A number of plant derived natural products including the natural oils have been shown to possess anti parasitic activity, as they have been used against different parasites *in-vitro* and *in-vivo*. De Mello et al. (2023) evaluated the antifasciolic activity of essential oils (EOs) from two plants, Geranium *(Pelargonium graveolens)* and Sour orange (*Citrus aurantium)*, on *Fasciola hepatica*. The essential oils from both plants show 100% efficacy to inactive egg hatching. The Geranium extract showed a mean mortality time of 15 h at both concentrations tested 0.0675 and 0.03375 mg/mL, while Sour orange extract promoted death within 18 h of incubation at concentration of 0.06375 mg/mL. The accumulation of liquid in the tegument was observed. It indicates that essential oils have potential ovicidal and adulticidal activities. Another research conducted by Da Silva et al. (2020) evaluated the Sunflower (*Helianthus annuus)* fixed oil and Cumin (*Cuminum cyminum)* essential oil against *Fasciola hepatica*. The *in-vitro* assay was assessed at different concentrations both fixed and essential oils and also the combination of both oils. The essential oil at concentration of 0.03 mg/mL showed 99% efficacy and the combination of both oils at 0.035+0.03 mg/mL showed 94% effectiveness, while the fixed oil was active insufficiently as an ovicidal. Overall, the results of the experiment showed that the essential oil of Cumin could be used as a new alternative for fascioliasis control.

Plant Active Compounds

Plant compounds and their active ingredients have great potential in the control of various parasites, thus interest is increasing for the search and use of new alternatives. The botanical-derived compounds harboring potential parasiticidal properties are tested as therapeutic agents worldwide. The most common phytochemical constituents of plants are diterpenoids, thymoquinone, curcumin, carbohydrates, terpenoids, fats, enzymes, amino acids, flavonoids, chicoric acid, phenols, polyphenols, alkaloids, artimisinin, saponins, anthocyanins, tannins, isoflavones and carotenoids etc. Interest in the studies with bioactive compounds has been growing as they show direct or indirect negative effects against endoparasites. Several natural diterpenoid molecules have been studied against parasitic trematodes, and their anthelmintic properties have been evaluated. In a study, Chakroborty et al. (2022) evaluated the use of nineteen chemically modified natural active compounds, abietic acid diterpenoid analogues (MC001 to MC088) were first evaluated for their anthelmintic activities against newly excysted juveniles (NEJs) of *Fasciola hepatica*. The six analogues that were proven effective against NEJs (MC008, MC009, MC010, MC052, MC058, and MC061) were secondly evaluated for their anthelmintic activities against adult wild strain flukes. From these analogues MC010 was highly effective against 8-week immature- and 12-week mature Italian strain flukes. The damage to the dorsal side of the fluke was observed. They deducted that the use of abietic acids can be a potential candidate for the development of new anthelmintics. Thymoquinone and curcumin are the active ingredients of *Nigella sativa* and *Curcuma longa,* respectively. Ullah et al. (2017) used these active ingredients as flukicidal agents against *Fasciola gigantica*. The worm motility and egg shedding were both time and concentration-dependent. The adult flukes were exposed to different concentrations (20, 40, 60 µM) of thymoquinone and curcumin. The reduction in motility was observed at 60 µM, but the worms remained alive for 3h post-exposure. The tegumental disruptions and spine erosion were observed in the posterior region and around the acetabulum. Thus, thymoquinone and curcumin have the potential to have a flukicidal effect.

Conclusion

Fasciolosis control using plant-based medicines is proving to be more effective than synthetic anthelmintic, i.e. albendazole. Moreover, plant-based medicines are a growing trend towards a sustainable and nature-friendly environment. In phytotherapy, the time and concentration-dependent factors are the most important; hence, determining toxicity is necessary. Further research using different plant extracts, oils, and their active compounds in this field should be evaluated. However, to confirm which concentrations effectively control eggs, miracidia, larvae, and adult stages is required. Moreover, the mechanism of action should also be understood through different methods like the molecular docking method to eradicate fasciolosis from the livestock industry completely.

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Chapter 60

Recent Advancements on Alternative Control Measures of *Histomonas meleagridis*

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ABSTRACT

Histomonas (*H.*) *meleagridis*, a unicellular protozoan parasite, is the causative agent of histomonosis, commonly known as blackhead disease, predominantly affecting turkeys and also chickens. Transmission primarily occurs through the intermediate host, *Heterakis gallinarum* (roundworm), with both either direct or indirect routes. The parasite's unique characteristics, including pleomorphism and reliance on hydrogenosomes for energy metabolism, pose challenges for control and treatment. Despite the impact of this disease on the poultry industry, there are limited approved prophylactics, therapeutics, or vaccines available for disease management. Traditional control measures, such as antihistomonal compounds like nitarsone and dimetridazole, due to regulatory restrictions and toxicity concerns necessitate the exploration of alternative strategies. Recent advances in disease control encompass use of vaccines, prebiotics and probiotics, plant extracts, nutraceuticals, and improved management practices. Prebiotics and probiotics offer promising avenues by modulating the gut microbiota to create an inhospitable environment for *H. meleagridis* colonization. Plant extracts have shown efficacy *in vitro* in treating *H. meleagridis* infection, providing a potential natural alternative to chemical treatment. Nutraceuticals, food-based substances with health benefits, are being explored for controlling histomoniasis on farms. Vaccination and management strategies like bedding/litter hygiene and biosecurity protocols are promising for disease prevention, but standardization and field administration remains a challenge. Overall, a multifaceted approach integrating novel control methods tailored to specific farm conditions is essential for effective histomoniasis management to reduce the impact of *H. meleagridis* on poultry production. By utilizing a combination of different control measures, the poultry industry can strive towards reduced disease incidence, under a healthy production environment**.**

KEYWORDS			
Histomonas meleagridis, Poultry, Nutraceuticals, Histomoniasis, *Heterakis gallinarum,* Efficacay	Received: 07-Jun-2024 Revised: 17-Jul-2024 Accepted: 13-Aug-2024	USP	A Publication of Unique Scientific Publishers

