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Complementary and Alternative Medicine: Chinese/ Traditional Medicine

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PREFACE

Traditional Chinese Medicine (TCM) has been practiced for thousands of years, offering unique approaches to health and healing that continue to influence modern medicine today. The book *Complementary and Alternative Medicine: Chinese/Traditional Medicine* explores TCM's rich tapestry of treatments, remedies, and perspectives, presenting its role in addressing contemporary health challenges. With a focus on both human and veterinary applications, this collection examines how TCM and traditional medicinal practices can serve as alternatives or complements to conventional therapies. This book delves into the immunomodulatory and anticancer properties of TCM, particularly its active ingredients in managing diseases like breast cancer. Other topics explore the benefits of herbal ingredients such as *Epimedium* for reproductive health, as well as the pathways through which TCM impacts cardiovascular health by regulating oxidative stress. These insights underscore the versatility of TCM in targeting critical health issues at a cellular and molecular level, showing promise in both preventative and therapeutic contexts. The integration of botanical therapies extends into discussions on zoonotic disease management and animal health, reflecting the growing importance of TCM in veterinary medicine. Studies on the use of *Withania coagulans* for gut health, *Moringa oleifera* in veterinary applications, and the potential of *Calotropis procera* as an alternative for treating theileriosis illustrate TCM's role in supporting livestock health and addressing infectious diseases in animals. Such approaches reflect a holistic view that recognizes the interconnectedness of human, animal, and environmental health. Additionally, the book highlights the medicinal applications of culturally significant ingredients like ginseng, turmeric, and manuka honey. Each of these natural substances has historical significance and modern relevance, providing therapeutic effects for conditions ranging from diabetes to neurological disorders. The properties of olive leaf extracts, copper, and kalonji oil are also examined for their health-promoting benefits and potential as alternative treatments, particularly for chronic illnesses and immune support. *Complementary and Alternative Medicine: Chinese/Traditional Medicine* further explores the role of TCM in managing metabolic disorders and infectious diseases. Treatments for conditions like hypertension with *Hibiscus sabdariffa*, and sepsis with TCM principles, demonstrate the effectiveness of traditional practices in addressing both systemic and acute health issues. The book also provides insights into ethno-veterinary practices and biocultural knowledge, with examples from Mexico and Pakistan, showing how traditional knowledge contributes to sustainable and context-specific healthcare practices worldwide. Alternative therapies for neurological conditions and genetic disorders, as well as evidence-based TCM treatments for arthritis and peripheral neuropathies, are also covered. Practices like acupuncture for arthritis and the use of biomarkers to guide TCM interventions reflect the growing integration of traditional knowledge with modern medical understanding, advancing a holistic approach to health that is increasingly sought by patients and practitioners alike. In summary, *Complementary and Alternative Medicine: Chinese/Traditional Medicine* bridges the ancient and the modern, the botanical and the biomedical, to provide a comprehensive look at how TCM can contribute to today's healthcare landscape. By examining TCM's therapeutic potential in both human and veterinary contexts, this book highlights the relevance and adaptability of traditional medicine. It serves as a resource for researchers, healthcare providers, and anyone interested in exploring the complementary possibilities that TCM offers in our search for a balanced, sustainable approach to health and well-being.

Editor

Contents

Chapter 01

Immunomodulatory Mechanisms of Traditional Chinese Medicine Active Ingredients in Breast Cancer

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ABSTRACT

Breast cancer is associated with high morbidity and mortality worldwide as it represents the most diagnosed cancer. While current therapies are mainly through surgery and chemotherapy, researchers have been involved in investigating more effective therapeutic options with less adverse effects on the patients. The use of active ingredients from traditional Chinese medicine represents a potential novel therapeutic alternative that has been widely researched as it has fewer negative impacts and can target multiple pathways. This chapter has summarized some drug compounds that have been studied to be beneficial in cancer treatment. Through a combined documentation of clinical trials and scientific research, this study has reported on the effect of TCM compounds on the tumor microenvironment. A sample of alkaloids, flavonoids, saponins, and polysaccharides have been reported on and their basis of immunomodulation in breast cancer documented. The mechanisms reported include upregulating immune responses in the TME and activation of T cells that are involved in tumor immunotherapy.

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INTRODUCTION

Breast cancer (BC) significantly threatens women's life and the safety of their health due to the high risk of disease and related death. The disease ranks top as the most diagnosed cancer in the world, with reports of the World Health Organization (WHO) indicating that BC accounted for 1 in 8 diagnoses of cancer and made up 2.3 million new cases diagnosed in 2020 (Arnold et al., 2022). Breast cancer occurrence and associated deaths have increased over the last three decades in both developing and developed nations. The condition constitutes 24.2% of all cases of cancer globally among females, recognized as the principal cause of mortality associated with cancer (Guo et al., 2024). The malignant tumor is linked with high morbidity and mortality, which makes it a critical issue in society. In 2020 alone, there were reported 685,000 deaths from female breast cancer (FBC), with future estimates showing the probable cases will hit 4.4 million in 2070 (Allahqoli et al., 2022). The FBC occurrence and death rates differ between countries as diverse factors interplay in contributing to the burden of the disease. While breast cancer survival has improved, inadequate screening, identification, and cost-effective therapeutics in the early phases contribute to the significant disparities in different countries (Lv et al., 2023). Knowledge on the epidemiology of breast cancer enables health systems to effectively and successfully prevent and control the problem through evidence-based policies and health planning.

There are varying disease symptoms associated with breast cancer. Estimated 30% of women with BC, a palpable breast mass is evident, and further visible clinical manifestations include dimpling, nipple discharge, edema, an orange-peel appearance, blistering, nipple retraction, and erythema. Hence, skin changes, blistering, ulcerations, and discharge are crucial markers (Feng et al., 2023). Among women with BC, a breast lump also represents the most common manifestation and predicts malignancy (Koo et al., 2017). Accordingly, public health education campaigns regarding cancer symptom awareness have been majorly focused on breast lumps. In low- and middle-income countries (LMICs), the lack of mammography-screening programs means that the diagnostic work-up and treatment of breast cancer involves women with BC symptoms self-presenting to primary medical care facilities where they are referred to institutions with the capability to diagnose the problem (Moodley et al., 2018). This situation creates a greater risk of a higher mortality risk of BC linked to the lack of early discovery and poor access to therapy. The initial diagnostic criteria for breast cancer involve imaging modalities based on mammography and ultrasonography, after which tissue biopsy is done to confirm the disease. As the typical testing and diagnostic technique, mammography imaging utilizes low energy 20-30 keV X-rays, with the sensitivity (true positive) of the method approximated at 75% (Iranmakani et al., 2020). Magnetic resonance imaging (MRI), positron emission tomography (PET), and scintimammography are also commonly used (Bhushan et al., 2021).

The current primary therapies for cancers are through surgery and chemotherapy, although researchers have been dedicated in recent decades to exploring more effective treatments (Chen et al. 2021). Comprehensive therapy also including radiotherapy, targeted therapy, and endocrinotherapy have significantly decreased the mortality rates of breast cancer (Mao et al., 2018). However, the associated severe adverse effects including immune system destruction and resultant lower quality of life have occasioned the search for more potent advanced therapeutics with low negative reactions and adjuvant therapy. One such approach is the reliance on TCM, traditionally utilized to alleviate tumor symptoms and improve life quality, as well as control the tumor size and prolong survival of patients (Wang et al., 2020). Hence, this chapter aims to evaluate the immune effects of the active ingredients found in TCM when used to treat breast cancer.

Traditional Chinese Medicine (TCM)

TCM traces its history to approximately 5000 years before common era (BCE) as alluded to in legend and mythology during China's Shang dynasty (1766-1122 BCE) when TCM was structured among traditional herbalists and healers highly esteemed at the imperial courts (Marshall, 2020). TCM's origin is linked to the need to provide various practical therapeutic solutions for treating diseases. Besides its wide application for thousands of years, TM is widely accepted as alternative therapy for cancer. Compounds derived from Chinese Herbal Medicine (CHM) such as berberine, resveratrol, and curcumin have been shown to demonstrate anticancer properties inhibiting human cancer development, angiogenesis, metastasis, and proliferation (Xiang et al., 2019).

As adjuvant therapy, TCM can enhance the immune function as they have an effect on immune cells in the tumor microenvironment and the adaptive immune cells (Chen et al., 2021). There are 400 tumor immune targets and corresponding 126,972 ligands contained in the TCM database on Immuno-Oncology, which affirms the active role TCM plays in immune function by modulating immune cells like T lymphocytes, natural killer cells, bursa dependent lymphocytes, and macrophage cells (Zhao et al., 2021). Several studies have also explored multimodal treatment using TCM and targeted pharmacotherapy or immunotherapy as part of improving treatment outcomes associated with efficacy, reversal of drug resistance, prolonging patient survival, and reducing adverse effects.

Immunomodulatory Effects from TCM with Alkaloids

Traditional Chinese Medicines are rich in diverse chemical components like alkaloids with multiple biological functions impacting innate and adaptive immunity. The antitumor effects exerted by the active ingredients of TCM can function by augmenting immunologic responses in the TME thereby decreasing macrophage cells and regulatory T (Treg) cells in the tumor tissue (Wang et al., 2020). The use of alkaloid components in TCM has been attractive due to their characteristic high-efficiency and low-toxicity when used as antitumor compounds in the medical field. The berberine (BBR) and matrine alkaloids used in TCM whereby they state that BBR isolated from *Coptis chinensis* inhibit the expression of proteins that mediate immune escape (Yang et al., 2023). Accordingly, berberine's immunomodulatory activity in cancer relates to targeting immune checkpoints, regulating the neutrophil phenotype, inducing the polarization of macrophages, increasing natural killer cell activity, and inhibition of inflammatory factor expression.

Meanwhile, matrine alkaloids, extracted from *Sophora flavescens*, show antitumor activity by promoting the apoptosis and differentiation of tumor cells, preventing tumor angiogenesis, propagation, and metastasis, preventing tumor drug resistance and telomerase activity, and increasing white blood cell activity to strengthen the body's immunity (Cao and He, 2020). The matrine alkaloids in TCM further enhance antitumor immunologic action by promoting the maturation, activation, and specialization of dendritic cells (DCs) while also promoting inflammatory cytokine secretion to enhance the body's immune function. From *in vivo* and *in vitro* research, berberine has demonstrated anti-proliferative activity against BC cells while also inhibiting tumor cell colony development and migration (Zhao et al., 2017).

Further, treatment of BC cells with BBR activated apoptotic cells due to the production of pro-apoptotic proteins dependent on the dose administered, as well as inducing cell death mediated by the mitochondrial pathway. From the *in vivo* results, BBR was shown to suppress the growth of BC cells. Yao et al. (2019) also emphasized berberine effect on triple negative BC (TNBC) cancer cell lines by focusing on the action of the active ingredient on the inflammatory reaction in tumor development. From the findings, it was determined that BBR antiproliferative effects were evident in the marked reduction in the viability of cells post-administering various berberine concentrations. BBR also suppressed the surviving fraction of breast cancer cells as shown by the colony formation assays while further suppressing the migration of the BC cell lines. Berberine impact on the secretion of inflammatory cytokines from the breast cancer cells and found that after treatment, there was a reduction in the concentrations of the inflammatory cytokines dependent on the administered dose (Yao et al., 2019). Berberine additionally downregulated the mRNA and protein production by targeting the inflammasome pathway, thereby preventing tumor development.

Table 1: List of TCM Natural Drugs and Immunomodulatory Mechanisms in Breast Cancer

TCM Chemical Component	Natural Drug	Immune Effects	References
Alkaloids	Berberine	Inhibiting protein expression, tumor cell apoptosis, differentiation, tumor angiogenesis, inhibiting tumor cell colony formation, etc.	(Yang et al., 2023; Yao et al., 2019)
	Matrine	Regulates apoptosis via mitochondrial pathway, autophagy, decreased cell viability, inhibits protein kinases	(Du et al., 2020; Mafi et al., 2022)
	Sinomenine	Suppressing WNT signaling, dysregulating anti-tumoral immune responses, cytotoxicity	(Li et al., 2022; Martin-Orozco et al., 2019)
Flavonoids	Kushenol	Autophagy, proliferation, apoptosis	(Kwon et al., 2020; Liu et al., 2023)
	Epigallocatechin gallate (EGCG)	Suppressing cancer cell growth, metastasis, proliferation, angiogenesis, MAPK activation, Akt, EKR cell cycle arrest, IDO activity	(Li et al., 2024)
	Icaritin	Decrease tumor burden, caspase-dependent apoptosis, mitophagy, apoptosis via mitochondrial pathway	(Wang et al., 2023)
Saponins	Ginsenosides	Apoptosis via TNF-α cytokines, proapoptotic gene expression, cytotoxicity	(Peng et al., 2022)
	Timosaponin AIII	Tumor cell death, inhibiting COX2 gene expression, cell cycle arrest	(Zhou et al., 2020; Zhang et al., 2021)
Polysaccharides	Ginseng polysaccharides	Phagocytosis, NO production, TNF-α	(Ni et al., 2010)
	Lycium barbarum polysaccharides	Cell cycle arrest, ferroptosis pathway	(Du et al., 2022; Mu et al., 2023)

The immunomodulatory effects of berberine have also been considered within the context of the immune escape characteristic of various cancers that bypass immune surveillance by suppressing the anti-inflammatory signaling proteins against pathogens.

Matrine (MT) is another major quinolizidine alkaloid from *Sophora flavescens*, which is extracted from Kushen, the dried roots of *Sophora flavescens*, and in vitro studies confirm MT's inhibitory action against the growth of murine tumors, including breast cancer cells. Its mechanism involves promoting apoptosis by a mitochondrial-mediated pathway. In one *in vitro* study evaluating the ability of matrine as an anti-cancer agent and its role in the regulation of apoptosis and autophagy, the epithelial cancer cell line MCF-7 was utilized to determine the mechanism of MT (Du et al., 2020). The experiment was guided by existing evidence confirming matrine ability to suppress proliferation, invasion and metastasis, and regulatory effect on oncogenes and inhibiting breast cancer cytokine production. Matrine has already been used as adjuvant therapy in China to improve survival rates over 5-year period and the quality of life in patients with BC and for immunity enhancement (Zhou et al., 2018).

Sinomenine is another alkaloid monomer extracted from *Sinomenium acutum*, which is another active ingredient in TCM with anti-angiogenesis and immunosuppressive pharmacological properties (Li et al., 2022). The sinomenine hydrochloride (SH) active form of sinomenine also has antitumor activity as it influences breast cancer cell proliferation, apoptosis, migration, and metastasis. SH suppresses the Wnt signaling pathway activity, with the pathway targeting breast cancer stem cell (BCSC) associated genes that play a part in maintaining the stemness, self-renewal potential, and cancer stem cells (CSCs) drug resistance. Wnt has been described as playing a crucial role in immune homeostasis, and pathway alterations in pathologies like cancer potentially dysregulate the protective anti-tumoral immune responses (Martin-Orozco et al., 2019). Hence, SH is able to inhibit the stemness of BCC by targeting glycoproteins that maintain the self-renewal of BC stem cells and by inhibiting Wnt signaling. Sinomenine hydrochloride also potentially prevents the viability of BC cell lines through causing apoptosis in a mitochondrial-dependent way, as well as by its cytotoxicity though increasing oxidative stress against cancer cell lines.

Immune Effects of TCM with Flavonoid Active Ingredients

Flavonoids, the yellow pigments mostly present in fruits and vegetables, act as antioxidants, anti-inflammatory, antitumor, and hypoglycemic agents. In traditional Chinese Medicine, there are several plants with flavonoid active ingredients with the potential to be involved in immunomodulation in breast cancer. Studies have investigated Kushenol E

(KE), a flavonoid derived from *Sophora flavescens*, for its activity against breast cancer cells (Kwon et al., 2020). KE demonstrated autophagy-modulating activity as it was capable of disrupting lysosomal positioning, thereby is a viable immunotherapeutic candidate owing to its lipophilic properties and improved binding activity for membranes and proteins. Liu and colleagues (2023) have further investigated the flavonoid extract Kushenol A, a monomeric flavonoid, for its biological function in breast cancer due to its potency to inhibit cancer cells. They found that Kushenol A repressed BC cell proliferation dependent on time and concentration, just as the active ingredient induced BCC apoptosis according to the dose. The apoptotic effect was linked to the enhanced production of pro-apoptotic proteins and decreased anti-apoptotic proteins. Kushenol A's inhibition of BCC proliferation was found to relate to inhibition of the pathway responsible for kinases that lead to cancer cell growth and tumor proliferation.

Epigallocatechin gallate (EGCG) is a polyphenolic flavonoid derived from green tea, *Camellia sinensis* (Fahmi et al., 2024). The anti-cancer effects of epigallocatecin-3-gallate have been reported, including its pharmacological actions in suppressing the growth of cancer cell, their proliferation, metastasis, and angiogenesis, also inducing apoptosis and enhancing anti-cancer immunity. EGCG mediates apoptosis by promoting pro-apoptotic proteins while reducing anti-apoptotic proteins, and the associated cell death involves inhibiting endoplasmic reticulum (ER) stress-induced protein kinases and acting on the phosphorylation process. Li et al. (2024) further reports the action of EGCG in preventing tumor development and propagation in solid tumors by reducing the stimulation of molecules like MAPK, protein kinase B (Akt), and extracellular signal-regulated kinase (ERK) to encourage cell cycle arrest. This process involves the upregulation of gene transcription involved in anti-proliferative effects against cancer cells, as well as triggering mitochondrial-mediated apoptosis by downregulating the associated proteins and attenuating malignant migration. In the tumor microenvironment, EGCG demonstrates immunomodulatory effects by regulating T lymphocytes, such as by upregulating the expression of proteases in natural killer cells. Accordingly, EGCG enhances the immune response in T lymphocyte infiltration and activation *in vitro* and *in vivo*, thereby useful for the improvement of anti-cancer immunity. The immunomodulation mechanism first relates to downregulating the expression of proteins suppressing the immune system in TME. Secondly, EGCG acts on indoleamine 2,3-dioxygenase (IDO) overexpressed in breast cancer and linked with the progression of disease and that aids in immune escape and immune tolerance in TME (Asghar et al., 2019).

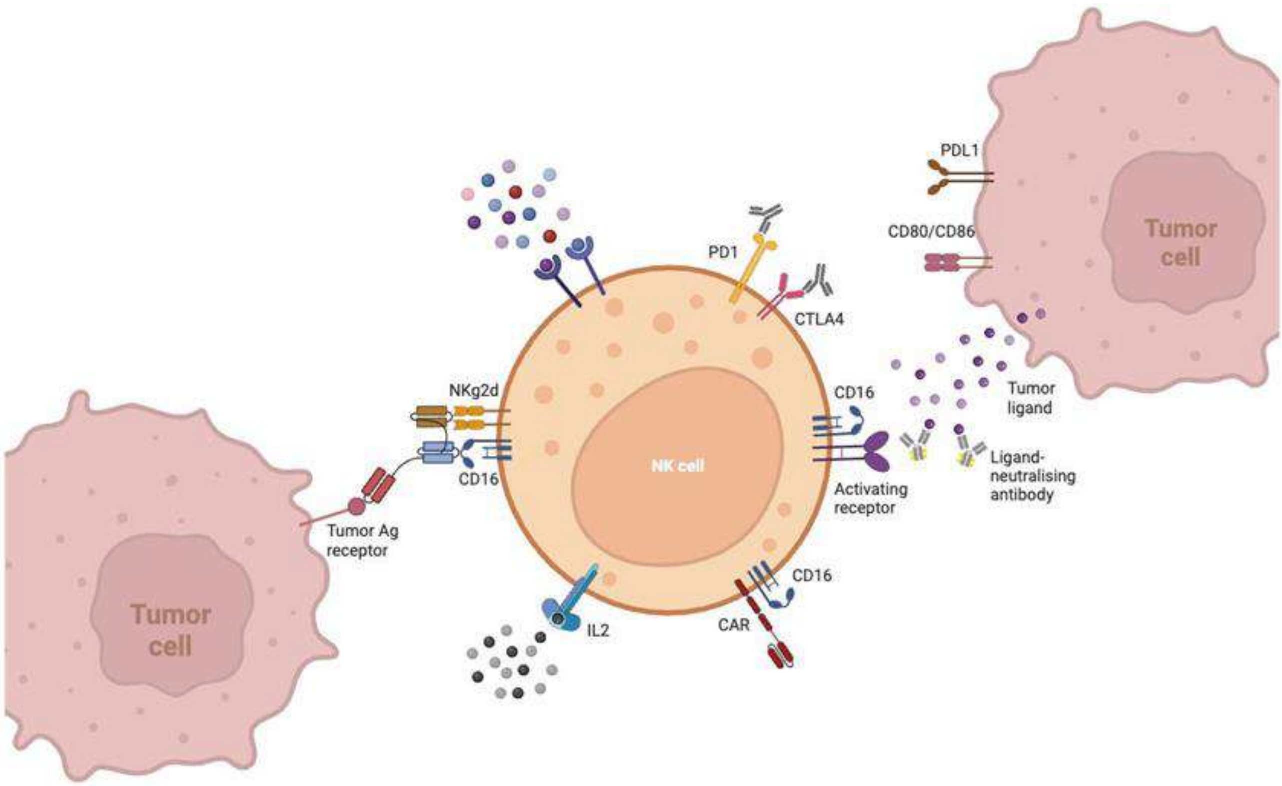

Fig. 1: Action of Natural Killer Cells in Breast Cancer Cells

IDO can catalyze tryptophan catabolism to prevent T lymphocyte multiplication, induce T-lymphocyte cell death, and increase immunosuppressive cell infiltration causing the suppression of the antitumor response of cytotoxic lymphocytes (Zhai et al., 2020). EGCG can also inhibit cancer progression by modulating angiogenesis signaling cascade and reducing proliferation rates (Tudoran et al., 2012). Further evidence indicates EGCG augments the anti-cancer cytotoxicity of natural killer cells associated with upregulated levels of proteins responsible for immune functions. The action on dendritic cells is also documented as EGCG may minimize immunosuppression and downregulate IDO to affect antitumor immunity, as well as regulating Treg cells.

Icaritin (ICT), a prenylflavonoid, is another immunomodulatory active component of traditional Chinese medicine derived from *Epimedium Genus* that can act on breast cancer cells. Hydrolytic product of icariin potentially decreases the burden of tumors in a T-cell dependent way, with the compound entered into clinical trials for treating advanced breast cancer. There have been considerations about the mediating role of icaritin in the immune response that alters TME and tumor T-cell response potential function. The antitumor effects have been confirmed as ICT inhibits tumor growth dependent on the dose, also slowing tumor growth. Based on the evaluation of tumor-infiltrated T-cell numbers and phenotypes, the evidence shows that icaritin upregulates T-cell numbers and percentage in the tumors, further confirming its induction of immunomodulatory cytotoxic T-cells against tumors (Hao et al., 2019). T-cell signaling that icaritin affects in the antitumor action as depicted from the identified upregulated and downregulated genes showed that ibiquitin-mediated proteolysis, glycolysis, lysosome, and cell cycle were impacted by the compound. The T-cell gene sets promoting the cell cycle were also identified as potentially encouraging the proliferation of the infiltrating T-cells. There is also action of icaritin on inducing adaptive immune response by the blockade of T-cell-negative regulatory pathways like the PD-L1/PD-1 axis in TME (Hao et al., 2019).

Icaritin immunomodulation in cancer, with evidence indicating its role in inducing caspase-dependent apoptosis and suppressing carcinogenesis. Additionally, it induces autophagic and apoptotic cell death while reducing cancer cell viability and inhibiting proliferation by reducing colony formation (Yu et al., 2020). Icaritin further promotes mitophagy, a selective autophagy process for eliminating damage mitochondria and preserving healthy ones (Song et al., 2020). The evidence further showed that ICT immune action in cancer cells relates to inducing immunogenic cell death (ICD) markers. *In vivo* and *in vitro* researches of icaritin autophagic effect on breast cancer have also yielded results that confirm the compound induces apoptosis by the mitochondrial pathway (Wang et al., 2023). From the same study, ICT exhibited antiproliferative and metastasis characteristics based on downregulating the enzymes involved in carcinogenic processes. Since the estrogen receptor is critical in the development of BC, the action of icaritin has been examined and evidence indicates this TCM active component decreases the estrogen receptor and EGFR protein expression, thereby inducing BCC apoptosis (Wang et al., 2017).

Immunomodulation of TCM Saponins

Ginsenosides, also steroid-like saponins, are extracted from *Panax ginseng* and have been shown in research to possess immunomodulatory characteristics with anti-cancer effects (Valdés-González et al., 2023). The active ingredient acts by regulating and reducing the expression of various proinflammatory mediators. Breast cancer, *Panax ginseng* Meyer contains a ginsenoside panaxadiol category called ginsenoside Rh2 that promotes cell death or cell cycle arrest by upregulating the TNFα cytokines responsible for the apoptotic process. Ginsenoside Rh2 further inhibits human breast cancer cell viability and colony formation, thereby reducing BCC proliferation. This active component's induction of apoptosis was reported to involve inducing the over-expressions of the estrogen receptor-β (ERβ) and TNF-α while downregulating ERα (Peng et al., 2022). Erβ overexpression in breast cancer is beneficial as it increases autophagy and results in reduced BCC viability, as well as inducing cell death and the expression of proapoptotic genes. Ginseng inhibitory action on BC cell line growth, underscoring how the extract depicted cytotoxic activities by reducing cell viability dependent on dose and time (Shabanah et al., 2016). Ginseng extract additionally induced DNA fragmentation that was crucial in programmed cell death, toxicity, and some phases of necrosis, all which were concentration dependent. It inhibits cell proliferation by inducing apoptosis through upregulating the tumor suppressor gene P53 which regulates the cell cycle. Accordingly, Rh2's antitumor role involves regulation of the immune system by enhancing immunogenicity and repressing breast cancer cell growth (Li et al., 2020).

Timosaponin AIII (Timo AII), a natural steroidal saponin isolated from *Anemarrhena asphodeloides* Bge, has been proven for its anticancer properties. According to, Timo AII selectively encourages tumor apoptosis but not in normal cells, which makes it a novel anticancer therapeutic compound. Its antitumor activity has been confirmed to be effective for various cancers like BC, with the molecular mechanisms involved including inducing ROS and ER stress, autophagy, pro-apoptosis, antimigration, antiproliferation, and anti-invasion of cancer cells (Zhou et al., 2020). Timosaponin AIII inhibition of BCC invasion and metastasis, especially regarding the multifunctional growth factor HGF (hepatocyte growth factor). Based on the results of their study, it was evident that TAIII inhibited HGF-induced invasive activity of the aggressive cancer cell lines in a concentration-dependent manner. Timo III further repressed HGF-induced COX2 gene expression of BCC, which means it inhibits the overexpression of the gene associated with driving mammary carcinogenesis and resultant angiogenesis (Harris et al., 2014). Report how Timo AIII induces cell cycle arrest at G2/M phase in BCC in a concentration-dependent manner, with associated down-regulation of cycle-related proteins. The cell cycle arrest process is further linked with the increased early and late apoptosis of BCC induced by treatment with TAIII dependent on the concentration. Timo AIII further downregulated the proteins involved in proliferation according to the concentration, meaning the saponin prevented cell multiplication and promoted BCC apoptosis by regulating apoptosis- and proliferation-related proteins (Zhang et al., 2021).

Immune Effects of TCM with Polysaccharides

Ginseng polysaccharides (GP) derived from *Panax ginseng* CA Meyer, have exhibited antitumor, antioxidant stress, and immunomodulatory effects in cancer treatment. Indicate that results of clinical studies underline the potential effect of GPs as effective adjuvant-based therapy of tumors, with the improvement of the patients' immune functions being the main mechanism of action. From experimental pharmacological research on GPs, there is evidence that these active components are a potential immunostimulant with combined benefits as anti-inflammatory, anti-oxidative stress, and antitumor characteristics (Tao et al., 2023). The mechanism of action of ginseng polysaccharides as an immunomodulator relates to how it affects immune cells by significantly improving the tumor inhibition rate and facilitating the recovery of NK cells killer ability and stimulating TNF-α and nitric oxide (NO) production that inhibit proliferation and induce apoptosis. By exerting an impact on immune cell types, GPs cause the secretion of cytokines or enhance their killing activity against BCCs as well as regulating the signaling pathways related to inflammation. Emphasized in their study that ginseng neutral polysaccharides improved macrophage phagocytosis and NO production, enhanced TNF-α levels in serum, stimulated the proliferation of lymphocytes, and increased NK cell cytotoxicity (Ni et al., 2010).