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INTRODUCTION

Histomonas (*H.*) *meleagridis* is a parasite that mostly affects turkeys and chickens and causes histomonosis, which kills 80 to 100% of flocks. There are no approved medicines, vaccines, or preventative measures to fight against this disease. It is often known as blackhead disease because it causes sulfur-colored diarrhea and, on rare occasions, a blue-colored head. Histomonosis is typically characterized by cecal and liver damage. It has become challenging to treat *H. meleagridis* since the removal of nitarsone in 2015 (Bleyen et al., 2010). *H. meleagridis* belongs to the phylum Parabasalia, class Tritrichomonadea, order Tritrichomonadi,da and family Monocercomonadidae (Beer et al., 2022). *H. meleagridis* is a pleomorphic parasite with single-celled body, axosytle, pelta, parabasal bodies, and hydrogenosomes, exhibiting characteristics of both amoeba and flagellates (Hess and McDougald, 2013). Cushman described histomonosis in turkeys over 100 years ago (Cushman S. 1893). After that, Chester and Robin reported that *H. meleagridis* parasite can also infect chickens. Based on the evaluation of 110 fresh stool samples, it was discovered that 31% of poultry in Lorestan Province, Western Iran, had *H. meleagridis* (Badparva and Kheirandish, 2017). Turkey's production fell from 6.5 million in 1900 to 3.6 million in 1920, indicating that histomoniasis posed a serious risk to poultry farming (Animal and Plant Health Inspection

Service, 1984). The prevalence of *H. meleagridis* in Pakistan is significant. Studies on the parasite's survival away from the host have shown that it can live on a variety of surfaces, which may contribute to its widespread distribution across Pakistani poultry farms (Umar et al., 2016). Blackhead treatment and prevention in veterinary medicine have been significant in the 20th century, with the use of commercial drugs. *H. meleagridis* strains in Pakistan exhibit varying sensitivities to different treatments. Research indicates that Pakistani strains of *H. meleagridis* are more susceptible to nitarsone than to metronidazole, suggesting the use of nitarsone instead of metronidazole to enhance the prevention and management of poultry histomoniasis. However, the European Union's ban on prophylactics and chemotherapeutics in food animals in the 1990s and early 21st century has increased outbreaks of *H. meleagridis*, making blackhead a significant turkey disease in the poultry industry (Bleyen et al., 2010). From June 2014 to September 2016, 13 outbreaks of histomoniasis affected eight meat turkey farms in Austria, resulting in 75,300 turkeys affected. 28,000 died or had to be euthanized, confirming the high fatality of the disease (Sulejmanovic et al., 2017) So, it becomes necessary to control *H. meleagridis* by reducing mortality, preventing disease and its spread, improving overall bird health and food safety, and maintaining a healthy poultry industry. High mortality rates in histomoniasis outbreaks are exacerbated by concurrent infection, as confirmed in a newly constructed barn with *H. meleagridis* and hemorrhagic enteritis virus (Durairaj et al., 2024). Stress in poultry production affects bird behavior, gut health, and disease susceptibility. Studies have shown that feed withdrawal and reduced crude protein diets can increase infection rates and cecal lesions in turkeys. Nutrition and gut health are crucial in histomoniasis disease progression. The study also found that fecal-oral infection could be a potential transmission pathway during commercial production (Fudge, 2022).

Life Cycle

Bilic and Hess, (2020) explained that *H. meleagridis* can be introduced into the caeca of its host by direct (oral) uptake of the protozoa from the other birds' caecal discharges, cloacal drinking, and indirect methods (earthworms) and start dividing in the lumen of turkey and chickens (Hu et al., 2004). *H. meleagridis* transmission primarily occurs through a cecal roundworm, *Heterakis gallinarum*, which acts as a vector for the protozoa, leading to infection in carrier birds like turkeys and chickens. Direct transmission can occur rapidly, after that *H. gallinarum* replicates and degrades the cecal lining of the host (Liebhart et al., 2017). Eggs of *H. gallinarum* will be eliminated from the host body along with the fecal material/feces and then become deposited in the soil as described in Fig. 1. At specific environmental factors, these eggs become embryonated. Other birds become infected by ingesting these embryonated eggs of the *H. gallinarum* (caecal worm), which contains *H. meleagridis*. *H. meleagridis* lacks mitochondria, hence it reproduces using a method known as binary fission, which relies on their hydrogenosomes as modified organelles for energy metabolism. Within the host or intermediate host, in vitro cultured *H. meleagridis* can live only for a few hours at most (Lotfi et al., 2012). *H. meleagridis* can infect chickens directly through the droppings of infected birds or indirectly through earthworms (Nguyen et al., 2015). *H. meleagridis* excretion in chicken lines after co-infection with *Heterikus*. *gallinarum* and *Ascaridia galli* have been studied.

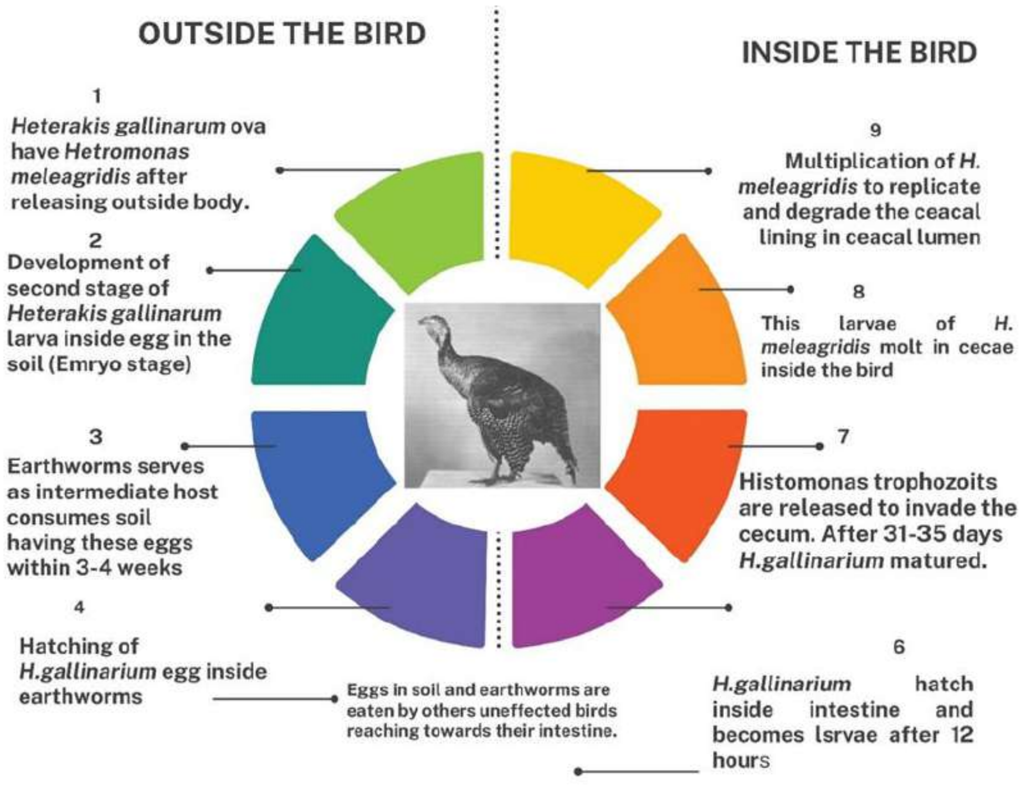

Fig. 1: Transmission of *H. meleagridis* via embryonated eggs of *Heterakis gallinarum*.

Chickens are less susceptible than turkeys to the disease but can serve as reservoirs. Turkeys and chickens show resistance to re-infection from *H. meleagridis*, with live-attenuated isolates as potential vaccines. Natural resistance against both parasites varies among chicken breeds, leading to distinct genetic lines for egg and meat production. (Zuidhof et al., 2014; Das et al., 2021; Hernandez, 2014; Beer et al., 2022).

Right; Inside the Bird; **Left: Outside the Bird**

Chickens experience less clear clinical signs of infection, leading to high mortality. Bloody stool, body weight imbalance, and egg production drop occur. Clinical signs typically develop 7-14 days after infection, with co-infection of coccidia potentially, broadening symptoms (Beer et al., 2022) while clinical signs in turkeys include drooping head and wings, prolonged standing, closed eyes, dark skin pigmentation, ruffled feathers, emaciation, and sulfur-colored feces (McDougald et al., 2020). With the help of microscopic examination of cecal content, cecal and liver scrapings, and histological examination of cecal or liver tissue from turkeys and chickens, *H. meleagridis* can be detected. Typical lesions are seen in the caeca caused by *H. meleagridis* after an experimental infection in chickens. PCR could be a useful tool for rapid and routine screening of *H. meleagridis* (Huber and Zenner, 2005).

Empirical Control Measures

In the past, efforts to prevent the disease focused on the effect of chemical substances. The empirical control measures of histomoniasis involves use of antihistomonal compounds like arsenicals, nitroimidazol es,nitrofu,rans and carbamates which were effective in the 1960s and 1970s. Additionally, chemotherapies like Histostat-50 and paromomycin were explored, but concerns about antibiotic resistance were raised in birds and human health (Collins et al., 2021). Many antihistomonal Compounds were used against histomoniasis as described in Fig. 2 from which following were used in the past:

Arsenicals (Nitarsone)

It disrupts DNA repair processes and cellular energy metabolism, causing cell death. Nitarsone, also inhibits ATP synthesis in *H. meleagridis*, leading the parasite death. The poultry industry has employed arsenicals particularly nitarsone to control blackhead disease, by reducing ceca lesion severity and mortality rates (Peek and Landman, 2013). Nitarsone is an organoarsenic compound. It is a poultry feed additive thastillt improves weight gain and feeding efficiency while preventing blackhead disease. In 2015, the U.S. market withdraw nitarsone, but its use in other countries including Pakistan stil persists (Abraham et al., 2014).

Nitroimidazoles (Dimetridazole)

Historically, nitroimidazoles like ronidazole, ipronidazole, ornidazole and dimetridazole were effective for treatment were very effective against *H. meleagridis* (Ellis et al., 1964; Liu et al., 2023). Nitroimidazoles, particularly 4-(3,4-dichlorophenyl)-1-methyl-5-nitroimidazole, have good activity against *H. meleagridis*, indicating the potential for controlling this protozoal infection. Nitroimidazole compounds serve as both antibiotics and antiprotozoal medications. The 5-nitro functional group of the imidazole ring is the active part of the nitroimidazoles that damage the parasite's DNA. Dimetridazole, an effective antihistomonal compound, to treat *H. meleagridis* infections in galliform birds, particularly turkeys and chickens (Van der Heijden, 2009; Umar et al., 2016; Liebhart et al., 2017).

Nitrofurans

The furan ring's 5-nitro group determines the mechanism of action for nitrofurans. The chemical is reduced by the enzyme nitrofuran reductase inside the cells to many reactive intermediates, which damage the DNA of microorganisms. It reduces cecal and liver lesion scores in infected birds similar to nitarsone (Umar et al., 2016). Nitrofurans like Nifursol were used against *H. meleagridis*, but in 2003, their ban left a gap in preventive measures, causing a resurgence of histomoniasis in poultry (Zenner, 2005).

Carbamates

Diethyldithio-carbamates, organic compounds derived from carbamic acid, inhibit enzymes like superoxide dismutases and metalloproteinases by replacing oxy-gen atoms with sulfur atoms. (Hogarth, 2012). In Vivo tests showed that these substances had the potentialto treat histomonosis. Additionally, dithiocarbamates, including diethyldithiocarbamates, have been recognized for their antioxidant properties and their ability to counteract oxidative stress induced by compounds like diclofenac. The use of above mentioned antihistomonal compounds was later banned due to toxicity concerns. Blackhead disease, a serious health concern in poultry, has currently no approved drug for use in the affected turkeys and chickens as the US has banned the use of antihistomonal compounds. Research on blackhead control is limited, focusing on preventive measures to reduce the parasite's impact on poultry populations, rather then availability of effective drugs (Clark and Kimminau, 2017).

Alternative Measures

Using antihistomonal compounds such as arsenicals (nitarsone), nitroimidazoles (dimetridazole), nitrofurans (nifursol), and carbamates(dithiocarbamates) for controlling *H. meleagridis* infections in poultry can pose several hazards, including toxicity concerns, the development of antibiotic resistance, environmental contamination, regulatory restrictions, and many other human health risks. All these compounds have historically been used to control *H. meleagridis* infections in poultry, but their excess use causes many risks. So, it is essential to explore alternative control methods to ensure safe poultry products and protect poultry, human, and environmental health. Following is an account of alternative control measures that can be taken for the treatment and control of histomoniasis.

Vaccines

Despite potential preventive measures like attenuated histomonads, production challenges hindered the widespread use of vaccines for treatment in turkey and chicken (Nguyen et al., 2020). Birds that recover from infection by antihistomonal treatment can develop resistance against histomonosis, supporting the idea of the use of vaccines. Attenuated histomonads stimulate immunity in turkey and chicken but do not offer protection. The parasite can be grown and attenuated in vitro, but only with bacteria. This is effective but intracloacal applications make use of live vaccines difficult (Hauck and Macklin, 2024). Liu et al. (2023) cloned the 1839-bp α-actinin 1-encoding gene of *H. meleagridis* an d expressed it in the Prokaryotic Expression Vector PET28a(+). Results revealed that Hmα-actinin 1 may be an important virulence factor and stimulate humoral and cellular immune responses against *H. meleagridis* infection in chickens (Liu et al., 2023; Hauck and Macklin, 2024; Liebhart et al., 2017). Mitra et al. (2021) examined the interaction between virulent and attenuated *H. meleagridis* and innate immune systems in turkeys and chickens. They found significant changes in TLR expression as the results of attenuated *H.meleagridis* exposure. The study suggests that Toll Like Receptors (TLR) expression is crucial for immune protection. Experimental trials show effective histomoniasis vaccination using attenuated *H. meleagridis* strain, but standardization and field administration are still required. No vaccines are currently approved for trethe atment of histomoniasis and comcommerciallyailable in poultry birds (Van der Heijden, 2009; Liebhart et al., 2017).