Lycium barbarum polysaccharide (LBP) is another active ingredient derived from *L. barbarum* (Chinese wolfberry), a TCM with potential anticancer properties related to its high activity and low toxicity. In a study by, they treated BCCs with LBP with the goal of ascertaining whether the compound reduced cell viability through ferroptosis, a cell death mechanism reliant on iron-dependent lipid ROS accumulation (Du et al., 2022). Based on the findings, LBP exhibited significant inhibition of the viability and proliferation of BCCs dependent on the concentration. The antiproliferative effect was linked to the induction of cell cycle arrest based on the upregulation of p21 and downregulation of Cyclin E expression, thus LBP arrested the cells at the G0/G1-phase. The investigations regarding LBP-induced cell death in BCCs showed the ferroptosis pathway was markedly enriched, thus acting as a key mediator in the process of BCC death. Tumor cell ferroptosis has been confirmed in research to promote the immunogenicity of BCCs and in augmenting PD-L1 antitumor immune response as the combined process significantly delays tumor progression (Mu et al., 2023).

Conclusion and Recommendations

The significance of TCM as immunomodulatory therapy in breast cancer has in recent years been promising as various active ingredients from TCM have been researched in clinical studies. As the burden of breast cancer becomes a concern for public health systems globally, there is increasing interest in researching the mechanisms of action of natural drugs in inducing tumor immunotherapy. This chapter summarizes various active ingredients of TCM with alkaloids, flavonoids, saponins, and polysaccharides to evaluate their immune action in breast cancer cells. Some of the mechanisms of action that have been reported include the upregulation of TME immune responses, increasing the activity of natural killer cells, inhibiting inflammatory factors, and T cell activation. While the evidence available is a step in the right direction regarding breast cancer immunomodulation, it is the recommendation of this chapter that more focus should be directed on the immune targets of TCM as the present research dwells on the action of the active ingredients on immune factor expression.

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Chapter 02

Effects of Epimedium on the Reproductive System and Semen Quality in Male Animals

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ABSTRACT

Epimedium, a perennial herbaceous plant belonging to the Berberidaceae family, boasts a medicinal history spanning over 2,000 years and has been extensively utilized in traditional Chinese medicine. It is considered non-toxic and primarily used to treat limp and injured penises, penile pain, promote urination, replenish vital energy, and strengthen willpower. Its distinctiveness lies in its nourishing effects on the kidneys and yang qi, which are capable of dispelling wind-cold, eliminating dampness, and strengthening bones and muscles. Epimedium exhibits protective effects on the male reproductive system of animals, promoting testosterone synthesis and sperm production and enhancing the microenvironment for sperm generation. It also positively contributes to the recovery of the male reproductive system after injury. Icariin, a compound found in Epimedium, can directly act on the sperm cell membrane, improving its fluidity and consequently enhancing sperm motility and acrosome integrity. By regulating the activity of sperm energy metabolism enzymes, icariin elevates energy metabolism levels, aiding in the enhancement of sperm motility and fertilization capacity, ultimately improving animal reproductive efficiency. Additionally, icariin possesses antioxidant properties, scavenging reactive oxygen species and reducing oxidative stress-induced damage to sperm. These mechanisms are not isolated but interconnected and mutually reinforcing, highlighting the significant advantages of icariin in enhancing animal reproduction through its multifaceted actions.

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INTRODUCTION

Epimedium, a perennial herb belonging to the Berberidaceae family, is also known by various names such as "Xian Ling Pi," "Yang Huo Ye," "Yang Jiao Feng," "San Jiao Lian," and "Qi Zhang Cao." It has a rich history of over 2000 years as a traditional Chinese medicinal herb, initially recorded in the "Shennong Bencao Jing." This ancient text describes its properties as spicy and cold, non-toxic, effective in treating flaccidity and traumatic injuries of the penis, pain in the penile shaft, promoting urination, benefiting qi, and strengthening the will (Ma et al., 2011; Zhang et al., 2023). It is renowned for its tonic effects on the kidneys and yang, dispelling wind and eliminating dampness, strengthening tendons and bones (Ma et al., 2011). The "Compendium of Materia Medica" further elaborates on its benefits, stating that it "nourishes essence and qi, tonifies the waist and knees, strengthens tendons and bones, and fortifies the heart." The 2010 edition of the Chinese Pharmacopoeia recognizes five species of Epimedium: E*pimedium brevicornu, Epimedium koreanum, Epimedium pubescens, Epimedium sagittatum*, and *Epimedium wushanense*. Epimedium is characterized by its pungent, sweet, and warm flavor, associated with the liver and kidney meridians. It enhances immunity and regulates blood pressure (Zhang et al., 2022). Additionally, both in vitro and in vivo experiments and clinical practice have demonstrated the broad pharmacological effects of Epimedium and its active components. Clinically, it has been utilized in the treatment of sexual dysfunction, soreness and weakness of the waist and knees, osteoporosis, arthralgia, memory loss, hypertension, breast lumps (Ti et al., 2017), viral myocarditis (Luo et al., 2024), bronchitis (Yide and Zhen, 2023), chronic hepatitis (Liu et al., 2023), climacteric syndrome, and middle-aged forgetfulness (Zheng et al., 2024).

Epimedium, as one of the traditional Chinese medicinal herbs, is a perennial evergreen herbaceous plant with a height ranging from 20 to 60 cm. This genus grows at 200 to 3700 m altitudes and is often found under cliffs, near streams, and wetland areas (Yu et al., 2023). Although species of Epimedium have also been discovered in East Asia, South Asia, Central Asia, and Europe, the vast majority are unique to China. China is this genus's most significant distribution area, with 47 species identified. These species are found in regions such as Shaanxi, Liaoning, Shanxi, and Sichuan. Fifteen of these species are commonly encountered in the Chinese herbal medicine market (Qian et al., 2023), with *E. koreanum, E. pubescens, E. sagittatum*, and *E. wushanense* being the most widely used and distributed (Zhang et al., 2022).

In recent decades, the traditional medicinal use of Epimedium plants has led to increasing knowledge about its active components and their pharmacological activities. Since the 1980s and 1990s, numerous flavonoids have been successfully isolated from Epimedium extracts. To date, 141 flavonoids, 31 lignans, 12 aurones, 9 phenolic glycosides, 6 phenylethanoid glycosides, 5 sesquiterpenoids, and numerous other compounds have been isolated from Epimedium extracts (Zhang et al., 2023). Among these compounds, flavonoids, particularly prenylated flavonoid glycosides, are the most well-known components (Yang et al., 2023). These flavonoids exhibit diverse biological activities both in vitro and in vivo. Compounds such as icariin (Fig. 1), epimedin A, epimedin B, epimedin C, bavachinin, bavachin, sagittatoside A, sagittatoside B, ikarisoside, specnuezhenide, luteolin, hyperoside, diphylloside B, diphylloside C, and others possess various biological activities including aphrodisiac, estrogen-like, antitumor, antioxidant, radioprotective, anti-inflammatory, antimicrobial, anti-hepatic virus, cardiovascular and neuroprotective, anti-aging, antidepressant, and anxiolytic effects.

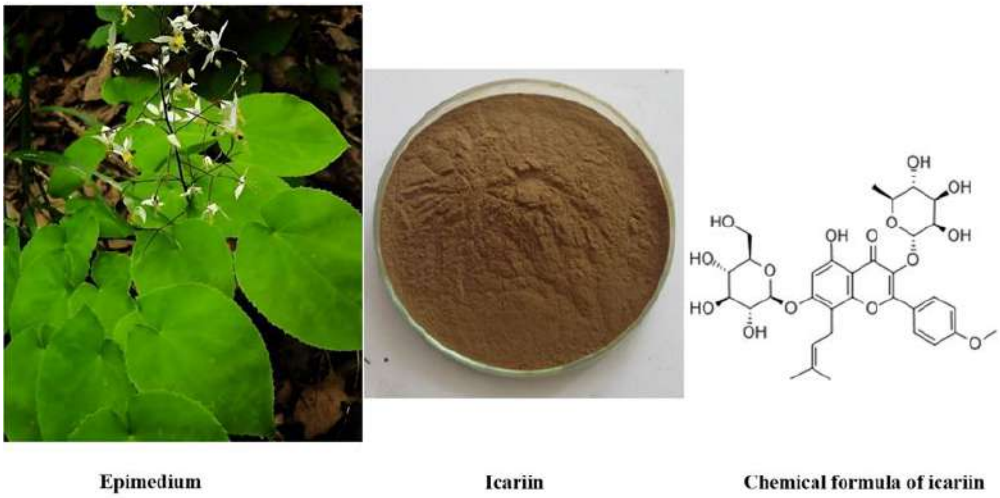

Fig. 1: Whole plant of Epimedium Herb, Herba Epimedii extract icariin and chemical formula of icariin.

Effects of Epimedium on the Reproductive System of Animals

Epimedium, specifically its active component icariin (Fig. 1), significantly impacts the gonads. According to Xiong Yuebin and Zhou Chuhua (1994), icariin notably increases the weight of the epididymis and seminal vesicles in mice without affecting the weight of the testes. This observation indicates a clear androgenic-like effect that stimulates the synthesis and secretion of testosterone, ultimately resulting in an increase in the mass of the epididymis and seminal vesicles. Furthermore, treatment with icariin in rats with cyclophosphamide-induced spermatogenic disorders significantly elevated serum testosterone levels, a finding also observed in roosters (Xuguang, 2007; Yongchao et al., 2021). This action may be achieved directly or indirectly by upregulating the activity of enzymes involved in testosterone synthesis, including steroidogenic enzymes such as CYP11 3β-hydroxysteroid dehydrogenase (CYP113β-HSD), and CYP1117β-HSD, steroidogenic factor-1 (SF-1) (Sun et al., 2019), steroidogenic acute regulatory protein (StAR), and peripheral benzodiazepine receptor (PBR)(Chen et al., 2014). Li Bo et al. (2008) discovered that icariin elevates testosterone levels in animals and regulates the expression of hypothalamic CRH and pituitary POMC genes, indicating that icariin may influence the reproductive system by stimulating the hypothalamus-pituitary-gonad axis, thereby enhancing male reproductive performance. Hormones secreted by the pituitary and testes act on the hypothalamus through negative feedback, binding to gonadotropin and sex hormone receptors to exert their effects (Xueyong et al., 2018). Epimedium is rich in trace elements such as Zn, Cu, Mn, Se, and Fe (Huiling et al., 2000), which play a crucial role in sperm formation and morphology and are closely related to various enzymes in sperm metabolism.

Qin Guanghui et al. (2014) found that icariin significantly ameliorates the pathological damage to mouse testes caused by tripterygium glycosides. The treatment group exhibited thicker seminiferous tubules, wider cellular layers, and more vigorous cell proliferation than the model group. In vitro and in vivo experiments have demonstrated that icariin promotes the proliferation of Sertoli cells, improving the microenvironment for sperm production and protecting male reproductive capacity (Fig. 2). This mechanism is associated with an increase in the phosphorylation levels of extracellular signal-regulated kinase (ERK). Studies have shown that icariin significantly induces ERK phosphorylation in Sertoli cells, and the ERK inhibitor U0126 almost completely blocks icariin-induced Sertoli cell proliferation, indicating that icariin promotes Sertoli cell proliferation in vitro through the ERK1/2 signaling pathway (Yanjun, 2015).

Additionally, research has revealed that icariin can significantly increase the level of estrogen receptor α (ERα) in vivo, suggesting that it can repair age-related damage to Sertoli cells by activating the ERα/nuclear factor-erythroid2 related factor 2 (Nrf2) signaling pathway in injured cells, contributing to the maintenance of male reproductive capacity(Fang and Zhujun, 2020). However, it has been found that the protective effect of icariin on male reproductive capacity is closely related to the concentration used, as excessively high concentrations of icariin can cause tissue and organ damage, impairing male reproductive function. In vitro cell experiments have shown that specific concentrations of icariin can inhibit the proliferation of mouse TM3 Leydig cells (Zixin and Zhiqiang, 2021), emphasizing the importance of appropriate dosing.

Fig. 2: Epimedium improves animal reproductive capacity through four aspects.

Studies have found that icariin can enhance the testis' antioxidant capacity, slow the decline of reproductive ability, and facilitate the recovery of reproductive organ damage. In one study, rats were fed with icariin, and it was found that icariin could activate the Nrf2/heme oxygenase-1 (HO-1) signaling pathway, enhance the antioxidant capacity of rat testis, and thereby alleviate testis injury caused by natural aging and slow down the decline of reproductive ability (Xu et al., 2019). Yu Jiehua et al. (2021) used icariin to study rats with oligospermia induced by adenine gavage and found that icariin had an excellent protective effect on the reproductive function of rats, and its mechanism might be related to enhancing the antioxidant capacity of rats. Another study found that icariin could increase testosterone concentration in the blood of mice with testicular tissue oxidative damage caused by nicotine. At the same time, the sperm concentration of mice increased, and the antioxidant enzyme activity of testicular tissue was enhanced (Ni et al., 2020). Similarly, injecting icariin into mice could reverse the decrease in epididymal sperm count and the destruction of testicular seminiferous tubules caused by di(2-ethylhexyl) phthalate (DEHP) (Sun et al., 2019).

Research has shown that icariin can regulate the central and peripheral nervous systems, stimulate the phosphatidylinositol-3kinase/protein kinase B (PI3K/AKT) signaling pathway, increase endothelial nitric oxide synthase (eNOS) in penile endothelial cells and serum nitric oxide levels, and promote penile erection in mice (Ding et al., 2018). Other studies have shown that icariin is an inhibitor of PDE5, which can specifically bind to the cGMP catalytic site, inhibit the degradation of cGMP by PDE5, and increase the concentration of cGMP in penile smooth muscle cells, contributing to erection. The effect of icariin on inhibiting PDE5 is significantly enhanced with increasing icariin concentration (Chau et al., 2019). Another study found that icariin could inhibit the activity of RhoA/Rho kinase in the intracellular tissue of the corpus cavernosum of hypertensive rats, relieve its inhibitory effect on eNOS activity, thereby weakening the smooth muscle contraction, relaxing the corpus cavernosum smooth muscle, and contributing to penile erection (Huiling et al., 2000). Gao Mengting et al. (2012) used 125I radioimmunoassay to determine the effect of different concentrations of icariin on cGMP levels, a substrate of PDE5 enzyme, in rabbit penile corpus cavernosum. The results showed that icariin could increase cGMP levels in the corpus cavernosum. Jiang Zhaojian et al. (2007) also used 125I radioimmunoassay to observe the effect of icariin on cGMP levels in rabbit penile corpus cavernosum smooth muscle tissue. The results showed that icariin could directly increase cGMP levels.

Effect of Epimedium on Sperm Quality in Animals

Impact on Boar Semen Quality

Studies have demonstrated that under ambient preservation conditions, icariin, a compound found in Epimedium, exhibits beneficial effects on boar semen quality. Specifically, it prolongs sperm survival time and enhances the conception rate (Zhenkun, 2019). Under low-temperature storage conditions, adding icariin at specific concentrations significantly improves boar sperm motility, vigor, and kinematic parameters while reducing sperm malformation rates. Furthermore, icariin enhances the antioxidant capacity of sperm, mitigating damage caused by oxidative stress. Adding a specific concentration of icariin to Modena diluent favors the preservation of boar semen at 4℃, extending its shelf life. Optimal results, in terms of sperm quality, are achieved by adding 15mg/L of icariin (Yanzhi et al., 2023). Incorporating Epimedium polysaccharides into freezing diluents improves post-thaw motility, plasma membrane integrity, and acrosome integrity(Ramgir et al., 2022). The post-thaw sperm vitality achieved by adding epimedium polysaccharides to the thawing solution is notable, as it has high plasma membrane and acrosome integrity rates. Additionally, different storage temperatures after thawing significantly impact sperm survival time, with room temperature appearing more favorable for maintaining post-thaw sperm vitality. This improves the reproductive capacity of pig sperm after thawing (Junwei, 2014).

The protective effect of Epimedium polysaccharides on sperm during cryopreservation of boar semen may be attributed to two primary mechanisms. Firstly, their antioxidant properties (Junwei, 2014). Polyunsaturated fatty acids, integral components of the boar sperm membrane phospholipids, are highly susceptible to lipid peroxidation cascade reactions induced by reactive oxygen species (ROS). Oxidative stress is a detrimental process during sperm freezing, as the abundance of polyunsaturated fatty acids in the boar plasma membrane renders them sensitive to oxidative damage (Zhenkun, 2019). When the balance between ROS production and elimination in the sperm environment is disrupted, excessive ROS can damage the sperm plasma membrane. Epimedium polysaccharides exhibit varying scavenging activity against hydroxyl radical and superoxide anion radical systems, potentially playing a significant role in maintaining the balance between ROS production and elimination. The protective effect on sperm exhibits a dose-dependent relationship. Icariin exerts its antioxidant effects primarily through two mechanisms: either as a direct antioxidant or by enhancing the activity of antioxidant enzyme. Zhang et al. (2010) found that icariin's neuroprotective effects in mice are mediated by its ability to directly scavenge excessively produced ROS and indirectly stimulate the expression and activity of cellular antioxidant enzymes, including catalase (CAT) and peroxiredoxin 1 (Prx1). This enhances antioxidant capacity, resulting in a significant increase in SOD activity and a reduction in MDA levels. Secondly, the osmotic effect of Epimedium polysaccharides may contribute to their protective role. These polysaccharides form an osmotic pressure outside the cell membrane, leading to dehydration and reduced intracellular ice crystal formation. Their interaction with phospholipids at the plasma membrane enhances sperm survival during cryopreservation.

Moreover, these sugars can offset or partially counteract the harmful effects of glycerol on the acrosome. Additionally, it is generally believed that aging may be associated with the accumulation of free radicals and a decline in immune function. Therefore, the solid immunomodulatory activity of Epimedium polysaccharides may confer an anti-aging effect on sperm, further contributing to their protection.

Effects on the Quality of Sheep Semen

The addition of single and compound extracts of Epimedium-based Chinese herbal medicines to the cryo-diluent of frozen semen in Shanbei cashmere goats can improve sperm quality after thawing, with the best results observed at a 10% volume ratio. Compound extracts containing Epimedium as the main ingredient are more effective in improving the quality of thawed semen than single extracts. A compound extract consisting of Epimedium, Morinda officinalis, Cuscuta chinensis, Actinolite, and Glycyrrhiza uralensis, when added at a 10% volume ratio, significantly improves sperm motility, sperm deformity rate, acrosome abnormality rate, room temperature storage time, and adequate storage time of thawed frozen semen in Shanbei cashmere goats. However, the specific mechanism behind these effects requires further investigation (Wenjun et al., 2011).

Studies on frozen semen in goats have shown that as the concentration of Epimedium polysaccharides increases, the total antioxidant capacity of sperm also increases(Zhu et al., 2024). The addition of 3.0 mg/mL of Epimedium polysaccharides significantly enhances the total antioxidant capacity and the activities of SOD and CAT enzymes in semen. Simultaneously, it significantly reduces the levels of MDA and ROS in goat semen, exhibiting a consistent trend that positively correlates with post-thaw sperm motility (Yu, 2019). Adding Epimedium polysaccharides to the diluent effectively inhibits lipid peroxidation reactions, minimizing the damage inflicted on sperm by lipid peroxidation. This intervention prevents the loss of intracellular enzymes and maintains the stability of cell membrane permeability, ultimately safeguarding the sperm. Adding 3.0, 4.0, or 5.0mg/mL of Epimedium polysaccharides to the goat semen freezing diluent can improve the total antioxidant capacity in the semen, significantly higher than the control group. Indeed, the protective effect observed on sperm can likely be attributed to the ability of Epimedium polysaccharides to significantly enhance the activities of SOD (superoxide dismutase) and CAT (catalase) antioxidant enzymes. This enhancement increases the levels of antioxidant substances within the sperm, thereby reducing oxidative stress and preserving sperm quality. SOD and CAT can regulate the balance of ROS and maintain the balance of the antioxidant system, thereby improving semen quality. However, studies have also found that when the concentration of Epimedium polysaccharides exceeds 3.0 mg/mL, the antioxidant enzyme activities of SOD and CAT in the semen decrease. That's an important point to consider. The observed protective effect of Epimedium polysaccharides on sperm may indeed suggest that its antioxidant capacity is not strictly dose-dependent. In other words, increasing the concentration of Epimedium polysaccharides may not always yield greater antioxidant benefits. This finding highlights the need for further research to determine the optimal concentration range for maximizing the antioxidant effects of Epimedium polysaccharides. Adding 3.0mg/mL of Epimedium polysaccharides to the goat semen freezing diluent significantly improves the post-thaw ATP level and high mitochondrial membrane potential proportion. However, as the concentration of Epimedium polysaccharides increases, the ATP level in goat semen initially rises and then declines. At higher concentrations of Epimedium polysaccharides, the ATP level and mitochondrial membrane potential decrease, suggesting an adverse effect on goat sperm. A potential explanation for the limited antioxidant capacity of Epimedium polysaccharides at higher concentrations could be their inhibitory effect on oxidative phosphorylation and glycolysis. This reduction in metabolic pathways may lead to decreased ATP levels within the semen, potentially affecting sperm function and viability. Since the mitochondrial membrane potential maintains ATP production through oxidative phosphorylation, a lower mitochondrial membrane potential may indicate the possibility of sperm cell apoptosis (Agnihotri et al., 2016).

According to traditional Chinese medicine theory, Epimedium has a sweet and warm nature and is known for its kidney-tonifying(Deng et al., 2012), yang-invigorating(Huo et al., 2020), bone-strengthening(Zhao et al., 2016), and wind-dampness-dispelling properties. Modern pharmacological studies have shown that flavonoids in Epimedium extracts exhibit significant antioxidant effects, inhibiting lipid peroxidation to varying degrees and protecting the membrane structures of sperm and sperm acrosomes. The polysaccharide components in Epimedium may also have an anti-ice crystal formation effect. Studies have demonstrated that low concentrations of Epimedium polysaccharides can enhance sperm protection, while high concentrations may adversely affect sperm. The complex composition and variable structure of high-concentration Epimedium polysaccharides can indeed lead to increased osmotic pressure in the solution. This hyperosmotic environment can pose challenges for sperm, causing them to dehydrate and shrink. Such stress can damage the cell membrane and disrupt protein stability, ultimately compromising sperm function and viability. This insight emphasizes the importance of using appropriate concentrations of Epimedium polysaccharides to achieve the desired antioxidant effects while minimizing potential adverse effects on sperm (Sitaula et al., 2010). Therefore, controlling the amount of Epimedium polysaccharides strictly added to the diluent is crucial to maintaining an appropriate osmotic pressure level.

Effects on Semen Quality of Other Animals

Beyond pigs and sheep, studies have also involved animals such as cows, rabbits, chickens, and mice (Ke et al., 2023; Yuan et al., 2014). The dilution of bovine frozen semen with a solution of Epimedium polysaccharide prepared in ultrapure water at a concentration of 2mg/mL was found to maximize the preservation of bovine sperm fertility, resulting in the highest artificial insemination pregnancy rate (Yaotian et al., 2023). Adding 0.20% icariin during the preservation of rabbit semen at 17℃ not only enhances sperm motility, plasma membrane integrity, acrosome integrity, and SOD activity, preventing a decline in semen quality that could affect pregnancy and litter rates but also effectively inhibits bacterial contamination during semen storage, preventing the occurrence of reproductive system diseases (Yunzhen et al., 2020). Icariin effectively scavenges reactive oxygen species (ROS) during semen preservation (Zhenkun, 2019), demonstrating scavenging solid capabilities against superoxide radicals, hydroxyl radicals, and 1,1-diphenyl-2-picrylhydrazyl radicals (Pan et al., 2016). The addition of icariin to semen diluents significantly improves the antioxidant capacity and SOD activity of New Zealand rabbit sperm. Extracts of Epimedium can improve semen quality and enhance the reproductive performance of aging breeder cocks by regulating reproductive endocrine hormones, enhancing the antioxidant capacity of seminal plasma, and reducing sperm damage. When the addition of Epimedium extract is 0.10%, the activities of GSH-Px and T-SOD in the seminal plasma of aging breeder cocks are the highest; at 0.15%, the MDA content in the seminal plasma is the lowest, and semen quality and reproductive performance are optimal (Shuyu et al., 2023). High doses of icariin can improve sperm motility and TNBP content in rats but do not significantly increase sperm density (Bin et al., 2018).

Summary and Prospects

Epimedium exhibits protective effects on the male reproductive system of animals, promoting testosterone synthesis and sperm production and enhancing the microenvironment for sperm generation. It also positively contributes to the recovery of the male reproductive system after injury, facilitating penile erection and treating premature ejaculation. Icariin, a compound found in Epimedium, can directly act on the sperm cell membrane, improving its fluidity and consequently enhancing sperm motility and acrosome integrity. By regulating the activity of sperm energy metabolism enzymes, icariin elevates energy metabolism levels, aiding in the enhancement of sperm motility and fertilization capacity, ultimately improving animal reproductive efficiency. Additionally, icariin possesses antioxidant properties, scavenging reactive oxygen species and reducing oxidative stress-induced damage to sperm. These mechanisms are not isolated but interconnected and mutually reinforcing, highlighting the significant advantages of icariin in enhancing animal reproduction through its multifaceted actions. The comprehensive understanding of the effects and mechanisms of Epimedium polysaccharides, especially at varying concentrations, on sperm health and antioxidant capacity, provides a robust scientific foundation for its application in animal reproduction. This knowledge can guide the rational use of Epimedium in animal breeding programs to enhance reproductive performance and sperm quality. In practical applications, administering Epimedium or its extracts to animals or including them in semen diluents represents a simple and effective method. The benefits of using Epimedium polysaccharides in animal reproduction extend far beyond just improving semen quality and reproductive function. These advantages also include an increase in pregnancy rates, a shortened breeding cycle, and ultimately, an increase in animal production. All of these factors contribute significantly to the overall profitability and sustainability of livestock production. Furthermore, for animal breeds experiencing reproductive disorders, the use of Epimedium and its extracts may offer a practical therapeutic approach. However, current research on Epimedium and icariin in animal reproduction presents some limitations, including the need for further investigation into optimal supplementation concentrations for different animal species and a deeper understanding of their mechanisms of action. Future studies should address these issues to provide more comprehensive theoretical support for the practical application of animal reproduction technologies. Meanwhile, with the growing research into herbal medicines and the continuous development of livestock production, the application of Epimedium and its extracts in animal reproduction is expected to become increasingly widespread.

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Chapter 03

Signaling Pathways and Targets of Traditional Chinese Medicine in Cardiovascular Disease

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ABSTRACT

Cardiovascular disease is the world top contributor to mortality and is associated with disability. The treatment goal of CVD is to reduce hospitalizations, decrease the mortality rates from heart disease, and limit illness-related disability. Various pharmacotherapies have been used to improve clinical outcomes for patients suffering from CVD, including aspirin, statins, antihypertensives, beta-blockers, and ACE-I/ARBs. These treatments remain inadequate and fail to address the burden of disease and have numerous side effects. Due to the unmet needs of Western medicine in controlling CVD, novel treatments have been considered in research as scientists ponder the efficacy of traditional Chinese medicine to prevent and control the disease. In this chapter, there is a focus on various signaling pathways and targets of TCM active ingredients in CVD treatment. The role of reactive oxygen species in causing myocardial infarction cell death has been documented, and this represents one target for TCM therapy. The anti-inflammation, anti-fibrosis, anti-apoptosis, anti-oxidant, and pro-angiogenesis mechanisms of TCM has been reviewed from clinical trials and scientific research as they represent the target pathways in CVD.

KEYWORDS
TCM, Cardiovascular diseases, Reactive oxygen species, Remodeling

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INTRODUCTION

The World Heart Federation (WHF) ranks cardiovascular disease (CVD) as the major contributor to mortality globally as it accounts for 17.3 million deaths annually and potentially 23.6 million deaths per year by 2030 (puerarin et al., 2017). CVD involves the pathological alteration of the heart or blood vessels and is also associated with disability worldwide. Various associated risks, such as inflammation, increased oxidative stress, hyperlipidemia, and hyperglycemia contribute to CVDs. Cardiovascular disease involves multiple body organs beyond just the cardiovascular system as the intestinal tract often experiences initial manifestations (Liu et al., 2024). CVDs mainly include coronary artery disease (CAD), transient ischemic attack, atherosclerosis, cardiomyopathy, hypertension, strokes, dyslipidemia, heart failure, and hyperglycemia (Gao and Hou, 2023). Alongside other metabolic abnormalities, CVD continues to increase in recent years as environmental pollution and excessive caloric intake become rife and contribute to the disease incidence and severity.

In the treatment and management of cardiovascular diseases, the goal of therapy is to reduce the amounts of hospitalizations occurring annually due to the morbidities, to reduce the number of deaths from heart disease, and to limit heart disease-related disability (Mittal et al., 2018). Both the modification of risk factors and implementing therapeutic strategies have been applied to reduce the mortality of CVD in many countries. Medical strategies that have been utilized to improve clinical outcomes in individuals with stable CVD include the use of aspirin, statins, and drugs for hypertension, beta-blockers, and angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor blockers (ARBs) (Leong et al., 2017). However, inadequate uptake of these pharmacotherapies potentially contributes to preventable CVD complications. The current treatment guidelines as documented by the American College of Cardiology/American Heart Association hypertension therapeutic guidelines whereby the target is for individualized therapy based on CVD risk. Based on the guidelines, patients with established CVD or diabetes have lower blood pressure targets as well as for individuals with a cardiovascular risk over a predicted 10-year period. Thus, blood pressure levels remain the target based on the indications for initiating treatment that lowers blood pressure while statin treatment is based on cardiovascular risk rather than cholesterol level in treatment initiation (Leening and Ikram, 2018). However, the associated side effects and costs of pharmacotherapy in CVD remain a challenge in reducing the disease burden.

The unmet needs associated with the use of Western medicine in controlling cardiovascular disease has led to clinicians considering novel treatments with the use of traditional Chinese medicine to prevent and control the disease. TCM passes as complementary or alternative medicine in Western contexts owing to the lack of objective and quantitative evaluation criteria (Hao et al., 2017). TCM is a holistic medical care system with a long history and has been proven to be efficient as CVD therapy with accompanying effects in strengthening the body (Gao and Hou, 2023). As part of treating CVD, myocardial infarction (MI) as a frequent form of ischemic heart disease (IHD) and accounting for a large proportion of CVD-related mortality. There is evidence confirming reactive oxygen species (ROS) role in causing cell death in MI and linked to its initiation, which means targeting a reduction of ROS levels is an important therapeutic goal (Jiang et al., 2022). Thus, antioxidants are crucial in preventing oxidative-stress related injury and improve the status of MI. Further, the mechanisms of action of traditional Chinese medicine in treating heart-related complications have been explored scientifically based on the acute myocardial ischemia (AMI) or doxorubicin (DOX)-induced cardiac toxic animal model (Wang et al., 2017). From in vitro experimental research, TCM possesses diverse characteristics of anti-inflammation, anti-fibrosis, anti-apoptosis, anti-oxidant, and pro-angiogenesis. Accordingly, TCM potentially functions in a multi-components and multi-targets mode as the biological pathways are interlinked.

With the history of traditional Chinese medicine use in treating cardiovascular diseases owing to lower costs and fewer side effects compared to Western medicine, the aim of this chapter is to explore the signaling pathways and targets of TCM in CVD. Based on existing research evidence, calcium is a second messenger involved in CVD pathogenesis, and malfunction in calcium signaling in the endothelium and vascular smooth muscle cells promote high blood pressure (Li et al., 2021). Calcium overload in cardiomyocytes also induces apoptosis and contributes to myocardial infarction and arrythmias. Accordingly, the multitarget and multicomponent nature of TCM can enable its regulation of multiple proteins involved in handling calcium and calcium signaling mechanisms in distinct CVD. Coronary heart disease development entails excess ROS production, which produces endothelial cells and smooth muscle functional disorder that cause imbalance between the antioxidation capacity and pro-oxidation agents. The resultant activation of inflammatory signals and apoptosis mediated by mitochondria are also implicated in CHD (Yang et al., 2019). Therefore, TCM mechanism of action entails modulation of oxidative stress-related signaling pathways in CVD therapy. CVD management with TCM also targets mitochondria as it is the main generator of ROS and is linked to multiple cellular signaling pathways responsible for regulating CVD progression (Gao and Hou, 2023). With more research, the specific targets and signaling pathways involved in treating cardiovascular diseases with traditional Chinese medicine can be documented, which can help as progress is made to use novel treatments with fewer side effects and multiple targets for CVD.

Action of Traditional Chinese Medicine on Cardiovascular Diseases

Oxidative Stress Signaling and TCM Compounds

Oxidative stress plays a role in the mechanism of cardiovascular diseases like atherosclerosis and coronary artery disease, which occurs when the antioxidation is not adequate to suppress reactive oxygen species (ROS) and other free radicals. Oxidative stress induces endothelia dysfunction in CVD and one active ingredient from the traditional Chinese medicine is astragaloside IV extracted from astragalus. Astragaloside IV has shown efficacy in reducing endothelial cells apoptosis occasioned by oxidative stress (Meng et al., 2021). The principal antioxidant enzymes that work against oxidative stress are superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) as they eliminate ROS. Hence, administration of astragaloside IV (AS-IV) potentially upregulates the expression of these enzymes as well as effectively improving endothelial-dependent relaxation damage and increasing endothelia nitric oxide synthase (eNOS) and nitric oxide (NO) quantities in vitro and in vivo (Meng et al., 2021). The antioxidation effect of AS-IV as it reduces oxidative stress in cardiomyocytes as well as counteracting oxidative stress in preventing heart failure through the Nrf2/HO-1 pathway. The antioxidation also relates to increasing antioxidant enzyme activity, with its action in protecting cardiomyocytes from oxidative damage linked to regulation of histone deacetylase (HDAC) activity including reversing oxidised low-density lipoprotein (ox-LDL)-induced low levels of eNOS in myocardial dysfunction (Xu et al., 2023).

ROS has been implicated for cellular damage through processes such as lipid peroxidation, protein cross-linking, and DNA cleavage, with cardiomyocytes particularly vulnerable to anoxic conditions due to the high need for oxygen. In traditional Chinese medicine, *Allium chinense* G. Don (Liliaceae) active components, especially *A. chinense* steroids (ACS), have been evaluated for their protective effects against cardiac injury. Ren et al. (2010) conducted one such study to determine the antioxidant action of ACS in cultured rat models using injured cardiac cells. Based on the findings, ACS showed inhibitory effects on lipid peroxidation as *A. chinense* exhibited the ability to prevent the formation of malondialdehyde (MDA) and nitric oxide, which are crucial markers for oxidative stress in conditions like CVD. Additionally, ACS inhibited the increase in calcium associated with oxidative stress-induced injury, thereby providing myocardium protective effects. Thus, TCM targets the ROS signaling pathways by scavenging ROS as part of its protection against oxidative stress shown in Fig. 1.

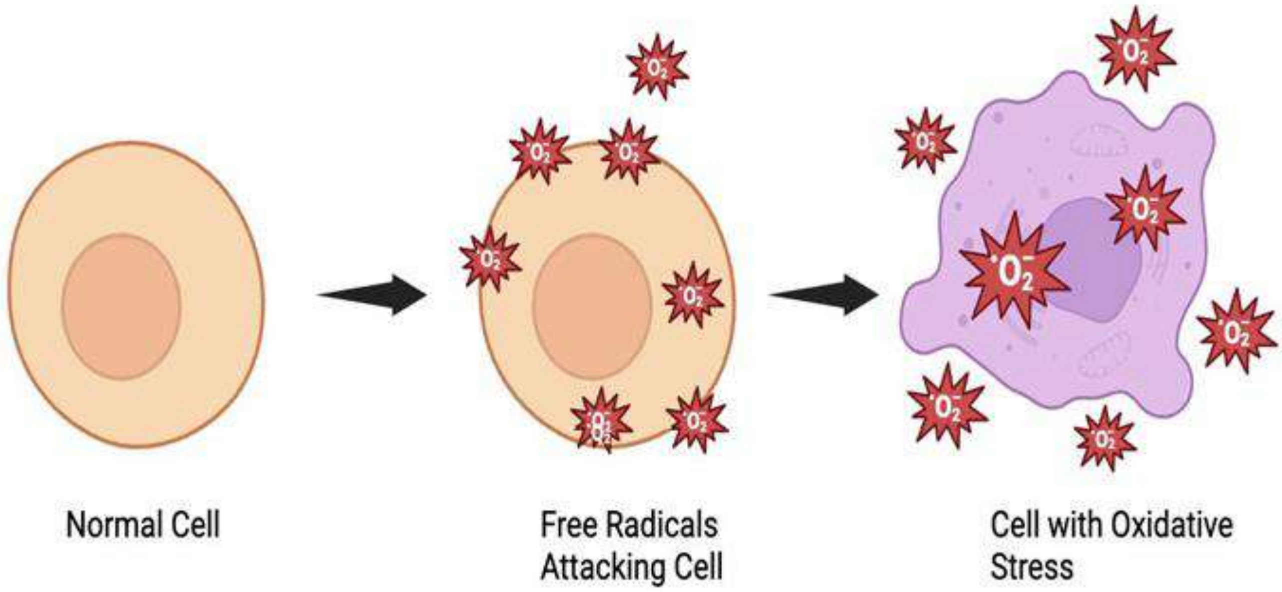

Fig. 1: Mechanism of Oxidative Stress in CVD.

Dihydromyricetin (DMY) flavonoid extract from vine tea (*Ampelopsis grossedentata*) has exhibited pharmacological activities in cardiovascular diseases such as atherosclerosis, a condition hypothesized to involve endothelial cell pathological dysfunction. The Nrf2 transcription factor remains inactive when unstressed but under oxidative stress, Nrf2 is activated and translocated resulting in heme oxygenase-1 (HO-1) transcription responsible for the antioxidant defense. Two signaling molecules, ERK and PI3K/Akt are involved in activation of Nrf2 and induction of HO-1. DMY, also ampelopsin, has been studied for its antioxidative activity as part of its protection against injury to the endothelial cell (Per Luo et al., 2017). Using human umbilical vein endothelia cells (HUVECs), DMY has been tested for its protective action against ox-LDL injured cells where the results demonstrated DMY treatment upregulated Nrf2 and HO-1 expression. The antioxidative effect is linked to Nrf2 translocation to the nucleus to enable phase II antioxidant enzyme transcription, as well as reversing p-ERK, p-Akt, nuclear Nrf2, and HO-1 downregulation induced by ox-LDL as part of its antioxidation ability (Per Luo et al., 2017). Further confirmation of antioxidant effect in cardiovascular diseases has been documented in lipopolysaccharide (LPS)-induced sepsis rat model where DMY affected the formation of free radicals and accelerated their elimination resulting in reduced intracellular MDA (Hao et al., 2022). It also lowered amounts of serum NO and MDA, thereby ameliorating the rat aorta reduced contractility.

TCM Compound Inflammation Targeting

Inflammation is common in the pathophysiology of atherosclerosis and other CVDs. Stumpf et al. (2013) explored the anti-inflammatory effect of Danshen (*Salvia miltiorrhiza* Bunge), a Chinese herb utilized as therapy for cardiovascular conditions like coronary artery disease as previous evidence demonstrated its anti-atherosclerotic effects. Using HUVEC, they investigated the mechanism of Danshen's protective effect based on vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin expression. Based on the results, Danshen suppressed VCAM-1 expression dependent on the dose, as well as downregulating ICAM-1 expression but without attenuation of E-selectin. Additionally, Danshen effect on cytokine release in HUVEC was studied as cytokines and chemokines are crucial in atherosclerosis etiology and progression, and the findings indicated significant attenuation of interleukins (IL) 6 and 8 as well as monocyte-chemoattractant-protein-1 (MCP-1). This study confirmed Danshen and its major components had an antiinflammation role as they targeted adhesion molecules, cytokines, and chemokines that play key roles as inflammatory mediators in atherosclerosis.

Quercetin is another TCM with therapeutic potential in anti-inflammation in CVD as it exhibits inhibitory effects on many inflammatory factors like IL-6, MCP-1, and vascular endothelial growth factor (VEGF). Several studies have also investigated the major pathway involved in quercetin's antiinflammation and the role of TNF-α activation of NF-kB signaling. Chen et al. (2020b) conducted one such study investigating the mechanism of quercetin in inhibiting TNF-α induced inflammation of HUVECs as they acknowledged NF-kB mediating the transcription of proteins involved in the inflammatory response factors. Natural drug effects on cell adhesion molecules were documented as quercetin downregulated the production of VCAM-1, ICAM-1, and E-selectin, which mediated leukocyte adhesion to endothelial cells in the pathophysiology of atherosclerosis. Quercetin was also shown to inhibit NF-kB and AP-1 pathway activation, which is an important anti-inflammation response. The natural drug also prevents chemotaxis of endothelial cells to monocytes and their adhesion while protecting endothelial cells and delaying atherosclerotic occurrence and development (Meng et al., 2022).

TCM antiinflammation has also been confirmed in CVD through targeting the toll-like receptor 4 (TLR4) whose activation results in inflammation. Studies have shown that licorice root (*Glycyrrhiza glabra* L.), specifically its glabridin flavonoid active component, exerts anti-inflammatory effect by suppressing VCAM-1, ICAM-1, and E-selectin in the endothelium (Markina et al., 2022). It also inhibits toll-like receptor 4 (TLR4) activation, causing the downregulation of proinflammatory cytokines and chemokines. Clinical studies on the anti-inflammatory effects of *Ligusticum wallichii* (ChuanXiong) extract in acute myocardial infarction (AMI) where the regulation of TLR4-NFkB signaling pathway was considered for its effect in the expression of IL-1β in myocardium (Yuan et al., 2014). Besides improving the left ventricular ejection fraction (LVEF) and reducing infarct area size, *L. wallichii* showed inhibitory activity against IL-1β protein in myocardium, serum, and hypothalamus. Further, the extract inhibited the expression of TLR4 and TRAF-6, thereby exhibiting anti-inflammation in AMI. *Ginkgo biloba* extract (GBE) is another TCM natural compound that has demonstrated anti-inflammatory activity in cardiovascular disease. According to a clinical study conducted by Zhang et al. (2022), 50 male Wistar rats with heart and brain inflammation were treated with GBE to test the action of the compound in reducing inflammation. The findings indicated that compared to controls, the treatment group showed increased Helper T Lymphocyte (TH) cells suggesting influence of GBE on the anti-inflammatory function. Serum cytokine levels were also measured as part of investigating the interlinkage of immune cells and inflammatory cytokines, with GBE downregulating IL-1β and elevating anti-inflammatory cytokine levels as part of exerting effects on immune homeostasis. GBE further diminished cardiac inflammation via NF-kB signaling mechanisms as depicted by the reduction in IL-1β, IL-1R, NF-kB, and IkB (inhibitor molecule protein) levels.

Myocardial Fibrosis Inhibition

Various studies have documented that *G. biloba* exhibited action against cardiac ventricular remodeling after AMI, especially against the generation of myocardial fibrosis following the infarct scar that forms after cardiac remodeling. An investigation using rat models with induced acute cardiac infarction tested the ameliorated effects of GBE and the mechanism of action on the TGF- β1, type I collagen, MMP-2, and MMP-9 expression and transcription (Li et al., 2015). The results showed that treatment with GBE inhibited myocardial remodeling following acute myocardial infarction, and the mechanisms involved related to a downregulation of TFG- β1, MMP-2, and MMP-9 genes, as well as reduced production of type I collagen, MMP-2, and MMP-9 in myocardial cells. This means that targeting the molecular and cellular mechanisms of ventricular remodeling with TCM compounds can be an effective strategy to manage myocardial fibrosis as this would inhibit or block various key pathological factors associated with ventricular remodeling, as further confirmed in Mesquita et al.'s (2017) work.

Researchers have studied the mechanisms of Chinese herbal formulations comprising Xue-Fu-Zhu-Yu (XFZYD), Tian-Ma-Gou-Teng-Yin (TMGTY), and Wen-Dan decoctions (WDD) in ameliorating myocardial fibrosis in rat models. In their study, Zhang et al. (2017) conducted a 4-week study where they measured the collagen levels and TGF- β1 to understand the action of the TCM formulas as they noted that TGF- β1 is important as a regulatory factor in fibroblasts proliferation and differentiation. The findings confirmed that the TCM herbal formulas markedly decreased the levels of myocardial collagen in the treatment groups, and the myocardial TGF expression was significantly downregulated based on the reduced brown granule deposits observed from the immunohistochemistry. Overall, XFZYD repressed fibrosis through TGF-β signaling disruption and reduced hypertensive myocardial fibrosis by further disturbing collagen secretion action by myocardial fibroblasts. A similar effect was exhibited by Sheng-Mai Yin (SMY), a TCM formular comprising of *Radix ginseng*, *Radix ophiopogonis*, and *Fructus schisandrae*. According to Ma et al. (2016), treatment with SMY in rats displayed a reduction of myocardial fibrosis through the mechanisms of suppressing PICP, PIIINP, MCP-1, TGF-β, IL-6, INF-y, and B-type natriuretic peptide (BNP). Therefore, the dose-dependent cardioprotective effects of SMY were confirmed as the formula prevented cardiac remodeling.

Anti-Apoptosis

Several traditional Chinese medicine compounds have exhibited antiapoptotic activity while used as treatment for cardiovascular diseases. Apoptosis drives cardiac hypertrophy development and remodeling, with the pro-apoptotic process linked to mitochondrial function and is further associated with excessive production of reactive oxygen species. One TCM natural drug that has been studied for its antiapoptotic effect is kaempferol, a flavanol-type flavonoid isolated from tea, vegetables, and fruits and also identified in medicinal plants like *Ginkgo biloba*, *Euophobia pekinensis*, *Equisetum spp*, and *Sophora japonica* (Ren et al., 2019). As confirmed in Che et al. (2017), kaempferol has exhibited anti-atherosclerotic effect by alleviating ox-LDL-induced endothelial cells apoptosis involved in atherosclerosis progression. This study used HUVECs to test the potential mechanism and molecular basis as inhibiting endothelial injury has been an optional treatment for CVD. From the results of the clinical trial, kaempferol demonstrated ability to attenuate cell injury and apoptosis as shown by its potential to abate the dramatic decrease in cell viability after HUVECs were treated with ox-LDL. The TCM natural drug further weakened cell injury dependent on time, as well as attenuating the increase in HUVEC apoptosis after ox-LDL treatment. Autophagic effect was also recorded because autophagy relates to apoptosis, with kaempferol exhibiting its ability to elevate LC3-II/I ratio and beclin-1 levels, which are crucial autophagy-related (ATG) proteins. The pathway targeted by the TCM active ingredient was the PI3K/Akt/mTOR pathway involved in regulating cell autophagy, which were responsible for the upregulation of the kaempferol-induced autophagy. The compound inhibited Akt phosphorylation as well as blocking mTOR phosphorylation, thus inactivating the PI3K/Akt/mTOR pathway represented the autophagic impact of kaempferol on HUVECs. Since the apoptosis of human aortic endothelial cells (HAECs) is also linked to initiation and progression of atherosclerosis through the formation of necrotic cores, the production of Bax, Bcl-2, and caspase has been subject of interest. Treatment with kaempferol has shown a reversal of the high ratio of Bax/Bcl-2 and level of caspase 3, thereby improving the condition of AS (Feng et al., 2021). Kaempferol also upregulates GPER production and activates the PI2K/AKT/Nrf2 pathway to inhibit oxidative stress, inflammation, and apoptosis that is attributed to loss of estrogen.

Table 1: Targets and Signaling Pathways of TCM Active Ingredients in CVD

Signaling Pathways and Target	TCM Ingredient	References
Oxidative stress signaling -Upregulating SOD, CAT, and GSH-Px -Nrf2/HO-1 pathway -HDAC regulation -Reversing oxLDL effect -Inhibit lipid peroxidation -Calcium signaling -Suppressing NO and MDA levels	Astragaloside IV *Allium Chinense* Dihydromyricetin	(Meng et al., 2021; Xu et al., 2023; Hao et al., 2022; Meng et al., 2022)
Anti-inflammation -TNF-α suppression -IL-6 and IL-8, MCP=1 attenuation -NF-kB signaling pathway -Chemotaxis prevention -TLR4 targeting -LVEF improvement -Infarct size reduction -IL-1*β inhibition* -TRAF6 inhibition -Increased Helper T Lymphocyte cells	Danshen Quercetin *Licorice root* ChuanXiong *Ginkgo biloba* extract	(Stumpf et al., 2013; Chen et al., 2020b; Markina et al., 2022)
Myocardial fibrosis inhibition -Inhibiting myocardial remodeling -TFG-*β*1, MMP-2, MMP-9 gene downregulation -Type I collagen suppression -Suppressed PICP, PIIINP, MCP-1, INF-y, BNP	*Ginkgo biloba* XFZYD/TMGTY, and WDD Sheng-Mai Yin	(Li et al., 2015; Mesquita et al., 2017; Zhang et al., 2016)
Anti-apoptosis -oxLDL inhibition -Autophagy -Targeting PI3K/Akt/mTOR pathway -GPER expression upregulation	Kaempferol	(Che et al., 2017; Feng et al., 2021)
Pro-angiogenesis -Augmenting VEGF protein expression -Akt phosphorylation -NO release -ANP and BNP reduction -VEGFA, Ang-1, and Ang-2 upregulation -Signal transduction pathways	Astragali radix Puerarin	(Chen et al., 2020a; Ai et al., 2015; Zhou et al., 2021)

Pro-Angiogenesis

Traditional Chinese medicine with cardioprotective factors have exhibited pro-angiogenesis action, with natural drugs like Astragali radix (AR) and *Angelica sinensis* Radix (ASR) having been investigated for their effect on myocardial infarction injury. Chen et al. (2020a) studied AR and ASR combined treatment for cardiovascular disorders to understand their protective effects on cardiac dysfunction in mouse models with MI. AR and ASR are the dried radix of *Astragalus membranaceus* and *A. sinensis* and both have been used to treat stagnant blood flow and promote blood circulation. Based on the study, AR and ASR combined therapy showed pro-angiogenetic results by significantly augmenting vascular endothelia growth factor (VEGF) protein expression, as VEGF is an important cytokine engaged in creating new blood vessels in ischemic heart disease. The natural drug combinations also increased Akt phosphorylation and acted on the

Akt/eNOS pathway responsible for regulating cell survival, migration, NO release, and tube formation, all essential processes for ischemic tissue damage repair.

Another TCM natural drug with pro-angiogenetic effect on myocardial infarction is puerarin, a bioactive ingredient extracted from the root of kudzu, *Pueraria lobata* (Willd.). Ai and colleagues (2015) have investigated the mechanism underlying puerarin cardiovascular effect, specifically on cardiac angiogenesis and myocardial function. VEGFA, angioprotein-1 (Ang-1), and angioprotein-2 (Ang-2) were subject to interest as they are important cardiac angiogenesis factors. From rat models of myocardial infarction, puerarin exhibited ability to reduce atrial natriuretic peptide (ANP) and BNP markers of heart failure thereby improving myocardial function. Further, the natural drug significantly improved severely damaged coronary angiogenesis as a response to left anterior descending coronary artery (LAD) ligation involved in cardiac injury. The pro-angiogenetic benefits were also linked to upregulation of VEGFA, Ang-1, and Ang-2 responding to LAD ligation stress. Puerarin action on signal transduction pathways in CVDs has been explored with reports on the effects on sodium (Na+), potassium (K+), and calcium (Ca+) channels as research indicate inhibition of K+ channel function in vascular smooth muscle cells (VSMCs) and is associated with pathologies like reperfusion (Zhou et al., 2021). The influx of CA2+ causes increased cytoplasmic calcium ion concentration and subsequent vasoconstriction. Thus, puerarin acts by regulating Na+, K+, and Ca2+ channels in cardiac myocytes and contribute to anti-myocardial damage and promoting angiogenesis. It also suppresses mitochondrial permeability transition pore opening, elevates protein kinase C, and promotes BKca channel opening as shown in rat ventricular myocytes.

Conclusion

The treatment and management of cardiovascular diseases remains challenging as there is an inadequate uptake of pharmacotherapies. Due to the unmet needs of using conventional medicine, clinicians have been considering the potential of novel treatments like traditional Chinese medicine to reduce the burden of CVDs. TCM is a holistic medical care system and this can be beneficial due to the multitarget and multicomponent nature as these natural drug compounds show anti-inflammatory, anti-fibrosis, anti-apoptotic, anti-oxidant, and pro-angiogenetic characteristics. This chapter has investigated the various signaling pathways and targets of TCM active components and documented several mechanisms of action and molecular and cellular pathways through which diverse medicinal extracts exert cardioprotective effects.

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Chapter 04

Regulation of Oxidative Stress in Cardiovascular Disease with Active Ingredients from Traditional Chinese Medicine

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ABSTRACT

Cardiovascular diseases pose a significant burden to the global healthcare system due to the associated substantial morbidity and mortality and the financial costs. The overproduction of oxygen radicals has been implicated in oxidative damage common in CVDs, which pose dangerous consequences for myocardial calcium handling and leads to arrythmias and cardiac remodeling. This chapter explored the scientific evidence focused on the targeting of oxidative stress in CVD with active ingredients from traditional Chinese medicine. The mechanisms of antioxidation were investigated for select bioactive molecules and the study found the benefits in attenuating lipid peroxidation and scavenging free ROS to protect against injury and remodeling of cardiac tissue damage. TCM compounds also target the pro-inflammatory cytokines that are implicated in CVD-related inflammation, leading to antioxidative deficiencies. The active components of several herbs used in TCM have been further shown to affect the antioxidation signaling pathways like ROS/ERK 1/2) and the Nrf2 oxidative signaling to ameliorate cardiomyopathic outcomes.

KEYWORDS		
Cardiovascular disease, TCM, Oxidative stress, ROS, Myocardial infarction	Received: 18-May-2024 Revised: 26-Jul-2024 Accepted: 17-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Cardiovascular disease (CVD) is a multifactorial disorder composed of numerous congenital and acquired illnesses, and the term collectively designates all conditions affecting the blood circulatory system. The conditions making of CVD include atherosclerosis and its subtypes like coronary artery disease (CoAD), and the two major complications namely myocardial infarction (MI) and ischemic stroke (IS) (Thiriet and Thiriet 2018). Pathophysiology of CVD as involving systematic and local inflammation related to disease development and advancement from endothelia dysfunction to clinical syndromes (Henein et al., 2022). Studies have linked inflammatory biomarkers to the prediction of CVD, independently of traditional risk factors. This explains why atherosclerotic pathology is the major cause of CVD as the pathogenesis of atherosclerosis is explained by increased oxidative stress and enhanced arterial wall inflammation (Scott, 2004). Epidemiological studies have confirmed the important risks for CVD as comprising smoking, low levels of physical activity, hypertension, alcohol use, and insufficient consumption of fruit and vegetables.

Cardiovascular diseases are a significant burden to the global healthcare system as the multifactorial conditions are associated with substantial morbidity and mortality as well as financial costs to the individual, government, and the community. CVD cases total 523 million, 18.6 million deaths, and 393.1 million disability-adjusted life years (DALYs), marking a significant increase over the past three decades (Sun et al., 2023; Roth et al., 2020). Hence, CVDs collectively remain the main contributors of mortality globally and lead to morbidity and contribute to excess costs on the health system. Elevated systolic blood pressure alone ranks as the main modifiable risk and attributable to premature CVD deaths (Vaduganathan et al., 2022). Hence, a combination of numerous determinants contributes to the prevalence of morbidity in diverse ways.

Overview of Oxidative Damage

There is mounting evidence linking cardiovascular disease development with pathophysiological chronic and acute overproduction of reactive oxygen species (ROS). Increased oxidative damage is a likely cause of CVD as any increase in ROS decreases the available nitric oxide and blood vessel narrowing, leading to high blood pressure. The deleterious effects of ROS include adversely affecting the capacity of the myocardia to handle calcium, subsequently triggering arrythmia and increasing cardiac changes through causing hypertrophic signaling and cell death (Senoner and Dichtl, 2019). ROS also enhance the formation of atherosclerotic plaque implicated in cardiovascular diseases. ROS is excessively produced when the mitochondria dysfunctions, irreversible damage occurs to the mitochondria and contribute to CVD progression (Dubois-Deruy et al., 2020). The mechanism of oxidative stress-induced progression of CVD has made ROS targeting a possible target for treating cardiovascular diseases. Antioxidants such as nutritional supplements and novel antioxidants have been researched and applied as therapeutic strategies for CVD (Wang and Kang, 2020).

Role of Traditional Chinese Medicine in Oxidative Stress

TCM history is approximated to span over 5000 years (Marshall, 2020). According to Matos and colleagues (2021), Five trespasses Phases (Elements) underline the impact and functional powers related to body function like the "qi," the "blood" or "xue", also the "jin ye" active and resting fluids effects, as well as the use of therapeutics based on syndrome differentiation. TCM primarily entail acupuncture and moxibustion, utilizing Chinese herbal medicine and nutrition, and Tai Chi "Taijiquan," "Tuina," and "Qigong" (Fogaça et al., 2021). While Chinese herbal medicine (CHM) efficacy is not as strong on CVD pathological process, its individualized nature with minimum adverse effects compared to Western medicine makes TCM a potential choice contributing to the health of CVD patients (Liu and Huang, 2016). There are a variety of traditional Chinese medicine whose bioactive compounds exert antioxidant effects and reducing ROS in CVD and boosting antioxidant enzymes while improving cardiac function (Jiang et al., 2022). Accordingly, this chapter investigates clinical evidence about how the active ingredients of TCM regulate oxidate stress in cardiovascular disease. The focus will be on the mechanisms of antioxidation of various Chinese herbal medicine when administered to individuals with cardiovascular diseases.