Prebiotics and Probiotics

Prebiotics redreducet infections, and boost immunological response in chickens, resulting in faster infection clearance (Pourabedin and Zhao, 2015; Ajuwon, 2016). Prebiotic Natustat showed efficacy against *H. meleagridis* in male turkeys, improving feed conversion ratios, reducing cecal and liver lesions, and increasing body weight compared to infected non-supplemented turkeys (Duffy and Power, 2005). Probiotics balance cytokines, improve barrier integrity and enhance both innate and humoral immunity (Prado-Rebolledo et al., 2017). Probiotics such as Lactobacillus and Bifidobacterium strains have shown promise in reducing the incidence and severity of histomoniasis. Researchers are investigating the use of prebiotics and probiotics to manipulate the gut microbiota of poultry animals by creating an environment that is less conducive to *H. meleagridis* colonization.

Plants Extracts

Recently, due to a lack of authorized and efficient medications to control *H. meleagridis* plant products have received a great attention. This was particularly preferred since active plant components may combat certain parasite infections through direct and indirect ways (Anthony et al., 2005). Different herbal compounds are effective against different protozoans (Grabensteiner et al., 2008; Harold et al., 2008; Aline et al., 2023). Essential oils commercial plants known as phytosynthese such as cinnamon (*Cinnamomum verum*), lemon (*Citrus limon*), rosemary (*Salvia rosmarinus*), garlic (*Allium sativum*), and thyme (*Thymus*) are surveyed for their antihistomonal effects and ability to suppress the growth of parasites when added to *in vitro* culture of histomonads (Bolouri et al., 2022; Hafez et al., 2006; van der Heijden, 2011). Additionally, one study investigated various plant extracts for their efficacy against *H. meleagridis*, with ethanolic extracts of thyme (thymus), saw palmetto (*Serenoa repens),* grape seed (*Vitis vinifera*), and pumpkin fruit (*Cucurbita pepo*) showing effectiveness *in vitro* (Zaragatzki et al., 2010).

Nutraceuticals

Nutraceuticals are dietary supplements used to improve health, prevent diseases, and support bodily function. With a global market of approximately USD 117 billion, they are categorized as herbal bioactive compounds. Nutraceuticals have shown promising results in treating various diseases. (Sachdeva and Bharadvaja, 2020). Researchers suggest the use of nutraceuticals for the control of hisomoniasis on farms. Schildknecht and Squibb (1979), found that when vitamin E was added to an antihistomonal compound such as ipronidazole, it improved the efficacy of the drug by reducing the morbidity and mortality of the birds to significant extent.

Managemental Practices

For turkey farming, regular change of bedding or litter is recommended after each flock is removed. It helps to prevent the spreading of histomoniasis (Clark and Kimminau, 2017). The *H. meleagridis* parasite has low tenacity and short survival time outside the hosts. However, it can survive in contaminated water or feces for up to 9 hours, potentially causing indirect transmission between farms therefore proper hygiene of farms should be practicised (Liebhart et al., 2017; Lotfi et al., 2012). Avoidance of overcrowding can reduce the risk of *H. meleagridis* transmission between birds. Recent research has shown significant correlations between flock management and histomoniasis (Callait-Cardinal et al., 2010). The farm's biosecurity strategies should adopted to control earthworms, beetles, flies, and rodents by minimizing flooding.

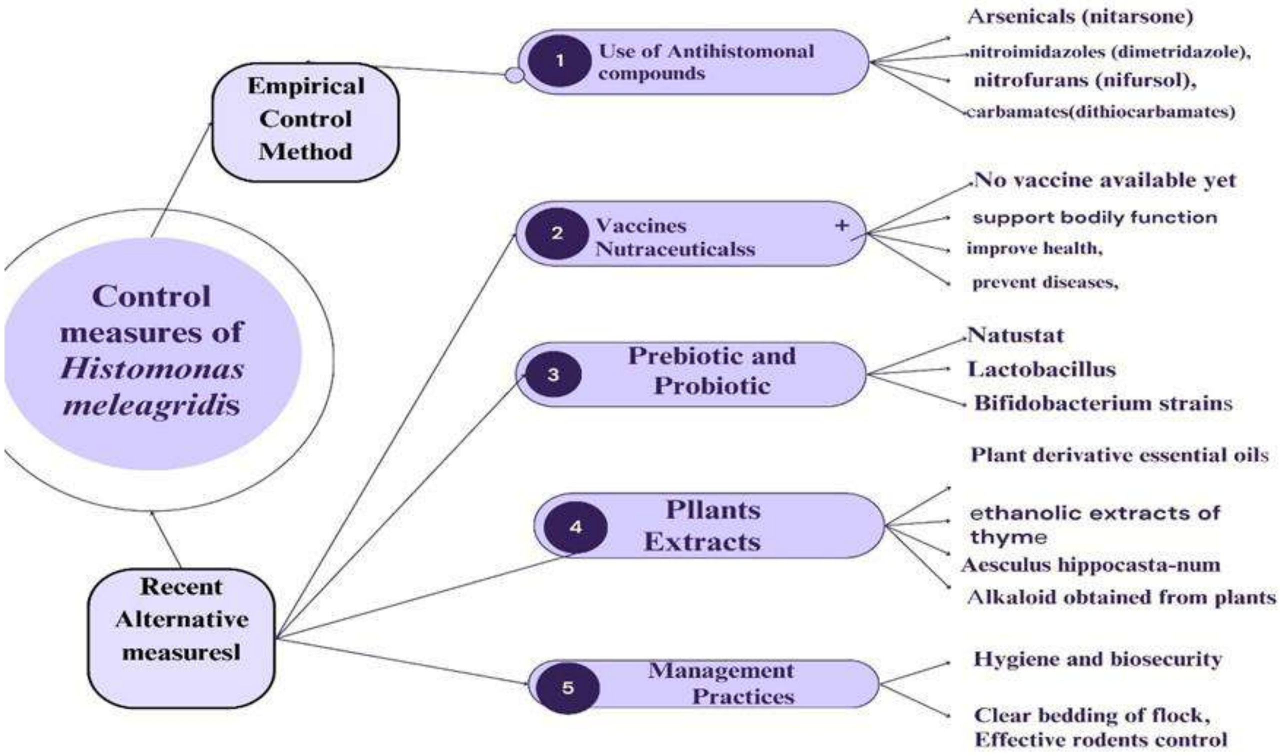

Fig. 2: Control Measures for *H.meleagridis*

Conclusion

The control of *H. meleagridis* requires a multifaceted approach due to the limitations and hazards associated with empirical antihistomonal compounds. Although compounds like arsenicals, nitroimidazoles, nitrofurans and carbamates have historically been effective, concerns regarding toxicity, antibiotic resistance development, and environmental contamination necessitate the exploration of alternative methods for the control of histomoniasis. Recent advances, including vaccines, use of prebiotics and probiotics, plant extracts, nutraceuticals, and management practices offer promising avenues for histomoniasis control. Utilizing a combination of these approaches tailored to specific farm conditions can enhance resistance in birds, reduce disease incidence and spread, and safeguard poultry and its related products. Continous research related to novel and alternative control strategies, along with stringent adherence to biosecurity protocols is crucial to reduce the impact of *H. meleagridis* on poultry production (turkey and chickens) to ensure the welfare of birds as well as consumers.

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Chapter 63

From Ancient Remedy to Modern Medicine: The Jujube's Medicinal Marvels

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ABSTRACT

The jujube fruit (Ziziphus jujube) has a rich history spanning millennia, deeply linked with traditional medicine systems and cultural practices across the world. This chapter explains the journey of the jujube and its evolution from ancient remedy to modern medicine. Beginning with an exploration of its historical and cultural significance, the chapter illuminates the revered status of jujube in Traditional Chinese Medicine (TCM), Ayurveda, and other traditional healing traditions. Supported by scientific evidence, the chapter elucidates jujube's diverse medicinal properties, ranging from antioxidant and anti-inflammatory effects to immunomodulatory activities. Drawing from a wealth of research, it showcases the fruit's potential as a therapeutic agent in the management of various health conditions, offering insights into its mechanisms of action and pharmacological effects. In tandem with its medicinal prowess, the chapter examines the modern applications of jujube in pharmaceuticals and nutraceuticals, highlighting the integration of jujube-derived compounds into diverse healthcare products. As the chapter draws to a close, it reflects on the enduring appeal of jujube as a medicinal and culinary treasure, rooted in ancient wisdom yet poised for modern innovation. Looking ahead, it offers tantalizing glimpses into the future of jujube research, proposing avenues for further exploration and potential applications in healthcare and nutrition. Through its comprehensive analysis, this chapter serves as a definitive guide to unlocking the full potential of the jujube fruit, transcending boundaries of time and tradition to chart a course towards a healthier, more sustainable future.

KEYWORDS		
Phytochemicals, Sustainable cultivation, Pharmacological research, Modern applications, Clinical studies, Health properties, Antioxidant effects, Farming techniques	Received: 23-Jun-2024 Revised: 07-Jul-2024 Accepted: 04-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

The jujube fruit, scientifically known as Ziziphus jujuba, is a small deciduous tree belonging to the Rhamnaceae family. Originating from southern Asia, particularly China, the jujube tree has been cultivated for thousands of years for its nutritional, medicinal, and cultural significance. The fruit itself is commonly referred to as jujube, red date, or Chinese date, and it varies in color from yellow-green to reddish-brown, depending on the ripeness. Historically, the jujube fruit has played a prominent role in various traditional medicine systems, including Traditional Chinese Medicines (TCM) and Ayurveda. It has been revered for its diverse medicinal properties and has been used to address a wide range of ailments. The jujube fruit holds immense cultural significance in regions where it is cultivated, with ancient texts and folklore often attributing mystical or symbolic meanings to it. The purpose of this review paper is to delve into the transition of the jujube fruit from being an ancient remedy to becoming a subject of modern medical research and application. By exploring its historical and cultural significance, as well as its evolving role in contemporary medicine, we aim to gain a comprehensive understanding of the medicinal marvels of the jujube fruit.

Historical and Cultural Significance

The historical and cultural significance of the jujube fruit spans millennia, with its roots deeply intertwined with the traditions and beliefs of various cultures. In China, the jujube tree is regarded as one of the "five sacred fruits," along with peach, plum, apricot, and chestnut, symbolizing longevity, fertility, and prosperity. References to jujube can be found in ancient Chinese texts such as the "Book of Songs" and the "Compendium of Materia Medica" by Li Shizhen, highlighting its esteemed status in traditional Chinese culture (Zhu et al., 2024).

Similarly, in India, jujube holds significance in Ayurvedic medicine, where it is known as "ber" or "bera." It is considered a tonic for the heart and liver and is used to alleviate conditions such as insomnia, anxiety, and digestive disorders. Jujube's presence in Indian folklore and mythology further underscores its cultural importance in the region (Gupta et al., 2012).

Across the Middle East and North Africa, jujube has been a staple in traditional medicine and cuisine for centuries. It is often consumed during Ramadan as a natural source of energy and hydration, and it is believed to possess aphrodisiac properties (Elleuch et al., 2011).

Historical Use in Traditional Medicine Systems

Traditional Chinese Medicine (TCM)

Jujube, known as "suan zao ren" or "da zao" in Chinese, has been an integral part of TCM for centuries. The earliest recorded use of jujube dates back to the Han dynasty (206 BCE–220 CE), where it was mentioned in the "Shen Nong Ben Cao Jing," one of the oldest Chinese pharmacopeias. In TCM, Jujube is highly esteemed for its capacity to invigorate and nourish the blood calm the mind, and harmonize the digestive system (Wang et al., 2021). It is commonly prescribed for conditions such as insomnia, anxiety, poor appetite, and digestive disorders. Jujube is often incorporated into herbal formulations such as the renowned "Si-Wu-Tang," which combines jujube with other botanical ingredients to nourish the blood and regulate menstruation (Wang et al., 2021).

Ayurveda

In Ayurvedic medicine, jujube holds a prominent place as well. Known as "ber" or "bera" in Sanskrit, it is valued for its cooling properties and ability to balance the doshas, particularly pitta and vata (Gupta et al., 2012). Jujube is considered rejuvenating herb in Ayurveda, and it is used to improve digestion, alleviate stress, and promote longevity. Ayurvedic texts such as the "Charaka Samhita" and the "Sushruta Samhita" describe jujube as a medicinal plant with diverse therapeutic applications, recommending it for various ailments ranging from digestive disorders to skin diseases (Chopra et al., 2002).

Cultural Significance in Various Regions

China

Jujube cultivation has been an integral part of Chinese agriculture and culture for millennia. The fruit is celebrated for its auspicious symbolism, representing fertility, prosperity, and longevity. In China, jujube festivals are held in many regions, where the fruit is showcased in various culinary delights and traditional ceremonies. Jujube trees are often planted in courtyards and gardens as symbols of good fortune and protection. Additionally, jujube wood is valued for its durability and is used in furniture-making and construction (Wang et al., 2021).