Mechanism of Oxidative Damage

ROS as the highly reactive chemical species that contain oxygen, including superoxide (O2), hydroxyl anions (OH-), and hydrogen peroxide (H2O2) (D'Oria et al., 2020). Levels of ROS in normal physiological conditions are strictly controlled through antioxidant enzymes activity, such as superoxide dismutase, catalase, and glutathione peroxidase. ROS in the heart is crucial for cell homeostasis at low concentrations as they control numerous physiological signaling pathways and biological processes. Oxidative stress (OS) as the overproduction of free radicals and the inability of the endogenous antioxidant cells to clear them, thereby resulting in a shift in the mitochondrial redox state and that of nuclease and other organelles (Donia and Khamis, 2021). Oxidative stress extremely damages macromolecules like lipids, proteins, and DNA. Endogenous ROS is primarily sourced from the mitochondria via the electron transport chain (ETC) and oxidative phosphorylation producing CVD by-products, with environmental elements like cigarette smoking, heavy use of alcohol, and radiation also encouraging ROS generation (Panda et al., 2022).

Mechanisms and Impact of Oxidative Stress in CVD

ROS accumulation induces endothelia damage, cardiac remodeling, vascular dysfunction, systemic inflammation, and immune cell activation, key processes implicated in CVD. The nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) system produces ROS and represents the primary oxidase system underlying vascular disease associated oxidative stress (Mourino-Alvarez et al., 2022). When NOX is excessively activated, it in turn activates other oxidase systems. The secondary mechanisms include uncoupling the endothelial nitric oxide synthase (eNOS), mitochondrial stress, and endoplasmic reticulum (ER) stress, all of which are linked to redox alterations in CVD. The disease-causing role of OS in heart failure (HF), noting that ROS mechanism in CVD entails negatively affecting myocardial calcium (Ca2+) disposition, causing arrythmias, and promoting hypertrophic signaling, cell death, and necrosis as part of cardiac remodeling. The potential risk factors that induce OS include aging, environmental factors, and genetic predisposition (Münzel et al., 2017).

Oxidative Stress Regulation

There is scientific evidence proving the efficacy of TCM in curing CVDs with accompanying effects of strengthening the body. Owing to the link between CVD and excessive production of ROS which cause mitochondrial dysfunction, a plethora of therapeutic substances like aspirin, leptin, and melatonin have demonstrated cardioprotective effects against oxidative damage through mitochondrial-related pathways (Gao and Hou, 2023). In like manner, TCM compounds have been studied for their effects in targeting mitochondria in CVD management. Traditional Chinese medicine properties rely on their active ingredients, classified as polyphenols, flavonoids, phenolic acids, glycosides, saponins, and polysaccharides among other active ingredients. Studies show the potential of TCM active ingredients in eliminating free radicals and protecting mitochondrial functions in CVD to guard cardiomyocytes (Chang et al., 2020).

In Vivo and In Vitro Studies

Curcumin

Curcumin is extracted from the rhizomes of turmeric (*Curcuma longa*) and has various biological properties in various diseases, including CVD. In a study involving 24 Wistar albino rats, curcumin was administered to investigate its cardiotoxic effect in doxorubicin-induced cardiotoxicity and to determine its mechanism of action (Shati et al., 2024). The rats were grouped in four, the first acting as control, the curcumin group, the DOX group, and the curcumin and DOX category, and the researchers assessed lipid peroxidation as MDA, AST, ALT, inflammatory markers as TNF-α, and oxidative markers as catalase (CAT) and superoxide dismutase (SOD). The study found DOX induced lipid peroxidation in the subjects, while administering DOX and curcumin significantly lowered the MDA, AST, and ALT levels than those exposed to DOX. DOX adjunct with curcumin also improved SOD and CAT reduction compared to DOX treatment. The TNF-α quantities were high in the DOX group, but treatment with DOX and curcumin mitigated TNF-α damage. The high lipid peroxidation in the rats indicated the effects of oxidative stress and antioxidative deficiencies in the cardiac tissue, and the abundance of ALT and AST after severe tissue injury were indicative of myocardial injury. The SOD and CAT level reduction marked oxidative stress association with cardiac damage, as SOD prevents hydroxyl (OH) radical formation by the conversion of O2- to H2O2. The study confirmed curcumin's antioxidant-sparing activity through the antioxidant pathway of scavenging free radicals, preventing oxidizing enzymes, oxygen quenching, and limiting availability for oxidative reactions. As the histopathological assessment suggested, curcumin enhanced heart-protective mitochondrial respiratory chain enzymes, which were also crucial in its antioxidative properties.

Wei and colleagues (2022) also investigated curcumin using New Zealand rabbits to determine the effect of the polyphenolic active compound in ameliorating ferroptosis in subjects with diabetic cardiomyopathy. Since cardiovascular is a common clinical complication of diabetes, the effect of elevated levels of blood sugar is implicated in problems related to the metabolization of lipids in cardiomyocytes and vascular endothelial cells. With pancreatic beta cells expressing antioxidant enzymes at low levels, they become at risk of excess ROS. The results confirmed curcumin promoted Nrf2 translocation, a crucial antioxidative regulator affecting glutathione synthesis expression and the generation of NADP+ thus neutralizing the accumulated superoxide. Intranuclear Nrf2 transfer enhanced antioxidant factor Heme Oxygenase-1 (HO-1) expression, decreasing intracellular oxides accumulation in the cardiomyocytes, impeding glucose-induced ferroptosis progression, and alleviating the depletion of glutathione peroxidase 4 (Gpx4) that protects against membrane lipid peroxidation in cells.

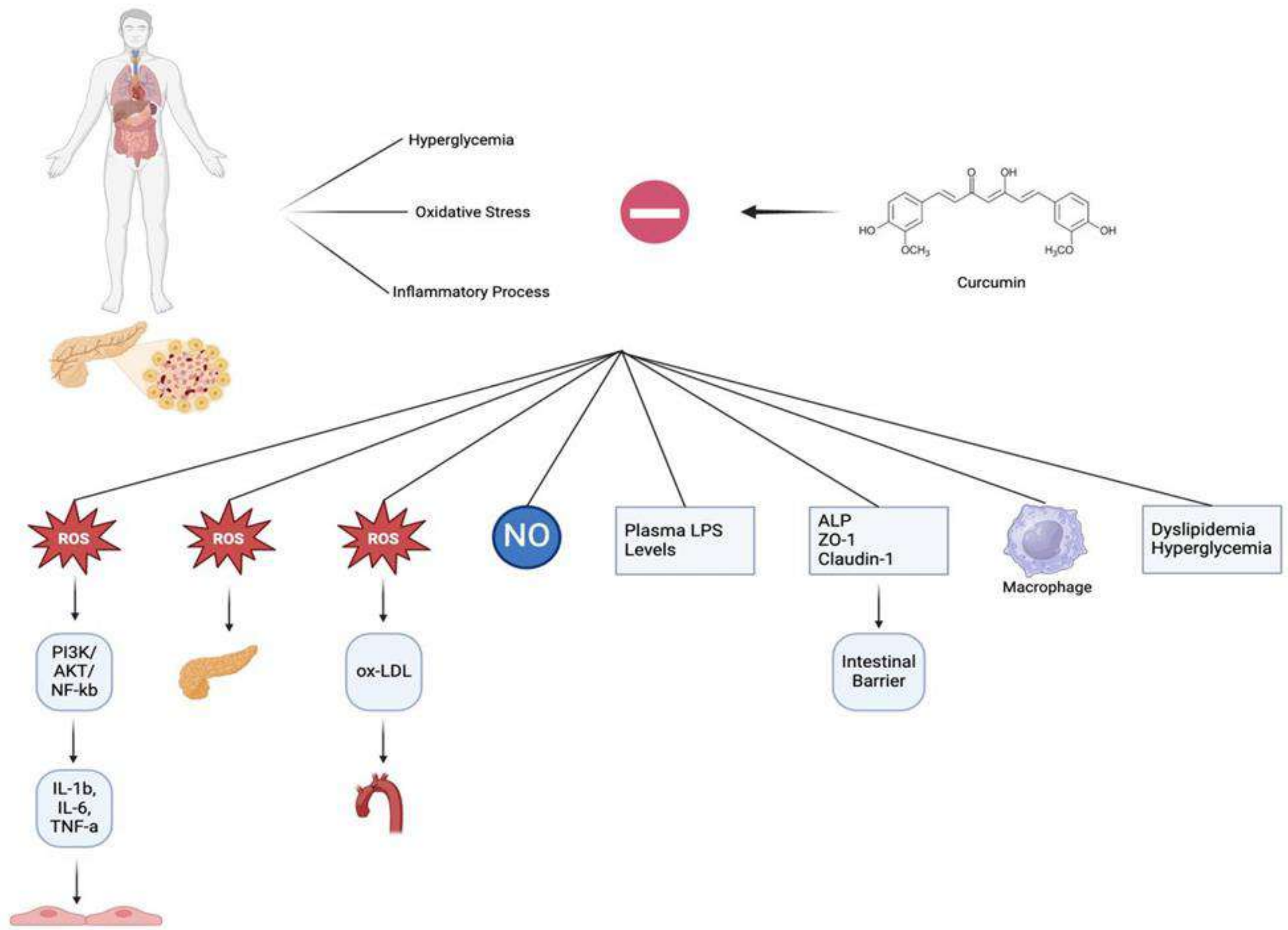

Fig. 1: Mechanism of Action of Curcumin on Blood Sugar Levels in Lipid Metabolism-Associated Cardiomyocyte Injury

curcumin effect on producing aldosterone-induced C-reactive protein (CRP) in vascular smooth muscle cells (VSMCs) and its molecular mechanism for subjects with atherosclerosis. Aldosterone has been reported to stimulate CRP generation in rat VSMCs through ROS ERK1/2 signal pathway (ROS/ERK1/2) (Zhang et al., 2020). When VSMCs were treated with curcumin, they exhibited reduced CRP mRNA and protein elevation caused by aldosterone, thereby alleviating inflammation. Curcumin bioactive ingredients further suppressed CRP production in the thoracic aorta wall. The antioxidant activity of curcumin was also exhibited by its diminishing the production of ROS in VSMCs through the mechanism of scavenging ROS. Curcumin interfered with ROS-ERK1/2 signaling as part of inhibiting the generation of aldosterone-induced CRP in VSMCs, which represents its anti-inflammatory effect (Zhang et al., 2020).

Quercetin

Quercetin, derived from broccoli, grapes, cherries, grapes, citrus fruits, berries, and onions has been reported in various studies for its protective benefits on conditions related to the heart or cardiac injuries. Quercetin for cardiomyopathic rates amelioration induced by DOXO. The Nrf2 oxidative signaling regulator was explored as the transcription factor regulates basal and inducible antioxidant genes expression and cardioprotective phase II detoxifying enzymes produced in the cardiovascular system. Healthy Sprague-Dawley rats were used and were randomized into control, DOXO, DOXO + quercetin 10 mg/kg, DOXO + quercetin 25 mg/kg, and DOXO + quercetin 50 mg/kg groups (Sharma et al., 2020). The results of the antioxidant effects of quercetin indicated the bioactive ingredient significantly improved Na+/K+ ATPase activity, Mg+2 ATPase, and Ca+2 ATPase. The levels of altered antioxidant levels of MDA, catalase glutathione (GSH), SOD, and catalase also improved with quercetin treatment compared to DOXO, as well as averting the downregulated Nrf2 gene expression after DOXO treatment. Quercetin further decreased the amounts of inflammatory cells and augmented cardiac muscle fiber morphology without focal necrosis. Thus, the compound directly exerted antioxidant effect by scavenging free radicals, and indirectly through reinforcement and protection of antioxidative enzymes against oxidative damage as it restored the SOD and catalase which were reduced in doxorubicin heart tissue. DOXO also lowered the levels of GSH non-enzymatic antioxidant biomolecules, which was rectified by quercetin as the rise in GSH concentrations meant the natural drug stimulated antioxidant enzymes by stimulating enzyme y-glutamylcysteine synthase. DOXO further decreased the activities of sodium (Na+), potassium (K+) ATPase while increasing calcium (Ca+2), and magnesium (Mg+2) ATPase due to lipid peroxidation leading to protein oxidation activating Na+ and K+ ATPase activity (Sharma et al., 2020).

Quercetin protective mechanisms and effects when the subjects were treated with different doses of quercetin. They tested the effect on apoptosis, inflammation, oxidative stress, and atherosclerosis (AS), also the potential relationship between the PI3K/AKT and the antiapoptotic and anti-inflammatory properties in the inflammatory and apoptosis response. The investigation on the AS protective effects indicated mice treated with the active component had substantially less AS in the entire aortic structures (Lu et al., 2016). The atherosclerotic plaques were fewer in the quercetin-treated subjects while also ameliorating the injured level and reducing the collagen levels. Quercetin mechanism of ameliorating atherosclerosis was through suppressing ROS production via regulating inflammation and apoptosis. The high H2O2 and O2- that caused elevated ROS were inhibited by quercetin, and the suppressed SOD activity and high MDA were enhanced and reduced respectively post-treatment. High fructose feeding of mice had also resulted in downregulated HO-1 and Nrf-2, and quercetin administration upregulated them, suggesting the bioactive molecule ameliorated AS via ROS inhibition. Since high fructose feeding inactivated PI3K signaling and caused AKT dephosphorylation and Bcl-2 inactivity, all mechanisms which were reversed by quercetin by regulating the protein production. The nuclear factor-kappa-B (NF-kB) was activated by high fructose feeding leading to inflammation, and quercetin downregulated this NF-kB signaling pathway to suppress inflammatory cytokines. Overall, the study confirmed quercetin antioxidant effect through multiple mechanisms described (Lu et al., 2016).

An *in vitro* experiment on the mechanism of anti-atherosclerotic effect of quercetin additionally explored the hypothesis of the bioactive molecule's inhibition of endothelial oxidative damage from oxidized low-density lipoprotein (oxLDL) via sirtuin 1 (SIRT1) activation (Hung et al., 2015). In this study, oxLDL with or without quercetin was administered to human umbilical vein endothelia cells (HUVECs). Based on the findings, it was confirmed that quercetin incubation promoted the expression of SIRT1, a protector repressing cardiovascular dysfunction. The study further investigated the oxLDL decrease of AMPK- α in atherosclerosis and the protective effects of quercetin, and it was determined the natural drug AMPK- α phosphorylation suppression. Resveratrol and DCHC SIRT1 activators, and AMPK activator AICAR markedly moderated the inhibition of AMPK-α phosphorylation. Quercetin further reduced the activation of NADPH oxidase and the formation of ROS, with the treatment also reversing AKT level phosphorylation that was impaired by oxLDL.

Gentianella acuta

Gentianella acuta (Michx.) Hulten is a TCM bioactive compound applied to treat arrythmia and coronary heart disease (CHD) and is popularly known as "Wenxincao" in China. Preclinical studies have already explored to understand the cardioprotective effect of the natural drug. In a 2017 study using an isolated rat heart model, Wang and colleagues explored the myocardial ischemia/reperfusion (I/R) injury protective potential of *G. acuta* xanthones. SDH, MDH, SOD, SOD, CAT, ATP, GSH/GSSG, MDA, LDH, and creatine kinase (CK) levels were evaluated. Bcl-2 protein and Bax protein expression was further measured. Following treatment with xanthones, there were significantly decreased hemodymic parameters, left ventricular developed pressure (LVDP) and coronary flow (CF) recovery rate compared to control. Xanthones additionally decreased LDH and CK than the I/R group, and there was decreased OS as exhibited by the enhanced SOD activity, CAT< GSH/GSSG ratio, and reduced MDA content than I/R rats. There was improvement in mitochondrial dysfunction following treatment with *G. acuta* as shown by upregulated ATP level and significantly increased

SDH and MDH activities, with Cyt c level upregulated and calcium concentration reduced. Xanthones further significantly reduced the pathological changes induced by I/R, and the effect on antioxidant activity was additionally scavenged free radicals such as hydroxyl, DPPH, and superoxide anion. The compound inhibited apoptosis as it increased the production of Bcl-2 and inhibited Bax expression.

G. acuta protective role has been verified in rat models of myocardial fibrosis. The pathway involved in the antioxidant effect of the TCM compound. The isoproterenol (ISO)-induced OS, fibrosis, and damage to the myocardia were tested via randomization of Male Sprague Dawley rats injected with *G. acuta*. Cardiac structural disorder, excessive collagen and malfunction of the cardiac, SOD, GSH, and MDA levels were measured to explain the mechanism of action (Li et al., 2019). It was shown the component improved myocardial ischemia lesions that were induced by ISO, as well as significantly inhibiting heart rate and improving left ventricular diastolic pressure (mLEVDP), LV systolic pressure (mLVSP), and the upper and lower limits of LV pressure. Elevated myocardial lesions were observed, and necrosis areas, deposition of myofibril and reduced inflammatory infiltrate noted, as well as decreased collagen deposition. Effects on oxidative stress by *G. acuta* indicated elevated SOD and GSH activities while MDA were downregulated, thus confirming the scavenging of free radicals by the TCM active ingredient. With ISO, TGF-β1 and CTFG were increased and NF-kB-p65 activated in myocardial fibrosis tissues but with treatment, the proteins reduced markedly and NF-kB-P65 activation inhibited (Li et al., 2019).

Guanxintai

Guanxintai (GXT) has been utilized to treat CHD and is composed of Ginseng, Astralagus, Rehmannia, Schisandra chinensis, Angelica root, *Salvia miltiorrhiza*, and Frankincense among other herbs. Explored the antioxidative mechanisms of GXT for the protective effect on ischemic cardiomyocytes. They used adult male Wirstar rats and their findings supported the beneficial role of GXT in reducing the degree of myocyte and interstitial cells damage as well as the infiltration of inflammatory cells that caused histopathological damage and fibrosis following MI. GXT suppressed cell apoptosis, protected against cardiomyocyte injury, and suppressed ROS production by suppressing the expression of NOX2 and NOX4, as well as inhibiting p38 MAPK activation (Yang et al., 2017).

Tianma Gouteng Decoction and YiQi FuMai Powder

Tianma Gouteng Decoction (TGD), a TCM active ingredient composed of 11 molecules including Lorantus parasiticus, Poria cocos, Eucommia ulmoides Oliv., Gardenia, Uncaria, achyranthes root, and abalone shell. They used mice models with angiotensin II (AngII)-induced hypertension and found that TGD significantly repressed diastolic and mean blood pressure levels as well as systolic blood pressure in a time-dependent manner (Deng et al., 2022). There was a reversal of ventricular remodeling by reducing the deposition of collagen fibers and reversing myocardial fibrosis. The regulation of OS transcription factor was linked to the upregulation of NO levels and the serum SOD and GSH-PX expression, while MDA expression was reduced, and HO1 and SOD2 in epithelia cells were substantially increased. TFEB protein expression in the aorta was increased significantly and this was the mechanism of reducing OS and inflammation (Deng et al., 2022).

Table 1: Mechanisms of Antioxidation of TCM Active Ingredients in Cardiovascular Disease

Active Ingredient	Mechanism of Antioxidation	References
Curcumin	Suppressing lipid peroxidation, scavenging free radicals, oxygen quenching, preventing oxidizing enzymes, enhancing mitochondrial respiratory chain enzymes, Nrf2 translocation, reduced CRP expression	Shati et al. (2024), Wei et al. (2022), Zhang et al. (2020)
Quercetin	Improved Na+/K+ ATPase, Mg+2, and Ca+2 ATPase, antiinflammation, Nrf2 downregulation, scavenging free radicals, reduced collagen, ROS suppression, reversed AKT dephosphorylation and Bcl-2 inactivity, downregulating KF-kB signaling, inhibiting oxLDL	Sharma et al. (2020), Lu et al. (2016), Hung et al. (2015),
Gentianella acuta	Improved mitochondrial function, free radical scavenging, inhibited apoptosis, improved MI lesions, heart rate, and left ventricular diastolic pressure, LV systolic pressure, NF-kB activation,	Wang et al. (2017), Li et al. (2019)
Guanxintai	Suppressed cell apoptosis, protection against cardiomyocyte injury, suppressed ROS, inhibiting NOX2 and NOX expression, MAPK inhibition	Yang et al. (2017)
TGD and YQFM	Reversed ventricular remodeling, regulating OS transcription factor, TFEB upregulation, enhanced mitochondrial function, reduced NADPH oxidase	Deng et al. (2022), Zhang et al. (2019)

As for YiQi FuMai (YQFM) powder injection, this compound consisting of the Radix of *Panax ginseng* C.A. Mey., Radix of *Ophiopogon japonicus* (Thunb.) Ker Gawl, and Fructus of *Shisandra chinensis* (Turcz.) Baill. They investigate the drug effects in heart failure induced by coronary artery ligation and cell hypoxia in rat ventricular myocytes. They showed YQFM enhanced mitochondrial function by promoting Mfn2 expression and reducing Drp1 phosphorylation at Ser616, decreased production of NADPH oxidase subunit like NOX2, P67, and NOX4, and inhibited ROS generation while reducing CAMKII phosphorylation. Thus, YQFM generally improved mitochondrial function in HF by ROS and CAMKII signaling inhibition (Zhang et al., 2019).

Conclusion and Future Prospective

This chapter has reviewed existing clinical evidence on the antioxidant effects of TCM active ingredients in cardiovascular diseases. The mechanisms of reactive oxygen species in CVD have been discussed and studies that show the mechanisms of TCM compounds in reducing OS been discussed. Based on the available evidence, animal model studies have evaluated numerous Chinese herbal medicines for their cardioprotective effects, including compounds like curcumin, quercetin, *Gentianella acuta*, Guanxintai, Tianma Gouteng Decoction, and YiQi FuMain Powder. The evidence confirms the antioxidant potential of these molecules and the associated pathways including acting against ROS production and inhibiting pro-inflammatory factors and decreasing collagen deposition. Future research directions can strengthen these preclinical studies by using more human models and exploring the potential of TCM ingredients in cardioprotective action. There still remains a research gap in human studies of antioxidation of TCM in CVD, and such experiments can be informative. The majority of the research also focus on a narrow subset of cardiovascular diseases, majorly myocardial infarction and atherosclerosis, and a delve into more cardiovascular disorders can inform more investigations.

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Chapter 05

Therapeutic Applications of Traditional Chinese Medicines, its Challenges and Future Prospectives in Treating Zoonotic Diseases

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ABSTRACT

Traditional Chinese Medicine (TCM) is a systematic healthcare system which is similar to other medicines. By using the different clinically and experienced based scientific models, traditional chines medicines were developed. For thousands of years, the Chinese nation has summarized and condensed a knowledge system in health care practice and continues to benefit the healthcare system. TCM treats ailments and promotes health by utilizing novel theories and methods. These methods include acupuncture, moxibustion, Chinese herbal medicine, dietetics, and other alternative treatments. This study summarized the history, types, therapeutic applications, main treatment strategies and methods, current challenges and development with future perspectives of TCM. It may provide a more comprehensive image of the overall TCM system.

KEYWORDS
Traditional Chinese medicine, Acupuncture, Antimicrobial mechanism, Therapeutic potential, Medicinal plants

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INTRODUCTION

Though the origins of TCM are unknown, some data suggest that it has been practiced for over 5,000 years. Acupuncture needles and evidence of herbal remedies have been found in some archaeological sites, suggesting a 4,000–8,000-year-old existence (Pan et al., 2014). The earliest reported documents about TCM theory and clinical practice are the "Yijing," also known as the "I Ching" or "Book of Changes," and the "Huangdi Neijing," also known as the "Yellow Emperor's Classic of Internal Medicine." It offers guidance and advice on personal emotional lifestyle, describing its changes and modalities. The "Huangdi Neijing" is as important to Greek medicine as the Hippocratic Corpus (Greten, 2007; Sertel et al., 2010). The Five Trespasses Phases ("Elements") and the teaching of "yin" and "yang" are among the most important TCM theories. "Tuina," "Qigong," and "Taijiquan," also known as Tai Chi, are the main practices, along with acupuncture, moxibustion, the use of Chinese herbs and dietetics, and the activity of effects and functional powers involved in body function, such as "qi," "blood," or "xue," as well as the impact of active and resting fluids, or "jin ye," and the differential diagnosis of syndromes. Ancient Chinese physicians proposed that everything is made of the same "substance," or "qi." TCM is used to treat a variety of acute and chronic conditions, including traumatology, emergency medicine, gynecology, internal medicine, dermatology, and treatments for the eyes, nose, and throat, in addition to treating their secondary manifestations.

Types of Traditional Chinese Medicine

Herbs and Plants

The most often utilized compounds in TCM are herbs. There are almost 11,000 herb plants listed in TCM-related pharmacopeia, with about 700 species being utilized regularly. Thousands of herbal formulations have been created and are frequently used in clinics for treating diseases. Theoretically, TCM herbal compositions can simultaneously regulate many targets within cells since they contain multiple potent components (Xu et al., 2019). Antibacterial herbs, such as Di Fu Zi, Jin Yin Hua, Pu Gong Ying, Da Huang, Huang Lian, and others, interfere with the metabolism and function of bacteria and reverse their resistance. Herbs with antifungal properties, such as Ku Shen Gen, She Chuang Zi, and Di Fu Zi, can contain volatile oils, terpenoids, aldehydes, flavonoids, alkaloids, and phenols. They also impede the growth of fungi. Bioactivity: induces paralysis, obstructs nutrition absorption, suppresses metabolism, and gets rid of parasites; may include phenols and alkaloids (Marshall, 2020).

Species that produce useful bioactive chemicals that have been cultivated and have therapeutic potential, medicinal plants have garnered significant interest in the treatment of neuropsychiatric and neurodegenerative illnesses (Moreira et al., 2023). With a continuous lifespan of more than 270 million years, *G. biloba L.* (Ginkgoaceae family) is said to be one of the oldest trees in the world, if not the oldest. Numerous pathologies, including diabetic cardiomyopathy, neurological diseases, cataracts, hearing loss, myocardial lesions, hippocampal neuronal lesions, morphometry testicular abnormalities, and liver damage, can be treated with the extract's advantageous qualities (Moreira et al., 2023). For instance, rhizomatous and Apiaceae plants are mostly used to treat pyogenic infections, common colds, coughs, asthma, rheumatic arthralgia, ulcers, and energy imbalances; fruits are primarily used to treat parasites, improve digestion, ease stomach discomfort, and regulate vital energy (Li et al., 2023).

Animal Products

Roughly 13% of the medications used in traditional Chinese medicine are said to be animal-derived. Animal-derived Traditional Chinese Medicine (TCM) is a health tonic that nourishes the body, enhances immune function, and aids disease resistance. Compared to plant-derived TCM, animal-derived TCM is considered more potent, making it an essential part of TCM due to its potent body-nourishing effect (Tang et al., 2020). TCM continues to advise using formulations that comprise a variety of animal tissues, including testicles and the penis of dogs, bears, or snakes, tiger bones, antelope, buffalo, or rhino horns, deer antlers, and snake bile (Still 2003).

Minerals

Rich in resources, minerals can be used as medications with notable therapeutic effects and are an integral part of traditional Chinese medicine (TCM). According to the idea of traditional Chinese medicine, mineral medications fall into five categories: insecticide, detoxification, hemostasis, sedative, and forceful cleansing of drainage. Certain minerals, such as magnetite and cinnabar, have hemostatic and sedative properties. Modern classifications concentrate on anion or cation components. Mercury, arsenic, lead, iron, calcium, aluminum, copper, sodium, and magnesium compounds are among the substances classified as cations (Zhong et al., 2022). It is primarily used in traditional Chinese medicine to treat intestinal, breast, urological, dermatological, hemorrhoidal, ulcerative, abdominal distension, amenorrhea, mouth sores, toothaches, and other digestive complaints (Tao et al., 2023).

Fruits

Certain fruits are also used in TCM, like mulberry. The dried, ripe fruit of the mulberry, known as *Mori fructus*, is picked when it is reddish-purple. It is a type of TCM used to support the kidney and liver. Eating mulberry fruit on its own is said to be able to alleviate "xiao-ke," a TCM symptom associated with diabetes mellitus. Mulberry fruit is high in flavonoids and polysaccharides, and research on modern pharmacology has demonstrated that the fruit's extract and its constituents all have good hypoglycemic action (Liu et al., 2023).

Role of Traditional Chinese Medicine

The globe is perpetually threatened by the prevalence of infectious illnesses. Traditional Chinese medicine (TCM) has the ability "to regulate significant variables, obstruct signaling pathways, and suppress microbial proliferation". TCM has strong antibacterial, antiviral, and anti-inflammatory properties that show exceptional effectiveness in treating bacterial and viral infections (Zou et al., 2023). In history, TCM has attained positive results in treating these illnesses by successfully limiting epidemics through public application (Ni et al., 2020). In the recent epidemic, numerous clinical applications have shown the considerable part of TCM in treating COVID-19, with reliable reports have been given to the scientific community (Lee et al., 2021). As an essential part of Chinese culture, Chinese herbal medicine, possesses exclusive benefits and plays a dynamic role in averting and treating infectious ailments. It can show improved efficacy with fewer side effects, decrease the severity of diseases and help in clinical retrieval. As a result, the use of herbal medicine, to treat infectious ailments has drawn more consideration (Ni et al., 2020).