India

In India, jujube holds cultural and religious significance. The fruit is commonly consumed fresh or dried and is often offered as a religious offering during festivals and ceremonies. In Indian mythology, jujube trees are associated with the god Krishna and the fruit is believed to possess divine attributes. Jujube trees are also planted near temples and sacred sites as a form of worship and devotion (Gupta et al., 2012).

Examples of Historical Texts or Traditions

Chinese Texts

The "Shen Nong Ben Cao Jing," an ancient Chinese herbal text, describes jujube as a tonic for the spleen and stomach, promoting digestion and vitality. Similarly, the "Compendium of Materia Medica" by Li Shizhen provides detailed pharmacological information on jujube and its various medicinal preparations. These texts highlight the esteemed status of jujube in Chinese medicine and its enduring legacy as a sacred plant.

Sanskrit Texts

Ayurvedic texts such as the "Charaka Samhita" and the "Sushruta Samhita" mention jujube as a medicinal plant with properties to balance the doshas and promote overall well-being. These texts describe formulations and therapeutic uses of jujube in Ayurvedic practice, emphasizing its role in maintaining health and vitality.

Islamic Traditions

In Islamic culture, jujube is mentioned in various Hadiths (sayings of the Prophet Muhammad) regarding its health benefits and spiritual significance. It is believed to have been consumed by the Prophet Muhammad as a natural remedy and is recommended for its nourishing properties. Jujube holds significance during Ramadan, when it is consumed to break the fast and replenish energy levels (Zhu et al., 2024).

Nutritional Composition

The nutritional composition of jujube fruit is a key factor contributing to its esteemed status as a health-promoting food. In this section, we will conduct a detailed analysis of the various vitamins, minerals, and phytochemicals found in jujube fruit, and explore how these nutritional components contribute to the fruit's numerous health benefits.

Vitamins

Jujube fruit is rich in vitamins, particularly vitamin C and vitamin A. A 100-gram serving of fresh jujube fruit typically provides approximately 69 milligrams of vitamin C, which is equivalent to 115% of the recommended daily intake (RDI) (Jin et al., 2012). Vitamin C is a powerful antioxidant that plays a crucial role in boosting the immune system, promoting collagen synthesis, and protecting cells from oxidative damage (Salehi et al., 2018).

In addition to vitamin C, jujube fruit contains significant amounts of vitamin A, primarily in the form of beta-carotene. Beta-carotene is a precursor to vitamin A and is essential for maintaining healthy vision, skin, and immune function. The presence of beta-carotene in jujube fruit contributes to its vibrant orange-red color and antioxidant properties (Salehi et al., 2018).

Minerals

Jujube fruit is a good source of essential minerals, including potassium, calcium, magnesium, and iron. Potassium is particularly abundant in jujube fruit, with a 100-gram serving providing approximately 250 milligrams, or 7% of the RDI (Yuan et al., 2016). Potassium plays a vital role in regulating blood pressure, muscle contraction, and nerve function, making jujube fruit beneficial for cardiovascular health. Calcium and magnesium are essential for maintaining bone health and muscle function. Jujube fruit contains moderate amounts of calcium, with approximately 23 milligrams per 100 grams, and magnesium, with approximately 20 milligrams per 100 grams (Salehi et al., 2018). While these levels may not be as high as those found in dairy products or leafy greens, jujube fruit can still contribute to overall mineral intake, especially for individuals with dietary restrictions or preferences. Iron is another important mineral found in jujube fruit, albeit in smaller amounts. A 100-gram serving of fresh jujube fruit provides approximately 0.48 milligrams of iron, representing about 3% of the RDI (Yuan et al., 2016). Iron is essential for oxygen transport, energy metabolism, and immune function, making jujube fruit a valuable addition to the diet, particularly for individuals at risk of iron deficiency.

Phytochemicals

In addition to vitamins and minerals, jujube fruit contains a variety of phytochemicals with potential health-promoting properties. These phytochemicals include flavonoids, phenolic compounds, and triterpenoids, which exhibit antioxidant, anti-inflammatory, and antimicrobial activities (Jin et al., 2012). Flavonoids such as quercetin, kaempferol, and rutin are abundant in jujube fruit and contribute to its antioxidant capacity (Yuan et al., 2016). These compounds help neutralize harmful free radicals, reduce inflammation, and protect against chronic diseases such as cardiovascular disease, cancer, and neurodegenerative disorders (Salehi et al., 2018).

Phenolic compounds, including phenolic acids and tannins, are also prevalent in jujube fruit and contribute to its bitter-sweet taste and astringent properties (Jin et al., 2012). These compounds possess antioxidant and anti-inflammatory effects and may help lower blood sugar levels, improve lipid metabolism, and enhance gastrointestinal health. Triterpenoids, such as betulinic acid and oleanolic acid, are bioactive compounds found in jujube fruit that exhibit various pharmacological activities, including anti-cancer, hepatoprotective, and anti-diabetic effects (Salehi et al., 2018).

Contribution to Health Benefits

The diverse array of vitamins, minerals, and phytochemicals found in jujube fruit collectively contribute to its numerous health benefits. The high vitamin C content helps boost the immune system, while vitamin A supports vision and skin health. Potassium helps regulate blood pressure, while calcium and magnesium support bone health and muscle function. Iron aids in oxygen transport and energy metabolism, and phytochemicals such as flavonoids, phenolic compounds, and triterpenoids exert antioxidant, anti-inflammatory, and other bioactive effects that may protect against chronic diseases and promote overall well-being.

Medicinal Properties

Jujube has been used medicinally for thousands of years in various cultures, including TCM, Ayurveda, and traditional Persian medicine. It is valued for its diverse therapeutic effects and is believed to exert positive influences on multiple organ systems, including the digestive, respiratory, and nervous systems. Traditional uses of jujube include promoting relaxation, improving sleep quality, alleviating anxiety and stress, and enhancing overall vitality and well-being (Hua et al., 2021).

In addition to its traditional uses, modern research has uncovered a plethora of bioactive compounds in jujube fruit that contribute to its medicinal properties. These compounds include polysaccharides, flavonoids, phenolic acids, triterpenoids, and vitamins, which exert various pharmacological effects on the body (Salehi et al., 2018). Jujube's medicinal properties are attributed to its antioxidant, anti-inflammatory, immunomodulatory, neuroprotective, hepatoprotective, and anti-cancer activities, among others (Jin et al., 2013).

Pharmacological Effects

Antioxidant Activity

Jujube fruit is rich in antioxidants, including vitamin C, flavonoids, and phenolic compounds, which help neutralize harmful free radicals and protect cells from oxidative damage (Yuan et al., 2013). Studies have demonstrated that jujube extract exhibits potent antioxidant activity in vitro and in vivo, scavenging free radicals and inhibiting lipid peroxidation. This antioxidant capacity may contribute to jujube's ability to prevent chronic diseases such as cardiovascular disease, diabetes, and cancer (Hua et al., 2021).