Mechanism of Traditional Chinese Medicine

The contrivances by which Chinese herbal medicine treats these illnesses mainly involve antiviral, antibacterial and anti-inflammatory properties. These effects are achieved by active ingredients in alkaloids, flavonoids, polysaccharides, saponins, tannins, and polyphenols. These synergistic effects can reduce the risk of drug resistance and enhance the overall therapeutic outcomes.

Antiviral Biochemical Pathway

Suppression of Viral Replication

A variety of methods has been found through which Chinese herbs, inhibit the replication of viruses, mostly associated with three stages: intrusive with the incursion of the virus, blocking the production of fully functional protein and impeding the replication of genes (Jiang et al., 2021; Chen and Ye, 2022). Active ingredients such as "alkaloids, flavonoids, saponins, quinones, terpenes, proanthocyanidins, tannins, polysaccharides, steroids, polyphenols, and coumarins extracted from these herbs" have demonstrated the capability to scavenge, inhibit RNA and DNA synthesis, and obstruct viral duplication (Abookleesh et al., 2022). By blocking these three stages, these constituents provide their antiviral actions. Herbal treatments target certain stages of the viral life cycle, namely viral attachment and entrance. Through their interactions with certain pharmacological targets, chemicals present in TCM Salvia miltiorrhiza, namely tanshinic acid B and tanshione IIA, have been shown to prevent viral entrance into cells (Elebeedy et al., 2021).

Among these components alkaloids are the largest group of an antiviral compound with a wide range of antiviral properties. Honeysuckle extract contains flavonoids that hinder the action of enzyme neuraminidase presents in influenza viruses. Viruses' releases from host cells by the action of neuraminidase, so by blocking its action the release of influenza viruses and its replication can be prevented (Li et al., 2021). In conclusion, Chinese herbs prevent the spread of viruses by interfering with the virus's ability to enter cells and replicate itself. This effectively averts the spread of viruses (Zou et al., 2023).

Initiation of Apoptosis

Moreover, Chinese herbal medicines play a major role by encouraging virus-infected cells to undergo apoptosis, which helps stop the transmission and reproduction of virus and play a vital role in the treatment of infectious disorders (Turpin et al., 2022). *S. baicalensi Georgis.,* contain a flavonoid compound baicalein which can bring apoptosis in cervical cancer cells infected with human papillomavirus (HPV), such as SiHa and CaSki cells by subduing the expression of "E6 and E7 viral oncogenes" (Kim et al., 2013). The spread of intracellular viruses can be hindered by self-apoptosis in infected cells.

Antimicrobial Biochemical Pathway

Suppression of Bacterial Growth

Chinese herbs explicate their capacity to suppress bacterial growth by interfering with the metabolic activities of bacteria. These herbs contain compounds such as flavonoids and flavonoid glycosides that can interfere with critical biological processes, including protein and nucleic acid production and bacterial enzyme activity. This can inhibit bacterial metabolic pathways and stop them from growing. Moreover, flavonoids can impair cytoplasmic membrane function, energy metabolism, and nucleic acid synthesis (Biharee et al., 2020). Several mechanisms have been proposed to explain the antimicrobial activities of these herbs, including: "disruption of cell membranes, inhibition of cytokinin, suppression of protein and DNA synthesis and inhibition of bacterial division and development" (Wang et al., 2019).

Bacterial Biofilm Disruption

Bacterial biofilm can efficiently break by certain herbs that have active ingredients like flavonoids, and xanthophyllin. The formation of healthy biofilm, attachment and survival of bacteria can be hindered by destabilizing the structure of the biofilm (Wang et al., 2019). Furthermore, by interfering with the gene regulatory network and bacterial signaling system, these active components can prevent the production of biofilms. The main components of bacterial biofilms include polysaccharides, lipids and proteins (Strahl and Errington, 2017). For instance, flavonoids are essential in preventing the growth of bacteria because they decrease biofilm formation, adhesion, pathogenicity pore proteins on cell membranes, and membrane permeability. It prevents the creation of bacterial nucleic acids, stops bacteria from producing energy, stops intrabacterial enzyme activity (Gupta et al., 2022).

Immunomodulatory Pathway

Immune Cell Activity Regulation

Herbal medications have the power to control the immunological response by regulating the immune system's over-activation or inhibition. This lessens tissue damage and inflammatory reactions brought on by bacterial infections. Herbs can improve the function of lymphocytes, natural killer cells, macrophages as well as alter immune cell activity. This increases boosting immune cell activity and the effectiveness of these cells in removing infections (Yang et al., 2021).

Immune-related Mediator Release Inhibition

The Chinese medicine can prevent the production of cytokines, inflammatory mediators and other substances produced during the inflammatory response. Herbal medicines have the capability to control inflammatory modulators. Lastly, this reduces inflammation (Chen et al., 2018).

Immune-related Signaling Pathways Inhibition

Chinese herbs contain active ingredients that can control immune-related signaling pathways. These include the successful interfering with the stimulation and transduction processes of inflammatory signaling pathways and blocking the activity of inflammatory signaling pathways such as NF-κB and AP-1 (Batlle and Massagué, 2019). Thus, inflammatory reactions become less severe (Borges et al., 2019).

Antioxidant Effects

Oxidative stress is a significance of infectious disorders that arise from microbial infections. To reduce inflammatory reactions and tissue damage, antioxidant compounds found in several herbs have the ability to scavenge free radicals and lower oxidative stress (Cui et al., 2018). Saffron, for example, reduces inflammation by scavenging free radicals and modifying the oxidative stress defense system (Bastani et al., 2022). Mechanism of Traditional Chinese medicine is shown in Fig. 1.

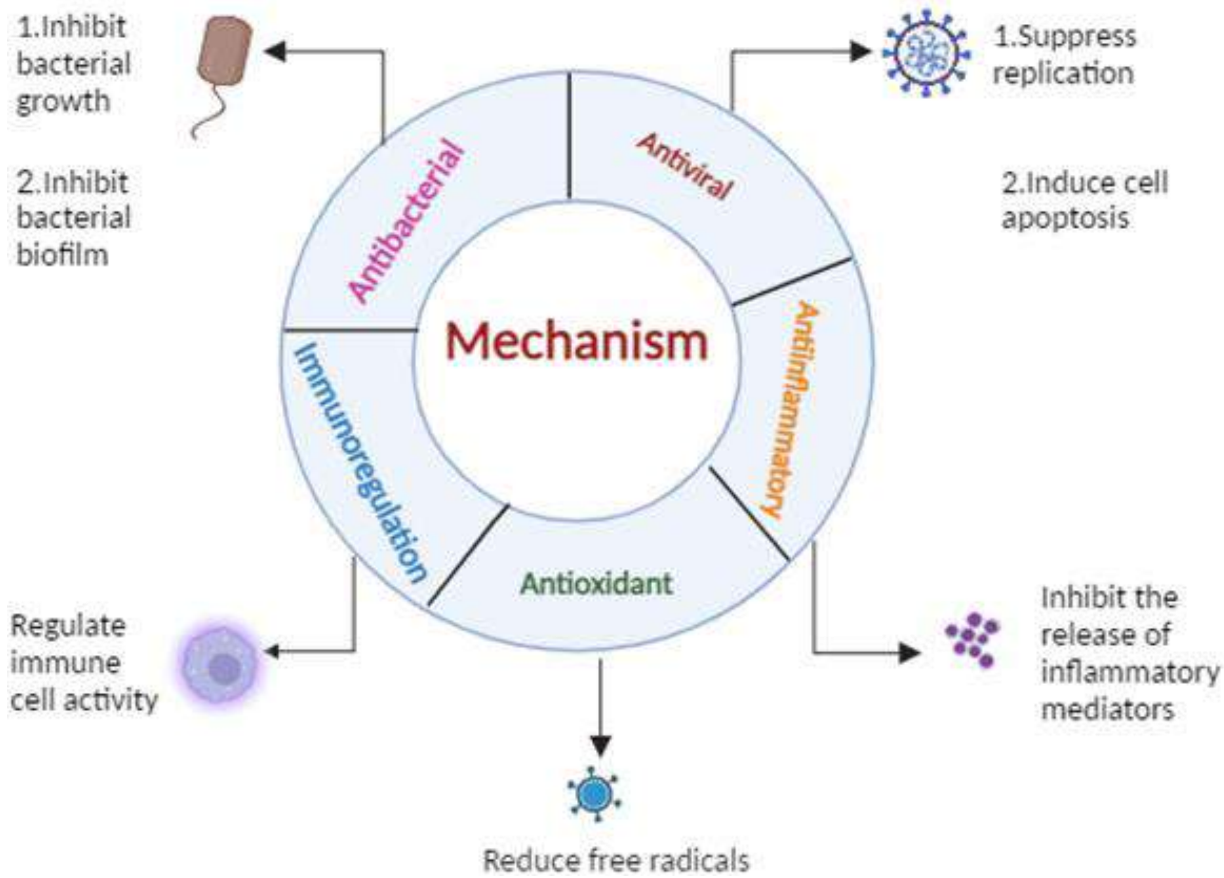

Fig. 1: Mechanism of Traditional Chinese medicine.

Recent Outbreaks and Threats of Zoonotic Diseases

Zoonoses are classified as infectious diseases that can naturally spread from vertebrate animals to humans, depending on the source of the infection. The causal agent could be bacteria, virus, fungus, ectoparasite, helminth or protozoans. Transmission of zoonotic infections can occur either directly or indirectly, since animals can act as mechanical vectors or reservoirs. Most of the time, a large number of domesticated and wild animals, including their excrement and the soil in their burrows, play a crucial part in keeping the illness in the wild and, to varied degrees, aid in its spread and real transmission across animal population and in human. From a global prospective, zoonotic infections are known to exist for many centuries and are primarily responsible for the emergence and resurgence of infectious diseases.

Viral Zoonoses

Zoonotic viruses and bacteria have been the primary cause of most emergent infectious disease episodes in recent decades, including the COVID-19 pandemic. Specifically, major global epidemics have been generated by coronaviruses, influenza-A viruses, arboviruses, and viruses that cause hemorrhagic fever. Though knowledge of the causes and dynamics of zoonotic epidemics has advanced recently, there are still gaps in clinical training and diagnostic capabilities (Judson and Rabinowitz, 2021). Animal feces release a variety of viruses into the environment, including rotavirus. Although these viruses are found in animal digestive systems, there is typically little knowledge of their importance in relation to food safety. When food animals are prepared and consumed, this causes severe acute respiratory syndrome (SARS) transmitted to people. The topic of whether food borne introduction is a potential pathway for the spread of these novel viral illnesses among humans has been brought up by these cases.

Bacterial Zoonoses

Zoonotic origins account for the majority of new infectious diseases that can spread through being in close proximity with an animal, usually by ingesting, breathing, or other methods that infect the skin, mucous membranes, and sometimes even the intact skin (Shepheard et al., 2013). Zoonotic diseases are spread by insects, which are significant biological or mechanical vectors (Gremião et al., 2017). Within the field of veterinary medication, *S. aureus* is a type of "gram-positive" bacteria that is frequently found in both healthy humans and animals. It is present on the mucous membranes and skin. Nevertheless, it has been identified as a noteworthy devious pathogen in cultivated rabbits and chickens, and it has also been documented to induce 'mastitis in animals' that produces dairy products (Vincze et al., 2013). Another common disease in the poultry sector is campylobacteriosis, which is spread by other livestock such as farmed cattle, pigs, or poultry that also have staphylococcosis. In humans, gastroenteritis is caused by two common bacteria that are *Campylobacter jejuni* and *C. coli* (Wolfs et al., 2001). In animals and humans, leptospirosis can be resulted due to contact with urine-contaminated water or soil. Leptospira is a prevalent bacterium found in various domestic and wild animals. It is transferred through urine (Lagadec et al., 2016).

Fungal Zoonoses

Fungus is indigenous to parts of southern China and Southeast Asia; the fungus may naturally occur in soil in these regions. While almost all fungi can survive in the environment for long periods of time, diseases have an evolutionary advantage because they can use vertebrate vectors for a portion of their life cycle. Humans are frequently not the fungus's ideal host; instead, it prefers to feed on animals. Fungal infections linked to sapronotic or zoonotic transmission represent a significant global public health issue. A number of these infections fall within the category of the most prevalent fungal disorders, including dermatophytosis (Moretti et al., 2013) sporotrichosis (Barros et al., 2011) and histoplasmosis (Bonifaz et al., 2011).

Therapeutic Applications of TCM in Treating Ailments

The methodical healthcare system was created via clinical experience and is grounded in a scientific regulatory framework. TCM uses distinct theories and methods to improve health and treat illnesses. Examples of these techniques include "Tuina," or Chinese bodywork or manual therapy, "Qigong" and "Taijiquan," or traditional biofeedback exercises, acupuncture, moxibustion, and Chinese herbal medicine and dietetics (Matos et al., 2021). Anti-inflammatory, anti-oxidative, antipyretic, antidepressant, antibacterial, blood vessel wall relaxation, skeletal muscle relaxation, and anticonvulsant action are just a few of the various effects that these combinations may produce (Shannon 2002). In this case, evidence-based integrative medicine may find Chinese herbal therapy to be a viable ally.

Traditional Chinese Medicine in Lung Cancer Treatment

TCM offers a potential lung cancer treatment as an adjuvant or maintenance therapy. Numerous clinical investigations have shown that TCM effectively treated lung malignancies (Li et al., 2018). Combining TCM with chemotherapy is an important adjuvant treatment that may help patients with lung cancer. The most extensively used treatment for non-small cell lung cancer (NSCLC) is TCM combined with platinum-based chemotherapy (Cao, et al., 2017).

Traditional Chinese Medicine in Neural Treatment

Chinese researchers have observed that a single substance and a combination of TCM can stimulate the proliferation, differentiation, and migration of brain stem cells while controlling their microenvironment. These findings suggested that neural regeneration and the restoration of neurological conditions like depression, ischemic brain injury, Alzheimer's disease and Parkinson's disease might both be improved (Ren and Zuo, 2012).

Traditional Chinese Medicine in Renal Treatment

TCM has been applied extensively in clinical settings to treat a variety of kidney disorders with positive therapeutic outcomes and regarded as a potential alternative therapy approach. It has been demonstrated that TCM, comprising individual herbs, mixtures, and active components, dramatically improves a range of clinical symptoms and has positive effects on "immunological inflammation, fibrosis, mitochondrial homeostasis, oxidative stress, podocyte damage, and RTEC apoptosis". In a puromycin amino-nucleoside rat model, TCM, such as the Yiqi Qingre decoction, may lower 24-hour urine protein levels and enhance renal function (Fang et al., 2019).

Traditional Chinese Medicine in COVID-19 Treatment

TCM herbal medicine has the potential to slow down the progression of disease and increase cure rates. There are several possible mechanisms of action that could account for the beneficial effects of TCM formulas, including the following: "COVID-19 treatment practice demonstrated that early intervention of TCM is an important way to improve cure rate, shorten the course of disease, delay disease progression, and reduce mortality rate". Moreover, TCM not only inhibits the virus but also has the potential to block infection, control immunological response, stop inflammatory storms, and aid in body restoration. Furthermore, the COVID-19 prevention and control procedures fully adhere to the philosophy of "preventive treatment of disease." (Ren et al., 2020).

Traditional Chinese Medicine in Various Fields

TCM is intended to treat both the underlying causes ("ben") and secondary manifestations ("biao") of various acute and chronic conditions; this includes treatments for the eye, ears, nose, and throat as well as "internal medicine, gynaecology, pediatrics, traumatology, external medicine, dermatology, and emergency medicine" (Matos et al., 2021).

Challenges in the delivery of Traditional Chinese Medicine

Although traditional Chinese medicines (TCMs) have a long history and are known to be beneficial, their multi-component nature—which includes proteins, volatile oils, alkaloids, flavones, anthraquinones, and glycosides—makes drug delivery strategies for TCMs difficult (Wang et al., 2019).

Artificial Intelligence

Though AI has had a big impact on TCM research, it's important to remember that TCM services are provided by people. By placing patients at the center and encouraging them to engage in discussions regarding diagnosis, treatment, and follow-up, shared decision-making (SDM) is an essential strategy for bridging the gap in evidence-based medical practice and enabling individualized therapeutic decisions (Li et al., 2023).

Integration with Modern Healthcare Systems

One of the oldest and most widely utilized complementary therapies in the world, traditional Chinese medicine (TCM) has impacted many other Asian medical systems. Traditional Chinese Medicine (TCM) treats the patient as a whole and uses a customized, holistic approach to relieve symptoms, in contrast to mainstream medicine, which treats the disease's symptoms. However, a lot of personal evidence exists that is difficult for scientific procedures to quantify, which has made mainstream, traditional medicine reluctant to accept it (Chan et al., 2015).

Big Data-Driven Data Science

Data science is essential to the advancement of TCM because it produces robust statistical models that enable inference from complicated TCM data. Precise relationships and conclusions may arise from this analysis. However, comprehending complicated TCM systems necessitates combining causal reasoning with subject expertise. Differentiating causal links and associations from big observational medical databases is difficult with conventional statistical machine-learning algorithms. Consequently, the success of TCM depends on the integration of domain knowledge and causal reasoning (Yang et al., 2024).

Quality Control

Concerns over the frequent incidence of adverse reactions and safety difficulties have been raised by the increased use of traditional Chinese medicine (TCM) preparations in clinical practice in recent years, especially TCM injections. To ensure the safety and efficacy of TCM remedies, quality control is essential. The complicated chemistry and uncertain identification of the active components in TCM remedies present significant problems in preserving their quality. The formulation preparation and quality control processes suffer from this complexity, which makes it challenging to identify important quality indicators (Yang et al., 2024).

Current Status

Natural medications are nature's weapon of choice for combating a wide range of illnesses. An increasing amount of research on the application of TCM for treating tumors has demonstrated the significance in recent years. When compared to traditional treatments, TCM offers the benefit of a special and innovative pharmacological mechanism that produces the same healing impact with less harmful side effects (Wei et al., 2023). Given their multi-component, multi-target, and multi-pathway effects, Chinese medicine and ethnic medicine with hemostatic effects provide special benefits and development potential in the prevention and treatment of clinical hemorrhagic disorders (Mu et al., 2023). Throughout its lengthy history of development and invention, TCM, a hallmark of Chinese civilization, has produced a distinctive philosophy of life, fitness, and the prevention and treatment of illnesses (Peng et al., 2023). TCM remedies affect blood flow and immune system function by modifying gut flora and its metabolites.

Research into the underlying mechanisms of TCM's anticancer characteristics is still in its early stages, with inherent limitations in existing thinking and approaches, despite some advances in understanding these capabilities (Wei et al., 2024). To provide a comprehensive understanding of the therapeutic mechanism of TCM for treating diseases, analytical research has been practiced for thousands of years in China and calls for a large volume, high-quality, and standardized database (Fung, 2024).

Future Perspectives in TCM Globalization

The most significant challenge for TCM globalization is to strengthen TCM itself, transforming it from its basic experienced or observational component into an evidence-based medicine. Since TCM is a practice-based medical field with a thorough understanding of the human body. Before applying for full marketing clearance, traditional Chinese medicines must offer credible and persuasive evidence of their safety, effectiveness, and quality, sometimes known as the three golden criteria.

TCM fundamental research should be supported by current scientific and technology approaches to areas such as chemical composition, active principles, pharmacodynamics, pharmacokinetics, toxicity, phytochemical profiling, quality assay methodologies, and so on. The Chinese central government should take a broad approach to developing a strategic plan, and funds should be set aside specifically to support research related to the international registration of TCM products with a long history of clinical use and special therapeutic qualities. This is another crucial issue from the perspective of national strategy (Wu et al., 2015).

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Chapter 06

Botanicals and Traditional Chinese Medicine

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ABSTRACT

About thousands of years ago, the use of traditional Chinese and botanical medicine has a vibrant history, with herbal and plant-based medications playing a significant role in treating several disorders and promoting well-being. Traditional Chinese medicine, rooted in herbal medications, have been a major source of modern pharmaceutical treatment, with various active complexes recognized and produced from florae. Traditional Chinese Medicine has been involved in disease prevention, treatment, and health improvement, which offer therapeutic choices for conditions ranging from cardiovascular disorders to autoimmune diseases and cancer. Traditional Chinese Medicine is deeply rooted in theoretical philosophies such as the "Yin Yang" and "Five Elements" which provided a complete outline for the understanding of diseases and health. The fundamental concepts like "Qi" and "Blood" highlight the importance of energy balance and circulation in sustaining health. TCM uses many herbs, with thousands of herbal formulas established and applied in clinical training. The therapeutic uses of TCM cover numerous disorders such as, cardiovascular disorders, cerebrovascular diseases, tumor treatment, and infectious diseases. Many clinical studies have confirmed the effectiveness of TCM formulation in different situations like, hypertension, coronary heart disease, Parkinson's disease, stroke, cancer, and malaria. These formulations often include many herbs and target multiple physiological systems at the same time to attain healing effects. Generally, botanical, and traditional Chinese herbal medicine proposes a valuable therapeutic method, which is categorized by multiple targeting features and low toxic adverse effects.

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INTRODUCTION

Plants and herbal based medicines have been used throughout history in different traditional medicine systems for promote well-being (Newton, 1991) (Jaiswal et al., 2016). Subsequently, plants are at the origin of the western pharmacopeia, as the major source of the modern pharmaceutical industry was the traditional medicines(Corson and Crews, 2007). A significant approach of Western pharmaceuticals is to identify the active molecular compound by the use of therapeutic effects of plants to chemically synthesize it (Li et al., 2015).

Due to the degeneration of the ecological system, the major resources of plants and herbal medicines have been in danger of extinction. TCM (Traditional Chinese Medicine) involves improving health, disease prevention, and treatment of several diseases such as autoimmune diseases, cancer and CVD (Cardiovascular Disorder) (Ma et al., 2019). TCM is a major source for pharmaceutical research and development. There are some Traditional Chinese Medicines which are shown remarkable effects in disease treatment, such as digitoxin, celastrol, artemisinin and quinine.

In 2015, Nobel Prize was awarded in Physiology and Medicine which is based on the use of artemisinin remedies to cure malaria (Su and Miller, 2015). Traditional plant studies involve to identifying herbal plants with similar phytochemical contents which help to identify the species that can be quantitatively and qualitatively relieved (Gospel Ajuru, 2017). Such global studies facilitate the utilization and protection of herbal plant resources which have been oppressed due to high commercial land.

Traditional Chinese Medicine (TCM) is based on two Chinese philosophies of "Five Elements" and "Yin Yang"(Wei Ling, 2020). About 2000 to 3000 years ago, Huangdi Neijing was the most ancient Traditional Chinese Medicine (TCM)(Catic et al., 2018). TCM basic theory includes Qi, meridians, blood and five zang organs and six fu organs (Hao et al., 2011). TCM divides the disease cause into two groups, internal causes and external causes. TCM distinguishes disorders according to interior, exterior, heat, cold, excess (Shi), deficiency (Xu) and eight principles Ying Yang (Matos et al., 2021).

The most common substances used in Traditional Chinese Medicine are herbs (Y. F. Chen, 2012). About 11000 herbal plants have been documented in several TCM-related pharmacopeia and approx. 700 herbal species are the most commonly used ones (Eigenschink et al., 2020). Traditional Chinese Medicine is the combination of multiple herbal formulas for disease treatment and thousands of herbal formulas have been created and are broadly useful in clinics.

Traditional Chinese Medicine formulas contain many effective ingredients that stimulate multiple targets simultaneously in the cells, which help to establish a stable physiological controlling system patients and disease treatment (Sucher, 2013) (Xu et al., 2019).

Overview of Botanical and Herbal Medicines in TCM

People have used herbal plants for healing for centuries. Botanical or Herbal plants and their products have been used with varying success to prevent and cure different diseases throughout history. Approximately 5000 years ago in Sumerian times, there are written records of medicinal plants and archaeological archives even suggest past use of herbal plants(Russo, 2007). The strong bond began to unwind in 1897, when Friedrich Bayer and Co. generated acetyl-salicylic acid (Aspirin) (Raskin et al., 2002).

Botanical and Herbal medicines are the use of plant herbs and plants extracts used for therapeutic purposes to provide support to different physiological systems, to cure, prevent and treat disease in humans or animals (Kumar and Kumar, 2009). In developing countries, about 70-80% of the world's population is dependent on non-conventional medicine treatment in primary healthcare as reported by WHO (Kumar and Kumar, 2009).

Importance of Herbs and Botanical TCM

Though Chinese massage and acupuncture have been well-known and adept in the west. Chinese herbology and clinical diagnosis are very significant components of Traditional Chinese Medicine (Dong, 2013). Traditional Chinese Medicine (TCM) has been carried out for the treatment of various clinical disorders in China. In 1950, Mao Zedong Chairman authorized an attempt to generate a formal medicine (Wei, 2013). The major change in this medicine is to eliminate everything that is considered to be illogical.

Yin Yang Theory of Traditional Chinese Medicine

Yin Yang is the two opposing forces of nature, which represent the understanding of dialectical phenomenon. The active interplay of these two opposite forces forms a unity. In ancient times, the sages permanently attributed inner strength, life forces, and movement to the opposite forces of Yin and Yang (M. Lu and Busemeyer, 2014). "Dao" or the dynamic rules of both the universe and the human mind is placed within the framework of the oneness of these opposites.

The Ying Yang concept was used by the ancient philosophers to convey how each of them corresponds to everything in the universe(M. Lu and Busemeyer, 2014)(Wang, 2013). For instance, everything in the world has "Yin and Yang" which was claimed by LaoZi in Dao de Jing. According to Yi Jing, every phenomenon in the universe is dependent upon "one Yin" and "one Yang". In Nei Jing and in Su Wen, it is stated the Ying Yang theory that (Lu and Busemeyer, 2014)

"Ying Yang is a theory of the universe, Heaven and Earth, everything follows these dynamic laws of change, including life and death. It is the answer to the mystery of life handed down from our intellectual temple. Medical treatment also must follow this law."

Everything is based on the "Yin and Yang" hypothesis, which was put forth by scientist Niels Bohr in the 20th century (Leong, 1926). According to this theory, Yang stands for one, odd, white, heat, light, disarray, and dispersal, and Yin for zero, even, black, cold, darkness, organization, and unity. These principles are always evolving, since they adapt to the distinctive patterns or laws of nature, known as the "Dao". To maintain balance between "Yin and Yang" leads to harmony with the "Dao"(M. Lu and Busemeyer, 2014). The Chinese culture, including geography, astronomy, digital art, classic literature, medicine and philosophy has been significantly impacted by the belief. Initially used for prediction, the Yi Jing has developed into a book of wisdom that offers predictions for the future and advice on what to do (Matthews, 2016).

About 2000 years ago, Traditional Chinese Medicine has been evolved (Chan, 2016). It was progressing from its early stages to advanced level by the continuous effort of physicians. In ancient time, the book of Nei Jing, Su Wen and Ling Shu involved a wide range of medical subject areas like diagnosis, therapy, physiology, prevention, pathology and medication (Unschuld, 2016). This comprehensive coverage laid the foundation for the development and refinement of Chinese medicine into its present form.

Yin Yang principle in TCM provides a background for the understanding of disease symptoms (Hu and Liu, 2012). The symptoms of diseases such as, poor blood circulation and fever are described by Yin Yang principle;

- "Yin" includes shortness of breath, cold limbs, listlessness, looks bleak, lack of desire to talk, loose stools, clear urine, pale tongue, no feeling of thirst, and thin weak pulse.
- "Yang" includes a fever, fast breathing, inflamed face and hot body, irritability, always feeling thirsty for cold drinks, excessive speech, constipation dry stool, pale yellow or red/pinkish urine, fast and powerful pulse, and tongue with yellowish layer.

For instance, high blood pressure may be caused by hyperactivity of "Yang" due to a deficiency of "Yin", while contact with cold and damp wind "Yin" may cause a cold body and to maintaining balance is contradicted by fever "Yang"(Gao, n.d.). For TCM diagnosis, it is important to apply Yin Yang principle accurately. In case of misinterpretation, it may cause misdiagnosis and unsuitable medication for the patient.

Five Element Theory

Traditional Chinese Medicine (TCM) practitioners integrate the Five Elements concept for medical consultations to evaluate and explain body imbalances (Pun and Chor, 2022). The Five Elements are fire, wood, metal, earth and water, which represent the distinct features of the human body (G.-M. Chen, 2007). Traditional Chinese Medicine links the element of earth with an examination of the astomach and spleen, while fire with in examination of the heart, pulse, and tongue. Water corresponds to bones and ears, wood to spring and eyes and metal to muscles and the mouth (Catic et al., 2018). Traditional Chinese Medicine (TCM) practitioners associate these five elements with 12 main organs of human body, considering them as an interrelated whole.

For instance, lungs and the large intestine are associated with earth, while spleen and stomach are related with earth. A circular cycle is formed by this interrelation where each element effects another, metal condenses water, earth affects metal, wood fuels fire, fire creates earth, water feeds wood (Reinprecht, 2016). The understanding of these elemental relationship is critical for the TCM practitioners in diagnosis and treatment of imbalances in body effectively.

Qi and Blood Theory

"Qi" and "Blood" are important concepts in Chinese Medicine, as blood is recognized in both Traditional Chinese Medicine(TCM) and WM (Western Medicine) literature because of its tangible nature and its importance in pathological and physiological processes (X. Wang et al., 2011). However, blood is recognized in Western Medicine, so the concept of "Qi" being intangible is not included. A new viewpoint on "Qi"arises due to presence of gaseous signaling molecules which offers experimental understanding (W. W. Li et al., 2013). H_2S is supposed as a fundamental element in "Qi" in TCM (D.-D. Chen et al., 2023). TCM detects Blood Stasis Syndrome as an important underlying pathology in many diseases, which is associated with the disruption of "Qi" flow.

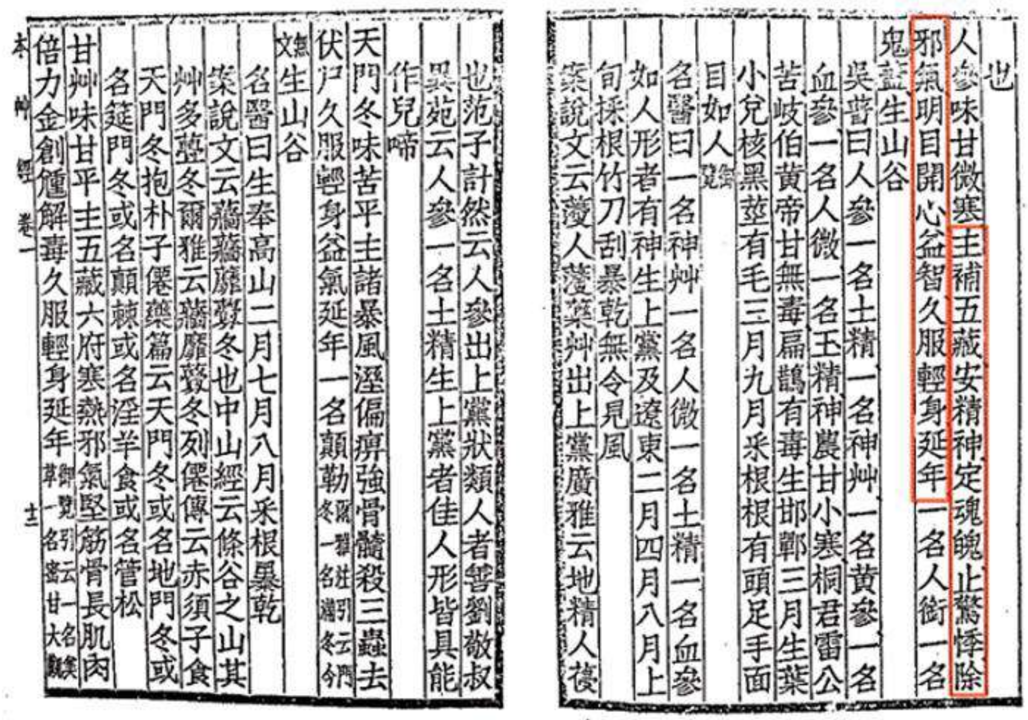
The important concept of TCM is that, "Qi" is supposed to be a dynamic source of energy for the body. "Qi" is maintained by the nutrients of the stomach and spleen and it inhales fresh air through the lungs, and "Qi" is generated from the parent's reproductive genetic essence (Cheng et al., 2016). As an important constitution of body, "Qi" maintains different physiological functions of body, such as, immune defense, distribution of nutrients, temperature, growth, cellular differentiation and complex molecular mechanisms (W. W. Li et al., 2013). Thus, "Qi" controls the normal development of life, from birth to growth, maturity to decline and death.

Botanical and Herbal Plants Used in Traditional Chinese Medicine

Ginseng (Ren Shen)

The most important ginseng herb is "*Panax Ginseng*", a traditional Chinese curative plant that has been used therapeutically in East Asia. In Japan, Korea and China the most valuable medicinal herb is Ginseng. The meaning of Panax is "all healing", it describes that the panax can heal all the body aspects. The most common Ginsengs are Chinese ginseng (*P. Notoginseng*), American ginseng (*P. Quinquefolium* L.) and ginseng (*P. Ginseng* Meyer) (Park et al., 2012).

Among the all varieties of Ginseng, P. Ginseng is the most extensively researched type, also received the most attention. It is temperature and soil-sensitive, therefore, it is cultivated in specific areas.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鬼蓋生山谷
吳普曰人參一名土精一名神艸一名黃參一名
血參一名人微一名玉精神農甘小寒桐君雷公
苦岐伯黃帝甘無毒扁鵲有毒生邯鄲三月生葉
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生山谷
名醫曰生奉高山二月七月八月采根暴乾
案說文云蘠蘼虋冬也中山經云條谷之山其
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名莚門冬或名顛棘或名淫羊食或名管松
甘艸味甘平主五藏六府寒熱邪氣堅筋骨長肌肉
倍力金創尰解毒久服輕身延年

Fig. 1: The prescription of Ginseng which explain the function of Ginseng. It was described in Shennong Bencao Jing which was written in 1st century and author is unknown(Park et al., 2012).

Liquorice Root (Gan Cao)

The popularity of herbal drugs is rising as alternative medicine globally. Drug-herb and herb-herb interaction is the common debating topic now a days, these combination therapies show potential and valid clinical benefits (Hazra and Singh, 2024). Liquorice (Glycyrrhiza) is the most common and found in approx. 60% of all prescriptions of TCM(Q. Zhang and Ye, 2009). Liquorice is derived from roots of Glycyrrhiza uralensis Fisch, Glycyrrhiza inflata Bat and Glycyrrhiza glabra L and is used widely in herbal medicines, and originate from Asia and Southern Europe (Fiore et al., 2005). It is popular in candies because of its sweet taste and sweets in Europe. In China, it is widely used in Traditional Chinese Medicines (TCM). According to Traditional Chinese Medicine Theory, liquorice is effective in the treatment of asthma, debilitation, fatigue, drug toxicity and extreme phlegm.

Astragalus (Huang Qi)

In China, Astragalus is known as Huang qi which is most extensively used herbal medication globally. The source of Astragalus is from the root of var. mongholicus (Bge.) Hsiao or Astragalus membranaceus (Fisch.) Bge or Astragalus membranaceus (Fisch.). Bge. This herb is well-known for its properties as refresher, diuretic, expectorant and hepatoprotective (Thorne Rese et al., 2003). Astralagus has exhibited its antihyperglycemic, antioxidant, anti-inflammatory, antiviral and immunomodulating activities (Jin et al., 2014). Usually, it was employed for the treatment of various health related issues such as, wounds, allergies, fever, uterine prolapse, loss of appetite, anemia, uterine bleeding and weakness.

In medical settings, it is utilized to treat gastrointestinal disorders like gastric ulcer and diarrhea and chronic phlegmatic disorders. Astralagus has been used for the treatment of renal disorder in Traditional Chinese Medicine for over 2000 years and is documented in the Shen Nong's Materia Medica, it was written in Han dynasty (Y. Zhang et al., 2019). Currently, the composition of Huang qi extract with water is used in the injections to treat various diseases.

Ginkgo Biloba (Yin Xing)

Ginkgo is scientifically known as "Ginkgo biloba", it is an ancient and exclusive deciduous tree and is well known for its therapeutic properties (Isah, 2015). Ginkgo extract includes a wide range of health benefits such as, anticancer, hepatoprotective, antihypertensive, antidiabetic, antioxidant, antimicrobial and immunostimulant activities (Noor-E-Tabassum et al., 2022). Moreover, it is known for its ability to combat neurodegenerative diseases and improve memory (Galil Hassan et al., 2016). The active primary compounds of the Gingko Biloba are the flavone glycosides like, terpene lactones, proanthocyanins, kaempferol, isorhamnetin, rhamnose, alkylphenols, D-glucaric acid, glucose, quercetin, ginkgolic acid and various other organic acids.

Traditionally, Ginkgo kernels have been consumed in nuts and also used in medicines(Galil Hassan et al., 2016). Ginkgo has shown many significant pharmaceutical applications, it is used for the treatment of Alzheimer's disease, vascular disease, vascular insufficiency, premenstrual syndrome, macular degeneration, liver fibrosis, vertigo, tinnitus, cardiovascular disease, impaired cerebral performance, memory issues and antidepressant-induced sexual dysfunction(Holmes et al., 2010).

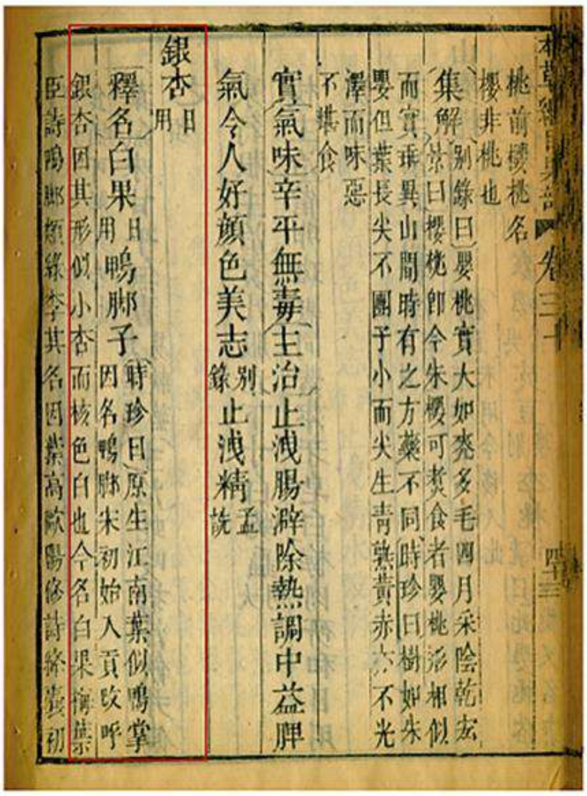

Fig. 2: The page shown in the picture is the 1st page of Ginkgo record and the highlighted text with red box is stated as; "Ginkgo (yin Xing) (daily use). Explanation of its name [alternate name] White Fruit (Bai Guo) (daily use) [other name] Duck Foot."(Chassagne et al., 2019)

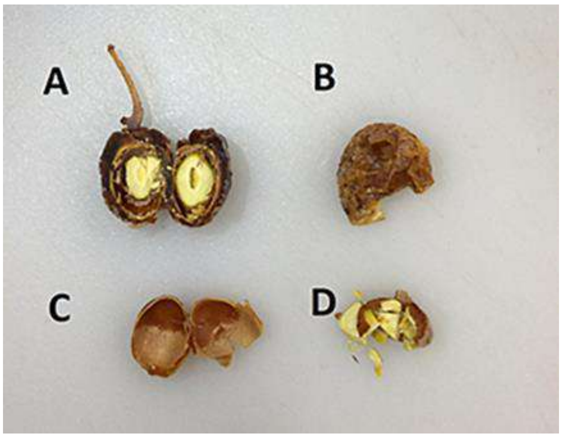

Fig. 3: Dissection of Ginkgo seed. A) Whole Ginkgo Seed. B) Seed Coat. C) Nutshell D) Seed nut or Kernel(Chassagne et al., 2019).

Therapeutic Uses of Traditional Chinese Medicine

Traditional Chinese Medicines play essential role in the treatment of cardiovascular disorder, cerebrovascular disorders, tumor treatment and infectious diseases.

Cardiovascular Disorder

Hypertension

In one of the clinical studies, Traditional Chinese Medicine used to treat hypertension. It was RCT (Randomized controlled trial) which consist of 251 hypertension patients, it was reported that the blood pressure of trial group after (24 hours) use of Tianma Gouteng granules were significantly lower ($p \leq 0.012$) as compared to non-trial group (placebo group)(D. Y. Zhang et al., 2020). Furthermore, it was confirmed that the use of Tianma Gouteng granules for hypertension is safe and effective and also no side effects.

Qian yang decoction contains 6 following drugs: Shudihuang (*Rehmanniae Radix Praeparata*), Gouteng (*Uncariae Ramulus Cum Uncis*), Danggui (*Angelicae Sinensis Radix*), Nvzhenzi (*Ligustri Lucidi Fructus*), Muli (*Ostreae Concha*), and Jili (*Tribuli Fructus*). This decoction has the result of pacifying the liver, tonifying blood, calming yang, and healthful Yin (Luo et al., 2023).

Coronary Heart Disease

In China, Chinese medicine has become popular, with the approximation of 1/3 patients in the big hospitals receiving the treatment program of Chinese medicine (Tachjian et al., 2010). In 1970s, the well-known renowned practitioners of TCM Prof. Chen Keji and Guo Shikui, they first proposed coronary heart disease treatment by undertaking blood stasis and activation of blood. With the help of clinical studies, they confirmed the effectiveness of Chinese medicine and also established Coronary Heart II (Luo et al., 2023).

Professor Chen proposed acute myocardial infarction pathogenesis by his clinical experience as the "combination of blood stasis with growth of filth and phlegm"(Luo et al., 2023). By using Yugeng Tongyu decoction, patient was treated with effects of refill Qi, removing turbidity, clearing bowels and activating blood, the incidence of disease complications and the rate of rehospitalization were reduced due to some critical events and the quality of life of patients improved by the use of a combination of conventional Western medicine.

Heart Failure

A randomized controlled trial (RCT) study confirmed the efficacy of Qili Qiangxin capsules, a formulation containing 11 drugs including, Renshen, Huangqi, Tinglizi (Lepidii Semen) and Fuzi (Aconiti Lateralis Radix Praeparata). The study revealed significant decreases in levels of N-terminal brain natriuretic peptide precursor (NT-proBNP) and improvement in parameters such as, New York Heart Association classification, 6 minutes' walk distance, and left ventricular ejection fraction (Li et al., 2013).

Cerebrovascular Disorders

Parkinson's Disease

In current years, TCM has revealed improvement in the treatment of Parkinson's disease and the complications associated with it. For Parkinson's Disease, a special Chinese medicine formula used which is known as Zishen Pingzhan granules, it consists of 12 herbal elements including Shudihuang, Tiannanxing (Arisaematis Rhizoma), Sangjisheng (Taxilli Herba), Tianma, Ezhu (Curcumae Rhizoma), Baishao (Paeoniae Radix Alba), Zhimu (Anemarrhenae Rhizoma), Baihe (Lilii Bulbus), Shichangpu (Acori Tatarinowii Rhizoma), Jiangcan (Bombyx Batryticatus), Yuanzhi (Polygalae Radix) and Gouqizi (Lycii Fructus). In a study, which involved 200 Parkinson Disease patients with depression who were already taking pramipexole (an antihistamine used for PD treatment), administration of Zishen Pingzhan granules or a placebo for 12 weeks resulted in significant improvement in depression scale scores and Parkinson;s Disease sleep scale scores among patients in the TCM group as compared to those in the placebo group (Ning et al., 2022). Additionally, TCM group patients confirmed improved safety and tolerability.

Stroke

Approx. 80% of the patients receive traditional Chinese medicine for the treatment of acute stroke during hospitalization. A Chinese herbal medicine formula (Dihuang Yinzi) which is effective for the treatment of various cerebrovascular diseases (Huang et al., 2010). A study was conducted on 87 patients with Ischemic stroke within 30 days of beginning. The patients were treated by using either Dihuang Yinzi or a placebo over a period of 12 weeks. The results presented significant improvement in Fugl Meyer score, assessing Barthel Index, motor function and daily living activities in the TCM treatment group as compared to placebo group (Yu et al., 2015).

Moreover, Wang et al (J. Wang et al., 2017) scientifically studied randomized controlled trials (RCTs) of Erigeron injection for the treatment of cerebral infarction and found potential benefits in reducing neurological damage and improving quality of life. However, they noted the requirement for higher quality studies to further support these results.

Tumor Treatment

Traditional Chinese Medicine plays an important role in the treatment of cancer at different stages and helps in the body recovery process, due to the many advantages of TCM including its ability of multiple targeting features of cancer and it's low toxicity (Qi et al., 2020). A randomized controlled trial of 5834 patients studied in cancer treatment by the use of Chinese medicine, it revealed that 70% of the patients in these trials showed improvement in quality of life, biomarker level and relief from symptoms when compared with conventional treatment group (C. L. Lu et al., 2021). These positive results were experimental whether Chinese medicine was used independently or in combination with the conventional cancer treatments.

Infectious Diseases Treatment

For Thousands of years Traditional Chinese Medicine has been used for the treatment of infectious diseases and as the research has progressed and the evidence supporting this statement has expanded. A study was conducted on 3428 expected women across four African countries with Falciparum Malaria concluded that one of the artemisinin combinations is dihydroartemisinin piperaquine, which was effective and established as safety profile (Pekyi et al., 2016).

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Chapter 07

Traditional Chinese Medicine as a Control Alternative for different Diseases

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ABSTRACT

Ancient Chinese medicine, evolving over millennia, works on the principle that illnesses arise from imbalances in vital energy flow. Reestablishing the harmony of this energy, known as qi, involves harmonizing the opposing energies of yin and yang, which manifest as cold and heat, internal and external, deficiency and excess within the body. Various methods are employed to preserve and restore qi for best health, with the most prevalent being herbal remedies and acupuncture. Herbal therapy employs blends of natural ingredients to address diverse ailments. These traditional concoctions can be analyzed as complete formulas or scrutinized on an individual herb basis. Administering a single herb in isolation may prove ineffective and potentially lead to adverse reactions. However, contemporary research in traditional medicine encourages the examination of individual herbs to enhance experimental precision. Moreover, the extensive array of herbal combinations available for testing poses a notable challenge. TCM often uses diagnostic classifications that diverge from contemporary scientific understandings of biology and pathology.

KEYWORDS
Chinese medicine, Therapy, Traditional health, Remedies, Formulas

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INTRODUCTION

Traditional Chinese Medicine (TCM) has a history of several thousand years. Inscriptions on diseases, medicines and treatment methods have been found on oracular bones from the Shang Dynasty (1766 to 1122 BC). In 1973, records of medical treatises, written on silk banners and bamboo tablets, were discovered in Mawangdui Tomb No. 3 in Changsha, Hunan Province. These records were transcribed during the Qin and Han dynasties (221 BC to 220 AD) and represent the oldest surviving Chinese medical literature. A famous classical work on medicine, the 'Inner Classic of the Yellow Emperor' (Huangdi neijing), emerged approximately 2000 years ago, laying the foundation for TCM as a scientific discipline (Keji et al., 2003).

Ancient healing methods originating in China have a rich history spanning 3,000 years. Its roots are found in the cradle of Chinese civilization, the Yellow River basin (Reyes, 2008). Over millennia of refinement and experimentation, it has evolved into a distinct and comprehensive theoretical framework that differentiates it from Western medicine (Zhuchen et al., 2020).

In the second half of the 20th century, this therapeutic approach made its way into Western countries, garnering wide acceptance among users who appreciate its non-invasive nature and strong focus on prevention, with fast and effective results (Reyes, 2008).

Although it has a traditional name, it keeps up with the advances of modern medicine and has gained recognition by the World Health Organization (WHO) as a scientifically validated form of medicine. Building on the rich tapestry of healing practices from Greek, Persian, and Arabic traditions, traditional medicine has secured its position as an official complementary modality in daily clinical practice, endorsed by the WHO.

It is important to mention that within traditional Chinese medicine as a control alternative for different diseases, the single health approach must be considered with an integrative vision in the search for solutions to problems for humans, animals and ecosystems (zoonoses, transmitted diseases by different vectors such as mosquitoes and bed bugs, antimicrobial resistance, food sectors, climate change and biodiversity). The concept of "One Health" has evolved in the last decade established by the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO, 2030).

In this chapter we show a general overview of traditional medicine as an alternative control for different diseases, and we focus on different topics such as: 1) Basics of traditional Chinese medicine; 2)The Theory of Yin-Yang; 3) The Theory of Five Elements; 4) Organ Theory of Zang and Fu; 5) Veterinary Acupuncture; 6) Therapy against some common veterinary diseases Reproductive disorders; 7) Back pain in equines; 8) Resuscitation; 9) Retained placenta; 10) Canine paralysis; 11) Conception rate and 12) Alternative medicine in the treatment of animal diseases.

Basics of Traditional Chinese Medicine

Traditional Chinese Medicine (TCM) is based on a holistic paradigm and recognizes that diseases are not isolated entities, but individual manifestations. It considers not only the condition of a specific organ but also the broader context of the whole organism, encompassing its manifestations, responses to external stimuli, and environmental influences (Tang et al., 2008). A central element of TCM treatment is its formulas, whose composition is multifaceted and includes numerous medicinal components. This approach offers the advantage of being multipurpose, multichannel, and interconnected (Zhuchen et al., 2020).

According to Ma et al. (2016) the foundation of TCM lies in a series of philosophical concepts integrated into its developmental framework. Based on philosophical and cultural theories, it evolves into intricate theoretical constructs such as the Yin-Yang theory, the 5 elements, the 8 principles, Zang-Fu organs, Qi and Blood, meridian systems, and various therapeutic modalities (Figure 1). For those unfamiliar with ancient Chinese philosophy, these frameworks may seem too abstract. In addition, TCM emphasizes personalized treatment approaches, which may be perceived as non-standardized by those unfamiliar with the practice, sometimes resulting in scrutiny or criticism (Ma et al., 2016).

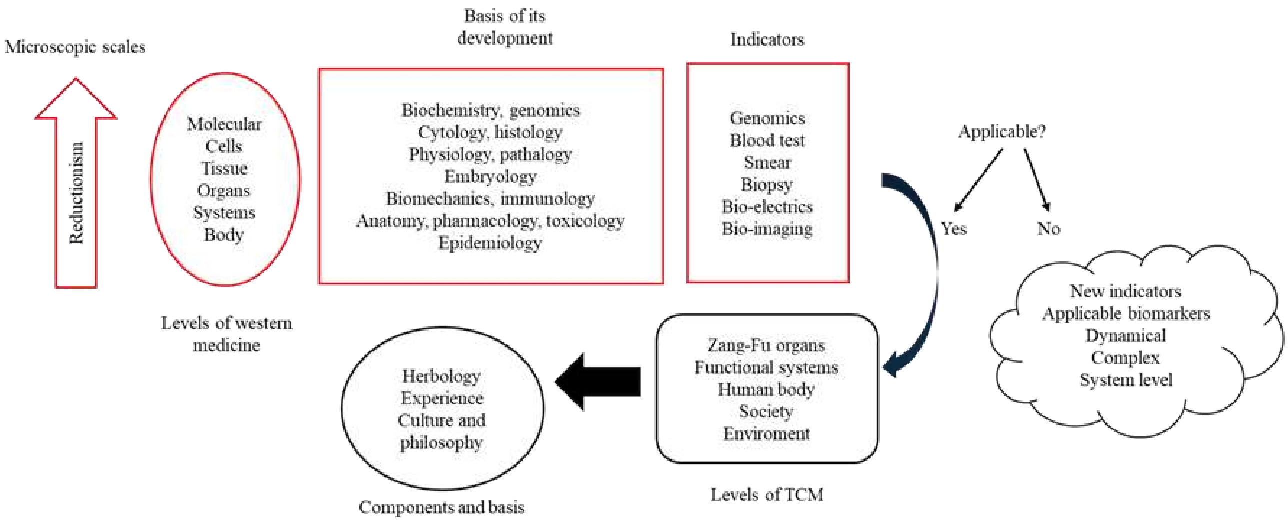

Fig. 1: Hierarchical structure of western medicine and traditional Chinese medicine (Ma et al., 2016).

The Theory of Yin-Yang

The concept of Yin-Yang articulates a universal criterion of characteristics that delineates two complementary and opposing sides of an inseparable entity. Yin embodies attributes such as lethargy, tranquility, receptivity, passiveness, obscurity, framework, inwardness, and descending motion. Conversely, Yang is linked with warmth, stimulation, mobility, vigor, illumination, spaciousness, ascending motion, and ascension. It elucidates the roles and interrelations of these facets within the ongoing process of metamorphosis and flux in the cosmos. This theory is harnessed in medicine to discern and juxtapose, thereby discerning physiological and pathological phenomena (Lozano, 2014).

The Theory of Five Elements

The doctrine of the five elements constructs a framework of correlations that categorizes universal phenomena into five groupings. These groupings symbolize inclinations of motion and alteration in the cosmos, aligned with the elemental forces of wood (mu), fire (Huo), earth (tu), metal (jin), and water (Shui). Consistent and explicit connections among them elucidate transformations in nature. Each of these elements is associated with different characteristics, organs, emotions, flavors, colors and seasons, among other aspects (Table 1).

The theory of the five elements also describes two types of relationships between the elements: generation relationships (sheng) and control relationships (ke). In generation, each element begets the next in the cycle (wood generates fire, fire generates earth, earth generates metal, metal generates water, and water generates wood). In control, each element controls another, maintaining balance (wood controls earth, earth controls water, water controls fire, fire controls metal, and metal controls wood).

This theory is used in TCM to diagnose imbalances and design treatments that restore harmony and balance in the body.

Table 1: Characteristics associated with the five elements theory

	Element				
	Wood	Fire	Earth	Metal	Water
Organs	Liver and gallbladder	Heart and small intestine	Spleen and stomach	Lungs and large intestine	Kidneys and bladder
Emotions	Anger	Joy	Worry	Sadness	Fear
Taste	Acid	Bitter	Sweet	Spicy	Salty
Color	Green	Red	Yellow	White	Black
Season	Spring	Summer	End of summer	Auutumn	Winter

Organ Theory of Zang and Fu

In ancient Chinese medicine, most human organs are classified into two sets: the five Zang and six fu organs. The five Zang organs encompass the heart, liver, spleen, lungs, and kidneys, considered as pivotal organs in human physiology. Meanwhile, the six fu organs include the gall bladder, stomach, small and large intestine, bladder, and San jiao, all pivotal for processing and transporting sustenance. The heart's physiological functions were conceptualized to regulate blood circulation, support cognitive functions, and manage speech. This explanation elucidates the heart's role in circulation logically, with the belief that its physiological function could influence human cognition (Sahmeddini, 2011; Catic et al., 2018).

Veterinary Acupuncture

Currently, veterinary acupuncture has an important therapeutic value, many scientific and medical works have proven this value, to treat various diseases in animals. In China, acupuncture has been used in veterinary medicine for thousands of years. Today, the art of acupuncture treatment has utilized modern techniques and ancient Chinese philosophy in its research. Although the use of veterinary acupuncture is thousands of years old, it was not until the 1970s that its value was recognized when the International Veterinary Acupuncture Society (IVAS) was founded in America (Krishna et al. 2005).

Therapy against some Common Veterinary Diseases

Reproductive Disorders

Veterinary acupuncture can be considered for the treatment of disorders of the reproductive system in farm animals. However, veterinary acupuncture is not effective in animals that have severe congenital defects, infections, or cancer of the reproductive system (Lin et al. 2001).

Back Pain in Equines

Back pain is very common in racehorses, traditional Chinese medicine mentions that the proper functioning of the liver, spleen, and kidney is important to maintain the integrity of the tendon, muscles, bones, and joints. When back pain becomes chronic, horses can become lame and even form muscle atrophy. Conventional treatment of back pain includes massage, rest therapy, and anti-inflammatory medications. Equine back stimulation and electroacupuncture could be a general therapy for horses suffering from chronic back pain (Wing-Wah et al., 2001)**.**

Resuscitation

The point of resuscitation and revival of consciousness (GV26) is the most used method of emergency resuscitation therapy in humans and animals. In animals GV26 is located at the lower edge of the nostrils, therefore a puncture in this area can resuscitate 90-100% of cases of apnea, and 40-50 of cases of cardiac arrest with a 5–10-minute stimulation. Cv26 can resuscitate animals from drug overdose and has sedative effects in cases of seizures. Therefore, GV26 stimulation may have beneficial effects in resuscitating animals (Rogers and Skarda, 1999).

Retained Placenta

Retained placenta is more common in cows, after calving the muscles of the uterus do not contract with sufficient force to expel the placenta, subsequently, metritis may form and there is a greater likelihood of death of the cattle. Acupuncture treatment can improve uterine contraction, especially at points such as V31-34, this therapy can help expel retained placenta (Lin et al., 2001).

Canine Paralysis

Many cases of paralysis are reported in veterinary medicine, often caused by trauma. Treatment may include surgery, chemotherapy, physiotherapy, and acupuncture. For the treatment of this problem, the veterinarian must make a good diagnosis, if the case is suitable for acupuncture the specialist must develop an effective therapeutic program, such as electroacupuncture, punctual injection, and electroacupuncture with lasser. The success of this therapy depends on the experience of the acupuncturist, the clinical condition of the patient, and the severity of the problem (Chan et al., 1996).