Anti-inflammatory Activity

Jujube fruit contains bioactive compounds with anti-inflammatory properties, including flavonoids, triterpenoids, and polysaccharides, which help modulate the body's inflammatory response (Salehi et al., 2018). Preclinical studies have shown that jujube extract can inhibit the production of pro-inflammatory cytokines and enzymes, reduce inflammatory cell infiltration, and alleviate symptoms of inflammatory conditions such as arthritis and colitis (Jin et al., 2013).

Immunomodulatory Activity

Jujube has been traditionally used as an immunomodulatory agent to enhance immune function and promote resistance to infections. Experimental studies have demonstrated that jujube extract can stimulate the activity of immune cells such as macrophages, T cells, and natural killer cells, as well as increase the production of cytokines involved in immune regulation (Hua et al., 2021).

Scientific Studies Supporting Medicinal Claims

Numerous scientific studies have investigated the medicinal properties of jujube and provided evidence supporting its traditional uses. For example, a systematic review and meta-analysis published in the Journal of Ethnopharmacology concluded that jujube extract exhibits significant anxiolytic and sedative effects, validating its traditional use as a calming agent (Gao et al., 2013). Similarly, clinical trials have demonstrated the efficacy of jujube supplementation in improving sleep quality, reducing anxiety, and alleviating symptoms of depression (Lorenz et al., 2019).

In addition to its effects on mental health, jujube has been studied for its potential benefits in managing chronic diseases such as diabetes and cardiovascular disease. Animal studies have shown that jujube extract can improve glucose metabolism, reduce insulin resistance, and protect pancreatic beta cells from damage (Jin et al., 2013). Furthermore, jujube supplementation has been found to lower blood pressure, improve lipid profiles, and enhance vascular function in animal models of hypertension and atherosclerosis (Yazdanpanah et al., 2017).

Health Benefits

Jujube fruit, revered for its medicinal properties for centuries, offers a plethora of health benefits that extend across various aspects of well-being. This section delves into the numerous health advantages associated with consuming jujube fruit or its extracts. We will explore how jujube may promote digestive health, improve sleep quality, boost immunity, and support overall well-being, backed by evidence from clinical trials or epidemiological studies. (Hua et al., 2021).

Promotion of Digestive Health

Jujube fruit has long been used to support digestive health in traditional medicine systems, and modern research continues to validate its efficacy in this regard. The fruit contains dietary fiber, which aids in promoting regular bowel movements, preventing constipation, and maintaining gastrointestinal health (Yazdanpanah et al., 2017). Additionally, jujube contains bioactive compounds such as polysaccharides and triterpenoids, which possess anti-inflammatory and gastroprotective properties. These compounds help soothe the digestive tract, reduce inflammation, and protect against gastric ulcers and other digestive disorders (Hua et al., 2021).

Clinical studies have demonstrated the beneficial effects of jujube supplementation on digestive function. For example, a randomized controlled trial involving patients with functional dyspepsia found that jujube extract supplementation improved symptoms such as abdominal pain, bloating, and nausea, compared to placebo. Similarly, animal studies have shown that jujube extract can enhance gastric mucosal defense mechanisms, reduce gastric acid secretion, and accelerate the healing of gastric ulcers (Wang et al., 2023).

Improvement of Sleep Quality

Jujube has been traditionally used as a natural sedative and sleep aid, and modern research supports its effectiveness in improving sleep quality and alleviating insomnia. The fruit contains bioactive compounds such as flavonoids, saponins, and polysaccharides, which exert sedative and anxiolytic effects on the central nervous system. These compounds help regulate neurotransmitter activity, promote relaxation, and induce restful sleep (Wang et al., 2018).

Clinical trials have provided evidence of jujube's sleep-enhancing effects in both healthy individuals and those with sleep disorders. A double-blind, placebo-controlled study investigated the effects of jujube concentrate supplementation on sleep quality in adults with mild insomnia disorder. The results showed that participants who received jujube concentrate experienced significant improvements in sleep duration, sleep efficiency, and sleep onset latency, compared to those who received a placebo. Similar findings have been reported in other studies, suggesting that jujube may serve as a safe and effective alternative to conventional sleep medications (Gao et al., 2013).

Boosting of Immunity

Jujube fruit is renowned for its immune-boosting properties, which have been recognized in traditional medicine systems for centuries. The fruit contains a variety of bioactive compounds, including polysaccharides, flavonoids, and vitamins, which help modulate the immune response and enhance resistance to infections (Yang et al., 2014). Polysaccharides derived from jujube have been shown to stimulate the activity of immune cells such as macrophages, T cells, and natural killer cells, as well as increase the production of cytokines involved in immune regulation. Epidemiological studies have provided evidence of jujube's immunomodulatory effects in human populations. A cross-sectional study conducted in a rural Chinese population found that individuals who consumed jujube regularly had lower rates of respiratory infections and higher levels of circulating immune cells, compared to non-consumers (Wang et al., 2020). Similarly, a prospective cohort study involving elderly adults found that higher dietary intake of jujube was associated with reduced risk of infections and improved immune function markers (Wang et al., 2023). These findings suggest that incorporating jujube into the diet may help support immune health and reduce susceptibility to illness. (A et al., 2021).

Supporting Overall Well-being

In addition to its specific health benefits, jujube fruit contributes to overall well-being by providing essential nutrients and promoting holistic health. The fruit is rich in vitamins, minerals, and phytochemicals, which exert antioxidant, anti-inflammatory, and other bioactive effects throughout the body. Regular consumption of jujube may help protect against chronic diseases, promote cardiovascular health, improve cognitive function, and enhance vitality and longevity (Hua et al., 2021).

Clinical trials and epidemiological studies investigating jujube's therapeutic effects have reported positive outcomes across various health parameters. For example, a randomized controlled trial examining the effects of jujube extract supplementation on cognitive function in older adults found significant improvements in memory, attention, and executive function compared to placebo (Mahmoudi et al., 2020). Similarly, population-based studies have linked jujube consumption to reduced risk of chronic diseases such as diabetes, hypertension, and cancer, as well as improved overall quality of life (Yazdanpanah et al., 2017).

Modern Applications in Medicine

Jujube, a fruit with a rich history in traditional medicine, is increasingly finding its place in modern healthcare as well. This section provides an overview of the integration of jujube into contemporary medicine, including its use in pharmaceuticals and nutraceuticals. We will examine jujube-derived compounds used in pharmaceutical formulations or dietary supplements and explore examples of ongoing research or clinical trials exploring jujube's potential as a therapeutic agent for specific health conditions (Yazdanpanah et al., 2017).