Conception Rate

A low bovine conception rate causes great economic losses worldwide and, in some cases can be treated by hormone therapy, but with less promising results. Some research shows that treatment with aqueous acupuncture achieved pregnancy rates of 67% after treatment (Lin et al., 2001). Other research reveals the inclusion of moxibustion points in the sacral area (BL31-BL34) and showed encouraging results in dairy cows (Hosaka, 1998).

Alternative Medicine in the Treatment of Animal Diseases

The use of medicinal plants for animal production is gaining interest due to concerns about synthetic antibiotic residues in animal food products (Kožárová et al., 2011). In addition, indiscriminate use of antibiotics in animals can lead to cross-resistance by various microorganisms (Chowdhury et al., 2014).

Chinese herbs have long been recognized for their effectiveness in controlling various animal diseases (Li et al., 2009; Jamil et al., 2022). Thanks to this control alternative, it has contributed to improve livestock production processes (Wang et al., 1998). Thus, ethnoveterinary medicine, which uses alternative or allopathic medicines, can be more economical and sustainable than synthetic pharmaceuticals (Xion and Long, 2020).

Several studies have reported on medicinal plants used for ethnoveterinary purposes by Chinese peoples. Most of the identified species are located in the families *Poaceae*, *Asteraceae*, *Compositae*, *Zingiberaceae*, *Rosaceae*, *Ranunculaceae*, *Papaveraceae* and *Labiatae* (Shang et al., 2012; Xion and Long, 2020; Luo et al., 2022; Liufu et al., 2023). These plants continue to be an integral part of the traditional medicine used to cure different ailments that affect animal production in rural communities.

Chinese people's use various parts of plants for ethnoveterinary purposes, such as leaves, flowers, roots, fruits, bulbs, seeds, branches and seedlings (Shang et al., 2012; Xion and Long 2020). Preparation methods include powders, decoctions, pills, ointments, tinctures, crushing, among others (Shang et al., 2012). Thus, traditional Chinese medicine has used medicinal plants to treat a wide variety of problems in animals, such as gastrointestinal, digestive, trauma, respiratory and reproductive diseases.

Gastrointestinal use: Gastrointestinal problems are one of the most common ailments in domestic animals, including: digestive problems, abdominal pain, diarrhea or ruminal impaction (Shan et al., 2020). Some plants have antimicrobial activity against different bacteria such as *Salmonella*, *streptococci*, *enterococci* and *Escherichia coli* (Guo et al., 2004; Lee et al., 2006; Sheng, 2011).

Antiparasitics: The mixture of different plant structures can have antiparasitic effect. Such as the flowers of *Lonicera japonica, Asarum heteropoides, Alisma plantago - waterica* and pomegranate peel (*Punica granatum*), which are used to control parasites in cattle, goats and sheep (Shang et al., 2012). Also, some essential oils have an antimicrobial effect (Si et al., 2006).

Trauma and fractures: Plants from different families such as *Amaranthaceae, Apocynaceae, Convolvulaceae, Menispermaceae, Euphorbiaceae, Caesalpinoidae, Dodonaceae, Malvaceae, Sapotaceae, Menispermaceae, Cucurbitaceae, Poaceae,* are applied by contact for fracture treatment (Babu et al., 2024).

Reproductive Disorders of Ruminants

Chinese veterinarians have explored the pharmacology of the role of traditional Chinese medicine, to treat problems such as fertility, abortion and retained placenta of cattle (Chen et al., 2015; Zuo et al., 2016). The effectiveness of traditional Chinese herbs in improving fertility of livestock, is well documented (Wang and Ma 2005; Huang and Chen, 2008; Shang et al., 2012; Zuo et al., 2016). Traditional Chinese medicine therapy was reported to improve estrus and ovulation of infertile dairy cows by 94 % and 79.4 %, respectively (Luo and Gu, 2009). Also, the fertility of dairy cows improved by 77.8 % (Zuo et al., 2016). Also, trichosanthin, an active substance extracted from the root of Trichosannthes chino, improved placental discharge time (Zuo et al., 2016). Cooked *Leonurus japonicas* is orally administered to pigs to treat retained placenta (Xion and Long, 2020).

The effectiveness of Chinese herbs in combating the aforementioned ailments may vary according to their origin (Gong et al., 2014). That is, the active ingredients of these medicinal plants may lose potency in the face of changes in climate and geographical location where they are grown (Liu et al., 2012). In addition, the active compounds of most of the plants used are unknown, which is necessary for these control methods to be recognized in other regions outside China (Gong et al., 2014). In general, Chinese ethnoveterinary medicine has shown potential in the control of animal diseases and can replace common antibiotics. As they are natural products, they are easier for animals to tolerate, which also makes them safer for human consumption.

Conclusion

TCM has gained popularity worldwide, in part due to its holistic and preventive approach, as well as its effectiveness in treating a variety of conditions. Although it has been the subject of criticism and debate in Western medicine, many patients and health professionals value its ability to complement conventional treatments. Traditional Chinese medicine has emerged in the veterinary field as a promising alternative for the treatment of various diseases. Through methods such as acupuncture, herbal medicine and massage therapy, it offers a holistic approach that seeks to treat not only the physical symptoms of the animal, but also the root cause of its disease. This allows for a more complete diagnosis and treatment. Its Non-Invasive methods can be less stressful for animals and have fewer side effects. In addition to using natural resources such as herbs and medicinal foods, which can be gentler and safer for animals, reducing the risk of side effects associated with synthetic medications. It is essential to continue to research and gather scientific evidence to support the efficacy and safety of TCM in the veterinary setting and to develop standardized treatment protocols for optimal integration into clinical practice. Ultimately, the recognition and acceptance of TCM in veterinary medicine depends on a careful balance between tradition and science, with animal welfare always at the center of any therapeutic approach. In summary, TCM offers a holistic, preventive and complementary approach in the veterinary field, which can improve the overall health and well-being of animals, especially in the management of chronic diseases and in the prevention of health problems.

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Chapter 08

A Journey into Traditional Chinese Herbal Medicine and Therapeutic Effects on Diabetes

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ABSTRACT

The rise in living standards of people and environmental changes has increase the diabetes incidence. It has emerged as the major health threat in modern society and placing a major burden on public health. Different treatments for diabetes have been clinically used to bring effective curing results. Each year millions of dollars in United States, are invested on the treatment of this disease but these treatments are not always effective and can lead to serious effects. Traditional Chinese herbal medicines has scored experience of many years and scientific foundation which is expected to provide qualitative foundation for the management of diabetes. There is a great difference between these traditional philosophical based medicines and modern clinical medicines for the treatment of diabetes. At present Traditional Chinese Herbal Medicines (TCHMs) are achieving admirable attention from professionalisms due to unique clinical advantages. These herbal medicines are based on unique theories and practices for effective measures against several diseases. From previous decades, the scientific research on Chinese herbal medicines is increased to validate their clinical approach. Herbs are the most commonly used substances for the cure of many diseases. The major components present in these help to treat diseases naturally without any adverse effects on human body. Diabetes is mainly associated with the inflammation and herbal medicines help to lower the blood glucose followed by controlling inflammation. This chapter will discover the philosophical base and ancient roots of traditional Chinese medicines as well as theoretical base of these. The main concern is to find out some Chinese herbs and discover their effectivity for treatment of diabetes. The standardization and clinical position of these medicines for cure of disease is challenged internationally. We will look at the standardization and clinical position of TCHMs for the cure of diabetes.

KEYWORDS		
Traditional Chinese medicines, Chinese herbal medicines, Diabetes, Herbal medicines standardization	Received: 29-Jun-2024 Revised: 05-Jul-2024 Accepted: 18-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Diabetes is one of the most threatening human disease and the incidence of diabetes is increasing day by day. Different treatments for diabetes have been used clinically to bring effective cure of this disease. The existing treatments do not seem to be doing any improvements to the quality of life of diabetic patient but instead these are bringing burden on patients. Traditional Chinese medicine is significant part of human medicine and there is huge difference between these and modern concerning medicines (Sun et al., 2021).

Traditional Chinese medicine (TCM) is an emerging science and cultural asset that is preserved by Chinese people for thousands of years. TCM is one of the most admirable achievements of Chinese medicines and response of fighting against various diseases (Wang et al., 2021). At present TCM is achieving admirable attention from scientists due to unique clinical impacts (Shen et al., 2021). TCM based on unique theories and practices for effective measures against diseases and intensify health. The main TCM theories consist of disciplines of Ying and Yang and five most common basic Chinese traditional elements. These widely explain the activity of effects and strength of functioning in body. The prehistoric Chinese physicians hypothesized that everything is made up of the same substance and link all the functioning (Matos et al., 2021). It is a practice recognized by the holistic concept of harmony between human body and nature. In TCM human body diagnostic method comprises of some major aspects that are auscultation, inspection, olfaction, palpation and pulse taking (Ma et al., 2021).

The concerning branch of TCM is Traditional Chinese herbal medicines (TCHM) which is also called Chinese Materia Medica that follows the same symptomatic procedure as acupuncture and Qigong. The main concern of CHM is the favorable effects of herbs and food on body. These are categorized according to thermal nature, flavor, organ system nature and functional effect direction. The thermal nature has warming or cooling effect on body and flavor relates to five stages, then maintain a balanced or particular organ network (Rodrigues et al., 2023). According to thermal nature the warm herbs and food such as peeper, chili, ginger has heating/warming effects on body, eliminating internal and external cold, mobilizing defense energy and increasing "Yang". Contrarily the cool nature herbs and food such as tomato, banana has cooling effect on body, eliminating internal heat and providing calming effect. Snug and cool herbs provide compassionate effect on body that strengthen and supplementing body fluids. Herbal treatment is the most common treatment used to cure diseases and is popular in western societies (Matos et al., 2021).

Chinese herbal medicines bound the combination of practices of native systems of medicines and curative experiences of several previous generations. These are not directly used for the treatment of diseases as many clinical procedures are applied before application. From last decades the research efforts have been increased in developing and developed countries to scientifically validate herbal medicines for the treatment of many threatening diseases such as diabetes (Khan and Ahmad, 2019).

The study of Chinese herbs pharmacology and their mechanism of action is important to generate way to integrate TCM into western health care system and medicines (Matos et al., 2021). By using the hot syndrome with the cold nature medicine and cold ailment with the hot nature medicine provides the best justification of properties of CHM (Wei and Wang, 2019). In this chapter we will look at the ancient roots of CHM and their philosophical base. We will focus on herbal heritage, exploration of Chinese herbs, types of ingredients and their role for curing diabetes. Specifically, we are interested in current situation of CHM for the healing of diabetes. Then we will explore practices within CHM, clinical position regarding their curing capacities and medicinal formulas. We will start with the discussion of philosophical base and extend it towards the progress of these medicines to prove them much important as conventional drugs for curing diabetes.

Ancient Roots of TCHM and Their Philosophical Base

Traditional Chinese herbal medicines are the combination of ancient philosophy, primitive knowledge of medicines, clinical practices, religious beliefs and regional culture. The establishment of TCHM is totally different from so called modern medicines as these always revolve around disease diagnosis and treatment by developing the core theoretical foundation of native philosophies (Dong et al., 2018).

Yin and Yang

Yin and yang generally relate to any complimentary groups such as spiritual/material, internal/external, hot/cold, male/female and inhale/exhale. It is important to know that these pairs are not opposite to each other but extremes of same process. If one loses its existence, then the other is nothing without it. According to yin and yang if you need healthy and long life then you should not over insert something or nor too little. The imbalance of yin and yang shows the symptoms of illness. For a professional of TCHM there are some methods to diagnose disease which are by outer appearance, by listening, by questioning and by contact. The treatment will be established on the base of symptoms, nature and physical condition of patient. Medicinal herbs can attack diseases and Chinese doctors included nutrition and diet therapy as important factor of health (Wang and Qu, 2021).

Zang and Fu

The theory of Zangxiang is also called the theory of Zang-Fu organs because it focuses on the study of Zang and Fu organs. According to this ancient Chinese theory, all the organs are divided mainly into 5 Zang and 6 Fu organs. The 5 Zang organs are liver, spleen, kidney, lung and spleen. The 6 Fu organs are small intestine, large intestine, gallbladder, stomach, urinary bladder and the triple energizer. Beside Zang and Fu organs, there are many other organs that are similar to Zang organs in functionality and with Fu organs in structure such as brain, bones, vessels and uterus (Yang and Jia, 2013). This theory focuses on the physiological functions and pathological changes in the Zang and Fu organs. The professionals generally treat diseases according to these changes (Liao et al., 2017).

Five Elements

Five element theory is the mainspring of TCHM and depends on five elements i.e., wood, fire, soil, metal and water (Yun and Duan, 2009). These five elements relate to the body organs as according to this theory nature is a whole and body is the part of whole. Five elements are used to lay out the physiology, pathology, diagnosis and treatment in the field of TCM (Liu et al., 2021). There are cosmic interactions between five elements and specific body organs (Ling, 2020). The TCHM practitioner use questions that can create space for patients to discuss their illness leading to understand the body conditions and then treat disease with holistic concept. The five element theory is deeply related with the Yin and Yang theory to provide base for traditional medicines (Ling, 2020).

Occurrence of Diabetes in TCHM

Diabetes is one of the life threating and chronic disease of human (Mahajan et al., 2018). It is characterized by the increased level of glucose in human body that can damage heart, kidneys, lungs, nerves and many other organs with the passage of time (Mughal et al., 2021). Diabetes was noticed in the Chinese culture in past ancestry (Bernal-Mizrachi et al., 2007). The medical monograph of Qin dynasty named as "Su Wen Qi Bin Lun" mention diabetes as Xiaoke and Paidan for the first time. A medical book of that time stated that individuals with the internal poor visceral organs are mostly victims of diabetes that describe that it is not a single organ attacking disease. A medical scientist of the Qing dynasty stated that severe mood swing sensitivity, impatience and depression can promote diabetes. Ancient Chinese scientists believe that diabetes occur due to improper diet, emotional imbalance, heat due to the yin deficiency and excessive desire. Traditional Chinese medicines play important role in the treatment of diseases so it took the attention of researchers of many countries for the cure of diabetes (Sun et al., 2021).

Chinese Herbs for Treatment of Diabetes

Herbs are most frequently used substances in the TCM for the treatment of many complex diseases. TCM herbal formulas contain many complex ingredients that interact with various organs of body and effective for the treatment of diseases (Xu et al., 2019).

Azadirachta Indica

Azadirachta indica is a curative plant that usually found in tropical and subtropical areas. Different parts of this tree are used for treatment of various diseases such chicken pox, cancer, diabetes, ulcer, respiratory disorder and dermal complications (Saleem et al., 2018). It contains nimbidiol compound that inhibit maltase-glucoamylase, sucrose-isomaltase, lactase and trehelase (Mukherjee and Sengupta, 2013). It not only increases the uptake of carbohydrates by muscles but also has therapeutic impacts on complexities of diabetes and can help to improve microangiopathy and heart injury that comes in existence as a worst effect of diabetes (Sun et al., 2021).

Cichorium intybus L.

Chicory (Cichorium intybus L.), a perennial herb cultivated worldwide, has been used mainly as animal feed, in food industry and as a source for insulin production (Perović et al., 2021). The role of chicory for action towards diabetes has always been focus of herbal research institutions that have shown that chicory seeds can effect glucose forbearance and metabolic status at diabetic condition (Sun et al., 2021). It can improve calcium and glucose homeostasis, lower blood pressure, improve liver function and can lessen blood system risk factors in patients of type 2 diabetes (Farhangi et al., 2016).

Rhodiola rosea L.

Rhodiola rosea L. is frequently used as traditional Chinese medicine and considered to have therapeutic effects for many diseases such as cardiovascular diseases, diabetes, sepsis, cancer and neurodegenerative diseases (Pu et al., 2020). The main ingredient of Rhodiola (Salidroside) has hypoglycemic effect in the treatment of diabetes (Sun et al., 2021). The role of this plant is not limited to hypoglycemic effect in the treatment of diabetes but also has therapeutic effect on variety of diabetic complications that occur due to diabetes such as diabetic nephropathy (Shati and Alfaifi, 2020). Salidroside can improve insulin resistance and use in the clinical treatment of diabetes (You et al., 2020).

Cornus officinalis

Cornus officinalis is commonly known as "Shanzhuyu" in China and native to the Shaanxi province of China (Dong, 2018). The alcohol extracts from plant can increase insulin secretion and upgrade glucose metabolism. Beside of its hypoglycemic effects, it also has therapeutic effects on kidney, liver, β cells and blood vessels (Qian et al., 2001). According to a clinical researcher's team from Iran, this plant can be used for the treatment of type 2 diabetes. The extract from plant can maintain blood glucose control by improving the amount of insulin secretion and by maintaining TG serum level in blood in sufferers with type 2 diabetes (Sun et al., 2021).

Dendrobium officinale

Dendrobium officinale is an orchid herb, widely present in China as well as Asia, Oceania and America. According to TCHM, it can facilitate glandular secretion, protect digestive tract, kidney, lungs and eyes (Li et al., 2020). It has been found therapeutic for the treatment of diabetes (Pan Li Hua et al., 2014). It can reduce the occurrence of diabetic cardiomyopathy by discouraging inflammation, chain oxidative stress and fibrosis (Zhang et al., 2016).

Cordyceps militaris

Cordyceps militaris is one the most important traditional Chinese medicine that is difficult and dangerous to obtain (Cui, 2015). Among all TCHM, this plant is most effective for the treatment of diabetic enteropathy and enter in stages of clinical trials. It also shows therapeutic efficiency for the treatment of diabetic complications (Kai et al., 2015). The obtaining procedure of this plant is difficult so it is not feasible and budget friendly for most of the diabetic patients for long term use (Yu et al., 2016).

Mulberry Leaf

Dried leaves of Mulberry are one of the most important herbal medicines of TCM. It is very common to cultivate this plant in various parts of China (Hao et al., 2021). In modern Chinese and western medicines dried leaves of mulberry tree are used as the therapeutic drug for diabetes and many other complex diseases (Liu et al., 2016). This plant's leaves have medicinal properties, but its roots, fruit and branches are also utilized to make herbal remedies (Abouzed et al., 2020). It can stabilize blood glucose level and reduce the chances of diabetes (Min et al., 2020).

Tea

Tea is the most important and popular drink across the world that is also used as medicine (Ng et al., 2018). According to traditional medicines of China, tea is medicinal drink for all kind of diseases (Zhou et al., 2021). The function of tea for therapy of diabetes has been frequently studied by the researchers and green tea, black tea and oolong are most commonly studied in diabetic research (Meng et al., 2019). Tea has curing effects on the diabetic complications (Renno et al., 2008). It can reduce risk of diabetes in adults through better blood sugar control (Islam, 2011).

Clinical Standardization of CHM for Curing Diabetes

Traditional Chinese medicines has played important role for the cure of many diseases with an old tradition and 2500 years of practice and refinement (Li et al., 2007). The Chinese government has advised several standards to encourage the advancement in CHM. The Chinese pharmacopoeia is the foundation of national standards of TCM (Song et al., 2011). The drug standards of ministry of health provides quality standards for herbs and all herbal products in market regarding TCM (Pan et al., 2011). The Chinese government also set many standards for the development of pharmaceutical industry such as regulation for new drug approval, good clinical practices, good agricultural practices and good manufacturing practices (Gai et al., 2007). The current reality is that current national standards mainly focus on quality, identification and processing of TCHM. The clinical standards mainly describe the functions, the adverse effects and precautions etc. but the usage, dosage, properties and efficiency is based on the traditional Chinese theories. Chinese government has also focused on the promotion of internationalization of TCMs in previous years (Zheng et al., 2021). There are many limitations regarding promotion of clinical standards of TCHM in western world (Louët, 2004). This is because the way of action of these medicines is complex and based on philosophical or holistic concept rather than course of medicines and diseases (Gai et al., 2008). Thus some professionals think, it is based on mysterious interpretations rather than scientific evidences (Stone, 2008). In the previous years there have been several randomized controlled clinical trials to compare TCHM and western medicines for the cure of diabetes (Li et al., 2007). Recently professionals built a combination to predict components of herbal medicines based on their chemical components (Long et al., 2011).

Conclusion

Traditional Chinese medicines follow the philosophical base, religious aspects and experimental practices to provide cure of many diseases. These traditional treatments focus on the condition of patient and symptoms rather than focus on the course of disease and medicines. According to Chinese philosophies all the things are made up of same material and the imbalance shows symptoms of diseases. Diabetes is one of the major diseases for which these medicines are now clinically considered. There are many herbs that are used for the treatment of diabetes. These help to lower the glucose level of blood and decrease the incidence of diabetes. These herbs help human body to maintained blood glucose and insulin level and normalize body condition. The efficiency of these herbs are considered beneficial for cure of diabetes but these are facing many problems in proving their validity in clinical research. The main reason is their complexity and their working mechanisms. Many researchers are working on these to standardize their position clinically. But the current evidences are not enough to promote TCHMs for the treatment of diabetes clinically. Chinese herbal medicines have great potential for treatment of diabetes and deserve more clinical attention. The more collaboration between modern and traditional doctors is required to get effective results.

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Chapter 09

Ginseng Root as Old Traditional Medicine and Therapeutic Effects on Cancer

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ABSTRACT

An important obstacle to the current anticancer therapy is the presence of cancer stem cells (CSCs), a popular or rare subpopulation of cancer cells that exhibit stem cell-like traits such as self-renewal and divided in a multi-stage lineage state via divisions that are symmetric or asymmetric division. CSCs are responsible for tumor initiation, heterogeneity, progression and recurrence. Even though CSCs play a significant role in the development of cancer and its progression, existing anticancer therapies cannot completely eradicate CSCs. Furthermore, the restricted therapeutic windows and efficacy of the anti-CSC medicines currently on the market point to the need for the optimization and development of a novel anticancer agent that targets CSCs. The traditional use of ginseng includes improving immunity and easing tiredness. Since ginseng has been used for so long and has proven to be safe it has become more well-known for its possible pharmacological qualities which may include anticancer benefits. The active components of ginseng, such as its saponin (ginsenosides) and non-saponin compounds have been the subject of various studies. These investigations have also revealed the pharmacological activities of the plants, which include anti-fatigue, anti-cancer and antidiabetic. In this chapter we will discuss about

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INTRODUCTION

Cancer remains a formidable global challenge, with its devastating toll continuing to escalate. By 2020, projections indicated that approximately 24.6 million individuals globally would be affected by cancer, constituting 12.5% of total deaths. This burden is particularly significant in China, where average of annually admitted patients suffering with cancer is more than 3 million, resulting in 2.5 million deaths (Hao and Chen, 2012). The WHO categorizes cancer as a chronic health concern comparable to hypertension and diabetes, with its prevalence rapidly escalating worldwide, set to become a significant source of death and sickness in the next decades. By 2030, the global death toll from cancer is expected to surpass 11 million. Population growth and aging are driving factors in this anticipated rise of cancer cases which can be projected from 12.5 million in 2008 to 20.7 million by the end of this decade. The profound impact of cancer underscores the urgent need for comprehensive strategies encompassing prevention, early detection, and treatment advancements to mitigate its devastating effects.

In the ancient times cure of cancer was done through different homebased traditional remedies and its cure was quite impossible. One in the millions people will be able to survive. There are several Chinese traditional medicines (TCM) which are used to cure different health problems in ancient times including herbal medicine, acupuncture treatments, therapy (tui na), meditation (qigong), and food treatment and ginseng root. Ginseng is basically a plant tuber which have curative or therapeutic abilities. It is widely recognized for its anti-inflammatory and anti-oxidant properties. It may also help manage blood sugar levels and treat some forms of cancer. Furthermore, ginseng may boost the body's defenses, expand brain task, lessen weariness or also decrease inflammation. Ginseng is widely known as a symbol of health vitality and wellness in all over the culture and in TCM. Ginseng had a wide use in ancient times and plays a great role as medicinal herbs spans millennia (Leung and Wong, 2010). The Panax genus, which includes ginseng species, is well-known for its therapeutic benefits, with the root being used in decoctions, teas, and powders to improve health and wellness. (Christensen, 2008).

Cancer is a chronic disease which can be cured by traditional methods. The objective of traditional cancer treatment (TCM), which includes surgical treatment, chemotherapy and radioactive therapy, is to improve the patient's quality of life (QOL) while either curing the disease or prolonging life (www.who.int).

It is recognized that the majority of cancer patients experience symptoms from both the illness and from the treatmen ts they receive. Traditional Chinese medicine (TCM) is a complete medical system that includes qigong, herbal medicine, acupuncture, tuina, and nutritional treatments (Liu et al., 2011). Anticancer treatments such as surgery, chemotherapy, radiation, targeted therapy, and immunotherapy are used to slow tumor development, increase survival time, and enhance quality of life. However, these therapies have disadvantages, such as inaccurate diagnosis, surgical difficulties, and resistance to standard treatments. Targeted therapy, a newer kind of cancer treatment, may more accurately detect and destroy cancer cells, but it can also have adverse effects on healthy cells. Immunotherapy, which includes cytokine infusions, cancer vaccines, and T-cell treatment, can boost immune cells to increase anticancer activity, but the advantages and costs remain unknown. Cancer prevention and treatment require more effective or complementary medicines. Ginseng root, a staple in traditional medicine for centuries, has garnered significant attention for its potential therapeutic effects on cancer (Attele et al., 1999). Renowned for its adapt genic properties and myriad health benefits, ginseng has been used in various forms across cultures, particularly in East Asia, as a remedy for ailments ranging from fatigue to immune system enhancement (Jang et al., 2010). Recent scientific studies have delved into its anti-cancer properties, exploring its ability to inhibit tumor growth, induce apoptosis in cancer cells, and mitigate chemotherapy side effects (Yun et al., 1980). Use of ginseng in traditional medicine, delve into its molecular mechanisms of action against cancer, and highlight the latest findings supporting its potential as an adjunctive therapy in cancer treatment. Through a synthesis of historical knowledge and contemporary scientific evidence, ginseng root is very effective in the fight against cancer. So in this chapter we will discuss the overview of ginseng root and its therapeutic effects on cancer, chemical composition and active components of ginseng, ginseng and cancer managements, and future challenges and directions.

Ginseng Root as Traditional Medicine

A popular herb in traditional Chinese medicine is Panax ginseng also known as ginseng (Hsu et al., 2013; Li et al., 2017). Ginseng from specific origins is more valuable than ginseng from other origins, the economics of ginseng production depend on a trustworthy technique for distinguishing geographical origin (Horacek M et al., 2010). Ginseng was originally recognized by the people of Korea aand Manchuria, and that it later traveled to China and was utilized as a medicine (Yang and Yeo, 2004). The majority of ginseng legends originate from Korea, with a small number from China and Japan. According to Korean folklore, the discovery of mountain ginseng preceded cultivation, meaning that cultivation started wherever and whenever seeds were discovered. Legends state that ginseng production dates back 1,500 years, mentioning the growers' family name and place. Growers of ginseng referred to the stem as "Joolg" rather than "Jool Gi", suggesting that ginseng cultivation may have started long ago at that point. Dong Yi's Bear Family was closely related to Osagoo and Shen Nong, indicating that ginseng farming at a rudimentary stage may have existed 4,000 years ago (Park, 2002).

More than 400 of the 11,146 medicinal species that the ancient Chinese recognized from 383 groups are currently in widespread usage worldwide (Drašar and Moravcova, 2004; Soleymani and Shahrajabjan, 2012; Ogbaji et al., 2018). p. ginseng is frequently referred to as the "king or lord of herbs" and highly valued in traditional Chinese medicine (TCM) across the majority of the world (Peng et al., 2008). East Asian ginseng, a member of the Panax genus and the Araliaceae family of plants, is commonly used as a herbal remedy due to its many health benefits (Wang et al., 2019). People from those regions have been using ginseng root and extract for the past 2000 years as a stimulant to reduce stress and weariness , bolster the body and mind, delay aging, and boost energy (Choi , 2008).

The main purpose of Korean Panax ginseng is to maintain the body's homeostasis. Modern science has identified the pharmacological efficiency of Korean gingseng as improved brain function, pain relieving effects, antitumor activity and preventive effects against tumors, enhanced immune system function, anti-diabetic effects, enhanced liver function, adjusted blood pressure, anti- fatigue and anti-stress effects improved climacteric disorder and sexual functions (Leung and Wong, 2010).

Axos, which means "medicine”, and pan, which means "all", are the Greek roots of the species Panax, which was initially utilized by the Russian botanist Carl A. Meyer. This suggests that ginseng is a panacea for all ailments. It was determined that Ginseng was safe medical herb that could be used on a regular basis to boost energy (Yun, 2001).