Integration into Modern Medicine

The integration of jujube into modern medicine reflects growing recognition of its therapeutic potential and the increasing demand for natural remedies. Jujube-derived compounds are being investigated for their pharmacological properties and potential applications in treating various health conditions. Pharmaceutical companies and researchers are exploring ways to harness the health-promoting benefits of jujube in the development of new drugs, dietary supplements, and functional foods (Hua et al., 2021).

Jujube-Derived Compounds in Pharmaceutical Formulations

Several bioactive compounds found in jujube fruit have attracted interest for their pharmacological properties and potential medicinal applications. One such compound is jujuboside, a saponin isolated from jujube seeds, which has demonstrated neuroprotective, anxiolytic, and sedative effects in preclinical studies. Jujuboside has been investigated for its potential use in treating anxiety disorders, insomnia, and cognitive impairment associated with neurodegenerative diseases such as Alzheimer's disease (Mahmoudi et al., 2020).

Another compound of interest is betulinic acid, a triterpenoid found in jujube fruit with anti-inflammatory, antioxidant, and anti-cancer properties. Betulinic acid has been studied for its potential in treating inflammatory disorders, metabolic syndrome, and certain types of cancer. Clinical trials are underway to evaluate the safety and efficacy of betulinic acid-based formulations in human subjects (Hua et al., 2021).

Jujube-Derived Compounds in Nutraceuticals

In addition to pharmaceutical applications, jujube-derived compounds are being utilized in nutraceutical products and dietary supplements aimed at promoting health and well-being. Jujube extract supplements are increasingly available in the market and are marketed for their sleep-enhancing, stress-relieving, and immune-boosting properties. These supplements typically contain standardized extracts of jujube fruit or specific bioactive compounds such as saponins, flavonoids, and polysaccharides. Jujube extract supplements are popular among consumers seeking natural remedies for insomnia, anxiety, and fatigue. They are often formulated as capsules, tablets, or liquid extracts and may be used as standalone products or in combination with other botanical extracts or nutritional ingredients. Clinical studies have shown promising results regarding the efficacy and safety of jujube extract supplements in improving sleep quality, reducing stress, and enhancing immune function (Yazdanpanah et al., 2017).

Ongoing Research and Clinical Trials

Research into the therapeutic potential of jujube continues to expand, with ongoing studies investigating its efficacy in treating specific health conditions and elucidating its underlying mechanisms of action. Clinical trials are underway to evaluate the effects of jujube-derived compounds on various aspects of health, including mental health, metabolic health, and immune function. For example, a randomized controlled trial is investigating the effects of jujube extract supplementation on cognitive function and mood in older adults with mild cognitive impairment (Mahmoudi et al., 2020).

Another clinical trial is exploring the effects of jujube polysaccharide supplementation on glycemic control and insulin sensitivity in patients with type 2 diabetes. The study aims to elucidate the mechanisms by which jujube polysaccharides exert their anti-diabetic effects and assess their therapeutic potential as adjunctive therapy for diabetes management (Mahmoudi et al., 2020).

Cultivation and Sustainability of Jujube (Ziziphus jujube)

Geographic Distribution

Jujube trees thrive in warm temperate and subtropical regions, with optimal growth conditions in areas characterized by hot summers and mild winters. The geographic distribution of jujube cultivation spans a wide range, including China, Korea, Japan, India, Iran, and parts of Europe and North America. Within China, jujube cultivation is particularly concentrated in the Northern provinces, such as Shandong, Hebei, and Henan, where the climate and soil conditions are favorable for its growth (Khadivi and Beigi, 2022).

Environmental Requirements

Jujube trees are resilient and can tolerate a wide range of environmental conditions, but they prefer well-drained sandy loam or clay loam soil with a pH range of 6.0 to 8.0 (Du et al., 2022). They require full sunlight for optimal fruit production and are drought-tolerant once established, although regular irrigation is necessary during periods of extended drought (Li et al., 2024). Frost can damage jujube flowers and young fruit, so frost-free areas are preferred for commercial cultivation (Xu et al., 2016).

Sustainable Cultivation Methods

Sustainable cultivation of jujube involves practices aimed at maximizing productivity while minimizing environmental impact and ensuring long-term viability. Integrated pest management (IPM) strategies, such as the use of biological control agents and pheromone traps, are employed to manage pests and diseases without excessive reliance on synthetic pesticides (Du et al., 2022). Additionally, organic farming practices, including composting, mulching, and crop rotation, help maintain soil fertility and reduce the need for chemical fertilizers (Li et al., 2024).

Conservation Efforts

Preserving genetic diversity is crucial for maintaining the resilience of jujube populations and safeguarding against the loss of valuable traits. Botanical gardens, research institutions, and germplasm banks play a vital role in collecting, preserving, and studying jujube germplasm from diverse geographic origins (Du et al., 2022). Conservation efforts also extend to in-situ conservation, where efforts are made to protect natural habitats and promote sustainable harvesting practices in wild jujube populations (Xu et al., 2016).

Conclusion

In conclusion, this review paper has provided a comprehensive exploration of the historical, cultural, nutritional, medicinal, and modern aspects of the jujube fruit (Ziziphus jujube). The historical and cultural significance of jujube in traditional medicine systems such as Traditional Chinese Medicine (TCM) and Ayurveda underscores its enduring appeal as a medicinal plant (Li et al., 2024). Through a detailed analysis of its nutritional composition, including vitamins, minerals, and phytochemicals, it is evident that jujube possesses a diverse array of health-promoting properties (Tang et al., 2022). Moreover, scientific evidence supports its medicinal properties, including antioxidant, anti-inflammatory, and immunomodulatory effects, highlighting its potential as a therapeutic agent in modern medicine (Xu et al., 2016).The exploration of jujube's health benefits, ranging from digestive health to immune support, further underscores its value as a functional food (Miklavčič Višnjevec et al., 2019). The integration of jujube into modern medicine, through pharmaceuticals and nutraceuticals, exemplifies its transition from ancient remedy to contemporary healthcare. However, sustainable cultivation practices and conservation efforts are imperative to ensure the long-term viability of jujube production and preserve its genetic diversity (Li et al., 2023). In light of these discussions, it is evident that jujube holds great promise for future research directions and applications in healthcare and nutrition. Future studies may focus on elucidating the mechanisms underlying its therapeutic effects, exploring novel formulations or delivery systems, and conducting clinical trials to validate its efficacy in treating specific health conditions. By advancing our understanding of jujube's medicinal marvels and promoting sustainable cultivation practices, we can unlock new opportunities for utilizing this ancient fruit to enhance human health and well-being in the modern world.

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