Chemical Composition of Ginseng

Carbohydrates, nitrogen containing chemicals, fat-soluble components, and ginseng saponin (ginsenosides) make up the chemical composition of ginseng. The molecular structures of about thirty different ginsenosides types have been identified. Ginseng saponin is found as a glycoside, which is an aglycone and sugar combination; hence the term ginsenosides. Ginsenosides the main active ingredient in Korean ginseng has mostly been utilized to define the ginseng quality standards. In addition, Korean ginseng has other useful compounds besides saponin, like antioxidant-rich phenolic compounds, cancer cells cytotoxic polyacetylene, essential oil sesquiterpene and acidic polysaccharides that are being researched extensively in relation to immune responses (Park, 1996). In addition to ginsenosides, P. ginseng is reported to include a variety of other potentially bioactive ingredients, including phytosterols, sesquiterpenes, flavonoids, polyacetylene, alkaloids and phenolic compounds. These ingredients may combine with ginsenosides to produce a range of effects. According to certain accounts ginsenosides work in tandem with other small substances to achieve their advantageous effects rather than acting alone. It remains unclear how the various component combinations interact to create the clinical effects of P. ginseng, despite prior attempts to comprehend the molecular mechanisms (lee et al., 2004; Richter et al., 2005; Houng et al., 1998).

Therapeutic Effects of Ginseng on Cancer

Network pharmacology by using techniques from systems biology, has become a valuable tool for comprehending how medications act therapeutically in complex biological systems (Hopkins, 2008). Specifically, it has been widely used in numerous research, including the identification of active substances and the prediction of active substances and the prediction of possible targets to assess and clarify the therapeutic benefits and mechanisms of herbal medicines (Li, 2013; Zhang et al., 2019). Ginseng is one of the most popular or famous natural products in the world and has been widely recommended to treat diseases and help for promoting health (Kim et al., 2024). Natural goods have long been considered promising candidates for pharmaceutical and efforts to identify natural products with anti-cancer properties are on the rise. Ginsengs varied pharmacological actions have made it a valuable tool for cancer medication research. Many researches have demonstrated ginseng anticancer properties (Ahuja et al., 2018; Lee et al., 2018; Kim et al., 2016). The necessity to determine the mechanism of action has increased in this field as numerous research have demonstrated the promising anticancer impact of chemicals derived from ginseng. Ginseng exhibits anticancerous effects in multiple facets of cancer progression, including as proliferation, invasiveness, angiogenesis and the establishment of drug resistance owing to its diverse range of bioactive chemicals (Kim et al., 2023; Yu et al., 2018). In particular, research has shown that ginseng derived chemicals make cancer cells more sensitive to anticancer treatments, suggesting that ginseng also reduces tumor heterogeneity (Li et al., 2015; Lee et al., 2014).

Ginseng Compounds and Pathways

Wnt/β-catenin Pathway and Derived Compounds of Ginseng

The Wnt/β-catenin route was first found to be activated in breast cancer but it has also been found in other cancer types. The Wnt/β-catenin pathway is essential for the survival of CSCs in a variety of cancer types including cutaneous and colon cancers (Vermeulen et al., 2010; Merlos-Suárez et al., 2011). Numerous studies have shown that different forms of ginsenosides can suppress the Wnt/β-catenin pathway in cancer cells, adipocytes and normal stem cells (Deng et al., 2017; Chen et al., 2022).

The Notch Pathway and Derived Compounds of Ginseng

This process releases the transcriptional regulator Notch intracellular domain (NICD) and is successively mediated by secretase and ADAM- family metalloproteinase (Saygin et al., 2019). Many of the pharmacological effects of ginsenosides have been reported to be mediated by the Notch pathway (Li et al., 2024). In cancer cells ginsenosides also takes part in the indirect control of the Notch pathway. Additionally, this discovery supports earlier discoveries that MDSCs give breast cancer cells stem- like characteristics NY interacting with the Notch and STAT3 pathways (Peng et al., 2016).

The Hedgehog (Hh) Pathway and Derived Compounds of Ginseng

The main components of the Hh pathway are smoothened (SMO) and patched (PTCH) proteins (Jiang and Hui, 2008). There have been some findings in lung cancer models, despite the fact that the relationship between ginsenosides and the Hh pathway has not yet been thoroughly investigated. In lung cancer cells, Rh2 suppressed the growth and the production of epithelial markers and further reduced the Express of genes involved in the Wnt or Hh pathways. According to proteomic studies Rh2 inhibits the Hh pathway by activating a-catenin, which prevents β-catenin and GLI from building up (Zhang et al., 2020).

Future Directions

Due to a lack of evidence the physiological activities and underlying processes of ginseng pharmacopuncture are still unclear. Animals have been the primary subjects of research on the safety of ginseng pharmacopuncture injections; nevertheless, additional empirical studies are required to confirm its safety in humans. To illustrate the pharmacological mechanism of ginseng pharmacopuncture and create the most effective solution in the future, studies on the pharmacokinetics of active components such as ginsenosides, polysaccharides, fatty acids, essential oils, and phenolic compounds as well as interactions between multiple components (e.g., a synergistic it antagonistic effect) of ginseng solutions for pharmacopuncture are required. Future research should examine the ingredients and effects of ginseng solutions prepared using different extraction techniques, starting with examining the pharmacokinetics and pharmacological interactions of each component in ginseng pharmacopuncture solution.

Future applications of ginseng pharmacopuncture technique will demonstrate its safety through a range of toxicity tests, including those that assess gene toxicity, carcinogenicity, development toxicity, toxicity from single of repeated dose administration, and patient efficacy through a large scale randomized controlled trail (RCT) with a suitable placebo control.

While ginseng pharmacopuncture has been utilized extensively in TKM clinics firmly contend that additional hard data is required in order to make the therapeutic modality safer and more generally employed in the future (Lee et al., 2019).

Conclusion

The anticancer potential of substances produced from ginseng is great, in spite of few restrictions. Ginsengs well established safety is its biggest benefit. Although the safety of ginseng extract varies depending on the specific ingredient, studies showing minimal cytotoxic effects on normal cells have led experts to predict relatively low toxicity. The synergistic effect in conjunction with traditional chemotherapy is very encouraging. Numerous studies have noted this in relation to controlling cancer stemness. For patient's ginseng can be utilized as a supportive therapy while more mechanistic research is needed for its proper use as the medicine for the treatment of cancer. Furthermore, these chemicals ability to target CSC in a wide range of cancers raises the possibility that they could be employed to treat different forms of cancer. This is because different types of compounds have different chemical pathways linked to their function. Thus, numerous preclinical studies have shown the anticancer properties of ginseng derived chemicals therefore further research will need a deeper understanding of the mechanism of action for their usage as anticancer medicines.

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Chapter 10

Environmental Knowledge and Biocultural Memory in Ethnoveterinary Practices, the Case of Mexico

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ABSTRACT

It is estimated that 60% of infectious diseases in humans are zoonotic. The COVID-19 pandemic increased concerns about issues such as antimicrobial resistance, food safety and environmental health. As a result, the WHO proposed the "One Health". At present, rural communities preserve extremely important traditional knowledge that contributes to global-scale problems. For example, the use of medicinal plants in livestock production provides evidence of empirically learned knowledge that helps to reduce the use of antimicrobials by offering a more natural alternative. The objective is to document the relationship between environmental knowledge and ethnoveterinary practices currently used in rural communities in Mexico. It is important to recognize traditional knowledge that contributes positively to the "one health" approach. Among the main findings is the diversity of medicinal effects that a single plant can offer, including its usefulness as anti-inflammatory, antimicrobial, immune stimulant, antiparasitic, among others. Currently, in Mexico there are rural communities that conserve and socialize this ethnoveterinary knowledge, recognize the medicinal benefits of plants, which serve as auxiliaries in the care of backyard animals. It is concluded that the use of medicinal plants in animal production is a sustainable alternative and also reflects the preservation of biocultural knowledge.

KEYWORDS		
One health, Ethnoveterinary, Antimicrobials, Zoonosis, Traditional knowledge.	Received: 09-Jun-2024 Revised: 15-Jul-2024 Accepted: 08-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Livestock activity in rural areas is presented as an alternative to reduce poverty, in addition to commercialization, part of it is destined for self-consumption (Espinoza et al., 2007; Trenti-Very et al., 2022). Among the constant problems in this sector are diseases that attack the digestive and respiratory systems of animals such as cattle, sheep, horses, poultry and rabbits.

Worldwide, there is increasing concern about the misuse of antibiotics, which, in addition to affecting animal health, has a negative impact on the human health. This is due to the high level of toxic residues contained in medicines and agrochemicals used in livestock production (Márquez, 2008) and are found in derived products such as meat, eggs, milk and honey (Beyene, 2016).

According to the Food and Agriculture Organization (FAO) of the United Nations (2024), 60% of the infectious diseases that humans can contract are related to bacteria, viruses, parasites or non-conventional agents due to zoonotic and food-borne diseases of animal origin. In addition, antimicrobial resistance is a growing problem. According to the Pan American Health Organization (PAHO) (2022) resistance occurs when microorganisms (bacteria, fungi, viruses and parasites) undergo changes when exposed to antibiotics, antifungals, antivirals, antimalarials or anthelmintics, among others. Therefore, the inappropriate and excessive use of these drugs increases the risk of spread in humans, animals, food and the environment. This is why, countries such as Peru and Argentina have banned the use of antibiotics such as colistin. (PAHO, 2022).

In addition to the sanitary and environmental problems, the use and supply of veterinary drugs also represent a high cost for producers (Espinosa, 2022). It is therefore necessary to rethink new strategies to reduce the health risk in humans and animals, as well as in economic, environmental and food safety aspects. International concern resulted in the "one health" approach that seeks a balance between human health, animal health and the environment (FAO, 2024), due to the direct link between these elements, it is necessary to find alternatives that contribute to minimize this problem.

The ethnoveterinary practices offer a sustainable alternative in environmental, socio-cultural and economic terms, that is, by using medicinal plants in the livestock production, the risk of creating antimicrobial resistance is reduced, preserving traditional knowledge, offering low-cost alternatives and improving the quality of meat and meat products. It should be noted that these activities are directly related to environmental knowledge in rural areas, as a result of the daily coexistence with the floristic diversity that is distributed in different areas of their territory. This knowledge has allowed them to know and use the biodiversity that surrounds them. In addition to this, there are the meanings that have been given to the flora that grows in different areas, because in addition to identifying some species as food, forage and housing, humans also recognize them for their medicinal benefits. This convergence between biological and cultural elements reveals the biocultural nature of this knowledge, transmitted from generation to generation, which also provides sustainable alternatives for livestock production. The purpose of this chapter is to document the relationship between environmental knowledge and ethnoveterinary practices that are currently used in rural communities in Mexico and that are constructed in the bicultural memories of those who possess this knowledge, the purpose of this documentary review is to make this knowledge and its importance as a contribution to the "one health" approach visible.

Methodology

A compilation, selection and systematic review of scientific articles available in databases of the following scientific journals was carried out; Science Direct, ResearchGate, Springer, Google Scholar, in addition to reviewing the websites of institutions such as the Food and Agriculture Organization of the United Nations (FAO) and the Pan American Health Organization (PAHO). Keywords such as "one healt" and "ethnoveterinary" were used and 75 articles were located, of which 38 were used because of their contribution to the fulfillment of the objective of this chapter.

Ethnoveterinary as a Contribution to the "One Health" Approach

Nowadays, the concern for healthier food consumption has increased due to the increase of chemical residues found in foods such as meat and poultry (Mangaberia da Silva et al., 2020). The increase of zoonotic diseases has a negative impact on human and animal health, as well as on the environment and the economy. The "One Health" approach highlights the intrinsic relationship between the health of people, animals and the space they share (González and Pimienta, 2022). It is therefore necessary to reduce the improper use of antibiotics in livestock production and to resume traditional practices such as the use of medicinal plants in the treatment of diseases, as it provides a more sustainable alternative for human health and an economic benefit to producers due to its low costs.

According to Balogun et al. (2019), plants produce substances such as terpenes, phenols and nitrogen-based compounds that benefit humans and animals, thus, offering treatments with medicinal plants provides positive results in production, in addition to being accessible and more economical (Rafique et al., 2021). Several scientific studies have documented the contributions of ethnoveterinary in livestock production, this type of practices that integrate the use of medicinal plants for animal health care offer a sustainable alternative in this sector (Chaachouay et al., 2022, Jaurez et al., 2022; Lee et al., 2022; Mendoza et al., 2022; Velázquez et al., 2019; Bhardwaj et al., 2011).

Bharti et al. (2016) conducted an analysis of *Withania somnifera* where they identified the medicinal benefits as an antifungal and antimicrobial agent, resulting from chemical actives such as alkaloids, steroidal lactones, withanolides and saponins. García et al. (2017) concluded that the use of *Chenopodium ambrosioides* can be an alternative in the diet of rabbits, because despite not resorting to any veterinary treatment, there was no mortality rate, the active compounds such as terpenes give it an anthelmintic effect antihelmíntico (Jaramillo et al. 2012) which contributes positively to animal health care.

Another species used in ethnoveterinary medicine is the *Curcuma* L., Molosse et al. (2018) used a concentrate of this species in sheep, which helped to boost the immune system because of components such as curcumin, this species is recognized in ethnoveterinary practice for its antifungal, antiparasitic and antibacterial functions (Mesa et al., 2000).

One of the most widely studied plants for its medicinal benefits is the *Azadirachta indica*, García et al. (2023) proved that the topical use of *Azadirachta indica* helps positively in the reduction of the *S. acaberi* mite. For its part Ikpendu et al. (2024) identified that the use of this species increases the immunomodulatory effects to attack the Newcastle disease virus in poultry. Similar effects of the uses of *Thymus vulgaris L*., which according to the reports by Belali et al. (2022) is a more sustainable alternative for broiler breeding, as it helps the immune system. The acaricidal effect of *Thymus vulgaris L*., on the red mite present in poultry was highlighted by Torres et al. (2023). Another species with favorable results in ethnoveterinary practice is *Allium sativum*, Pinzón et al. (2020) corroborated that the use of this species improves meat quality due to its antimicrobial effect and Saastamoinen et al. (2019) confirmed its reliability as an expectorant in equines.

The contribution of the scientific sector is relevant because the use of polyherbal mixtures offers a more sustainable option in livestock production (Jaurez et al., 2022; Lee et al., 2022; Mendoza et al., 2022; Velázquez et al., 2019), these practices contribute directly to the "one health" approach, since they offer more economical and less harmful alternatives for humans, animals and the environment. Among the objectives proposed by "One Health" is to reduce the spread of zoonosis and antimicrobial resistance, taking as a reference that the latter belong to the same families used in antibiotics used in humans, so the risk of increasing bacterial resistance is present (Zunino, 2018).

In the scientific sector, the use of medicinal plants offers favorable results; the chemical composition of certain species results in efficient medicinal effects (Table 1), which, in addition to offering sustainable alternatives in ecological terms, contributes to reduce the risk of contagion by zoonosis and reduces the costs in this sector.

Table 1: Medicinal effects of various plants.

Scientific name	Family	Composition of biochemistry	Main effect	Reference
Allium sativum L.	Amaryllidaceae	Phenols, polyphenols, phytosterols, vitamin A and C.	Antimicrobial, antidiabetic, antiparasitic, immunostimulant, anti-inflammatory, antioxidant, anthelmintic.	Pinzón et al., 2020; Saastamoinen et al., 2019; Ramírez et al., 2016.
Curcuma longa L.	Zingiberaceae Martinov	Curcumin, demethoxycurcumin, bisdemethoxycurcumin	Anticancer, anticoagulant, anti-inflammatory, antimicrobial, antioxidant, immunostimulant.	Sainz de Cos, 2014; Witkin, J. M. and Li, 2013; Mesa et al., 2000.
Chenopodium ambrosioides L.	Amaranthaceae	α-Terpinene, p-cymene, 4-carene, trans-ascaridol, carvacrol. monoterpenoids, sesquiterpenoids and flavonoids.	Analgesic, anthelmintic, antioxidant, antiparasitic.	García et al., 2017; Jaramillo et al., 2012;
Azadirachta indica A. Juss.	Meliaceae	Azadirachtin, nimbidine, sodium nimbidate, nimbolide, gedunin, gallic acid, margolone and polysaccharides.	Anticancer, anthelmintic, antihepatotoxic, antipyretic, anti-inflammatory, antifungal, antiparasitic, antiseptic, antiulcerogenic.	Ikpendu et al., 2024; Gualtieri, 2004; Pijoan, 2004.
Thymus vulgaris L.	Lamiaceae	Flavonoids, such as luteolin, apigenin, naringenin, eriodictol, cirsilineol, salvigenin, cirsimaritin, thymonin and thymusin. In addition to triterpenes (ursolic and oleanolic acids), saponins, tannins	Antibacterial, astringent, spasmodic, antitussive, antiseptic, expectorant.	Torres et al., 2023; Belali et al., 2022.
Withania Somnifera (L.) Dunal	Solanaceae	Alkaloids such as: Isopelletierina, Anaferina, Cuseohigrina, Anahigrina, Tropina. In addition to withanolides, withanoferins, saponins.	Adaptogenic, antibacterial, anti-inflammatory, soothing, cardioprotective, immunostimulant, neo-protective.	Periyasamy et al., 2023; Bharti et al., 2016

Source: Own elaboration, 2024.

Scientific research has made it possible to identify chemical components found in various plants. to which antimicrobial, immunostimulant, anti-inflammatory effects, among others, are attributed. It is worth mentioning that this is the result of approaching the ancestral knowledge that rural communities have around the world.

Traditional Knowledge and Ethnoveterinary Practices

The use of medicinal plants in rural communities is part of the inheritance between generations, these practices reflect the environmental knowledge of the surroundings and also, it is a more economical alternative for the prevention of diseases in livestock production (Jaurez et al*.,* 2022). This ethnoveterinary knowledge has been built and tested through the experience of men and women in the backyard animal husbandry.

Mexico is one of the countries with the greatest biodiversity in the world, which allows rural communities to take full advantage of the flora that is collected and cultivated in these territories. One of the most widely used species in the rural environment is the *Allium sativum* L., Santos and Hernández (2023) documents its use in the prevention of respiratory diseases, endoparasites and diarrhea in poultry-by-poultry producers San Cristóbal Amatlán, Oaxaca. This species can be offered in remedies such as water with vinegar and garlic for the treatment of influenza in chickens in communities of Tabasco (Nava et al., 2018) is also used by women in the Altos de Chiapas for submandibular edema in oviniculture (Perezgrovas, 2014). Camacho et al. (2009) documented the use of *Allium sativum L*. to treat Newcastle disease in turkey guinea pigs in communities of the Costa de Oaxaca.

The use of local plants denotes the biocultural knowledge that rural communities in Mexico possess, that is, in addition to recognizing the flora that grows in the spaces they inhabit, they also give it a medicinal meaning that is part of their cultural expressions inherited within the family nucleus. This is why species such as *Senecio salignus* is commonly used for digestive system affections in animals such as horses, cows and sheep in communities of the Zongolica mountain range in Veracruz (Torres and Martínez, 2021).

The ethnoveterinary medicine reflects local knowledge and practices that are built over time and that are shared within the family and community nucleus. This corpus integrates symptoms in the animal, suitable plants and the elaboration of remedies. For example, when a sheep or goat has abdominal pain, according to producers in Coixtlahuaca, Oaxaca, it presents symptoms such as lack of appetite and low energy is offered tea of *Mentha spicata* L., *Matricaria recutita* L. y *Origanum vulgare* L. (Salinas et al., 2017).

The use of medicinal plants is an alternative that allows rural populations to minimize the use of antibiotics, for example, in Santa Maria del Oro, Nayarit, in order to expel placental residues, cattle producers first use leaves of *Vitex mollis* Kunth cooked in the pasture (Pérez et al., 2019). The existing knowledge on medicinal benefits provides a glimpse of a contribution to the "one health" approach, as it integrates environmental, economic and cultural elements (Figure 1).

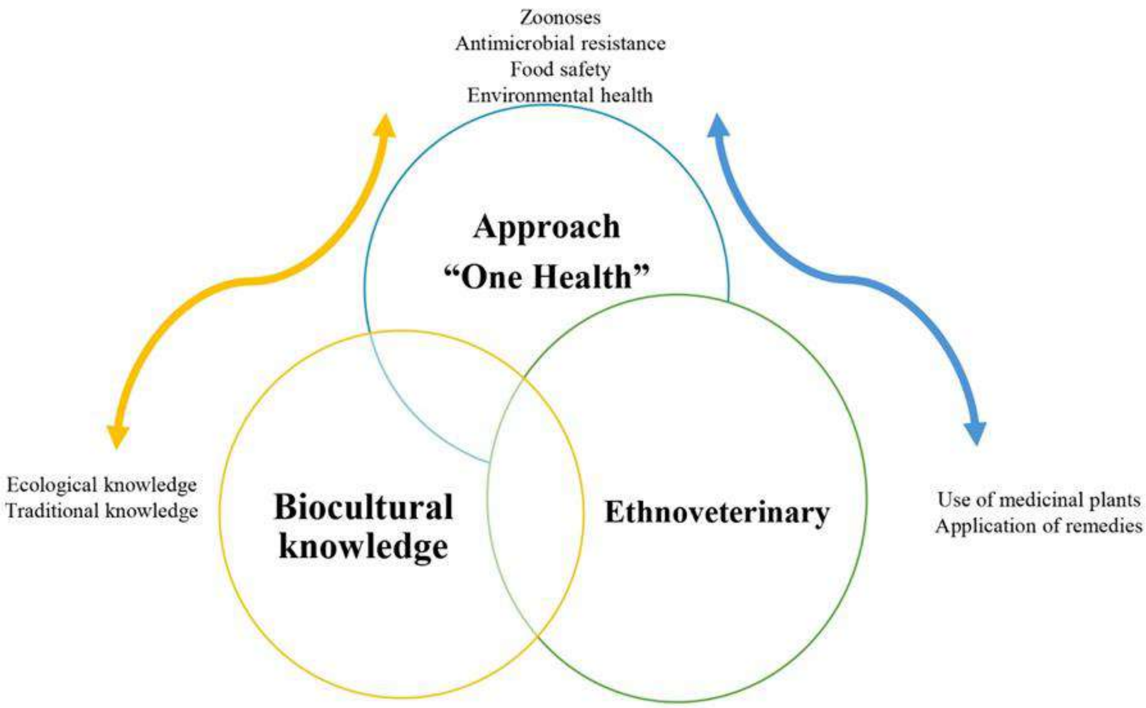

Fig. 1: Relationship between bioculturality and ethnoveterinarianism. Source: Own elaboration, 2024.

Biocultural knowledge integrates biological and cultural elements, which are reflected in the use of medicinal plants in backyard animal production. These practices contribute to the one health proposal since they offer sustainable alternatives in ecological, economic and food safety terms. The central point where sociocultural knowledge, ethnoveterinary science and the one health proposal converge makes visible the importance of conserving traditional knowledge, these contribute to the availability of flora but also to the continued use of medicinal plants and allow new forms of management in animal production.

The ethnoveterinary practices in rural communities integrate elements that are part of biocultural knowledge. Women and men use medicinal plants that they identify as suitable for treating certain diseases and ailments in their livestock. They even recognize the characteristics and behaviors of animals when they are sick, which shows that knowledge is holistic and is socialized among family and community members, even in spaces such as local markets. This knowledge is current and practiced, so that the conservation of this type of praxis offers alternatives that contribute to the "one health" approach, since in the first instance natural alternatives are used, which, according to what has been learned, are less harmful to animals and therefore to humans.

Conclusions

After the pandemic caused by SARS-CoV 2, the concern about facing a new zoonotic pandemic increased, resulting in awareness of the indiscriminate use of antimicrobials in livestock production. For this reason, it is necessary to take up biocultural knowledge that is preserved in rural communities, since these practices reflect the uses and management of the territory, but also their concern to offer healthier food. It should be noted that the use of medicinal plants in livestock production is directly related to culture and includes different forms of management and use of the territory, in addition to integrating an ancestral empirical process, which denotes a dynamic knowledge that has developed over the years and according to the experiences of those who practice it. The ethnoveterinary knowledge is still alive in rural communities and it is of utmost importance to preserve it, since local knowledge can contribute to and reduce problems that affect the world. The "one health" approach seeks to reduce the inappropriate use of antimicrobials and for this reason, it is important to return to traditional practices that are sustainable in environmental, social and economic terms.

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Chapter 11

The Biological Significance of Manuka Honey

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ABSTRACT

Honey is a pure natural organic product, commonly used as food and medicine from ancient times. Manuka honey has globally recognized as most competent type of honey which is derived from diverse origin of New Zealand and Australia. It has multiple unique properties to add its therapeutic worth in the medicine. These exponential qualities are attained due to complex composition of manuka honey in which phenolic compounds are the most abundant than other honeys in the global market. Manuka honey is a main contributor to cure many infections which are facing antimicrobial resistance now-a-days like *Pseudomonas aeruginosa, Proteus mariabilis, Enterobacter spp., S.aureus, S.epidermidis, E. coli,* and MRSA (methicillin resistant S*taphylococcus aureus*). Moreover, it has evident curative role in oxidative stress, cancer, and any kind of wounds. These beneficial properties are rising the need and interest of using manuka honey in the medical world.

KEYWORDS
Manuka, Honey, UMF, Antibacterial properties

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INTRODUCTION

Honey is a natural, sticky, flavorful, sweet, and highly nutritive food product which is being consumed alone from the earliest times in the human history (Alvarez-Suarez et al., 2014). Besides a natural component of human food, it is a wonderful cost-effective medicinal product with multiple bio-active qualities such as anti-inflammatory, antibacterial, antioxidant, wound healer, and anti-cancerous properties (Patel and Cichello, 2013; Alvarez-Suarez et al., 2013; 2014). Honey has wide range of other activities in cosmetics (Juliano and Magrini, 2018; Kowalczuk et al., 2023), dermatological problems, preservation and moisture provision to the skin and wounds (Pavlačková et al., 2020). It is a natural botanical product of bees which collect flower nectar and secretions of flower sucking insects and break it down into simple sugars to form honey in the hive. After which it goes through various processing units to be purified for human consumption and use for medical treatments. It has variety of flavors, odour, color and consistency depending upon the type of flower nectar (Teye et al., 2024). The honey production depends upon the season variations, honeybee keepers, and the purposeful usage in the subsequent fields like research, medicine, food etc. In 2019, the annual estimated production of natural honey is about 1.85 million tons globally which is recently reported by Fei et al., (2024). China is the largest honey producer as well as exporter with approximate production of 200,000 tons yearly (Fei et al., 2024; Teye et al., 2024).

Despite of emerging trends of modern chemo-therapies in medical field, honey has not lost its significance due to its powerful antimicrobial and wound healing capacities (Patel and Cichello, 2013). There are variety of commercial honeys being available in the global market (such as acacia, alfalfa, heather, clover, apple and orange blossoms, dandelion and many other wildflowers) but manuka honey is the most popular and effective honey which distinguish it from the rest of honeys. The medical significance of manuka honey is due to its unique antimicrobial responses that are not achievable with most effective chemical drugs. This feature adds to the medicinal values of manuka honey with respect to the rest of medical drugs and homeo-therapeutic treatments (Carter et al., 2016)

Origin of Manuka Honey

Manuka (*Leptospermum scoparium*) is basically a shrub, natively found in the New Zealand and the South East

Australia (Alvarez-Suarez et al., 2014; Johnston et al., 2018). This plant was named as Manuka from the Maori language of the local community in New Zealand. It is an aesthetic plant having white, red and pink colored flowers, often used for garnishing in Southern California (Patel and Cichello, 2013). Manuka honey is a fresh raw material of manuka plant produced by specific bee i.e. *Apis mellifera* honey bees (Johnston et al., 2018). However, *A. mellifera* bees collect the fresh sweet nectar from it and process to transform into a natural honey. Due to its high demand, a bulk quantity is being produced from the New Zealand and then shipped to the world. This is how the organically produced effective manuka honey is available to food and medicinal markets (Hegazi et al., 2022).

Composition and Efficacy

The composition of manuka honey is complex which consists of proteins, carbohydrates, macro and micro minerals and fatty acids (Johnston et al., 2018). It contains simple and complex sugars in supersaturated solution form. These sugars are mainly glucose, sucrose, maltose and fructose (Patel and Cichello, 2013). The unique feature of manuka honey's composition from other typical honeys is the presence of unusual amount of methleglyoxal (MGO). This component is the basic differential part of this honey which is responsible for its potent antimicrobial, wound healing and anti-cancerous properties. Furthermore, other essential components like phenolic compounds, organic acids, fatty acids, ascorbic acid, flavonoids and peroxides are the main constituents of this medically proven honey (Johnston et al., 2018).

Methyleglyoxal is produced from the conversion of dihydroxyacetone (DHA) present in manuka nectar. This process of conversion takes place inside the nectar. The efficacy of honey is directly proportional to the quantity of methylglyoxal present in it, and manuka honey is documented for containing ample amount of methylglyoxal. Consequently, the application of this honey has gained popularity in medicinal therapies for bacterial infections and cancer treatments. A term called **'Unique Manuka Factor** or (UMF)' is designed grading system to categorize the quality of manuka honey based on the presence of absolute quantity of MGO in it (Johnston et al., 2018; Nolan et al., 2019). In the fig.1, all the main components of manuka honey are illustrated along with their potential qualities that contribute to its therapeutic values in the medical field.

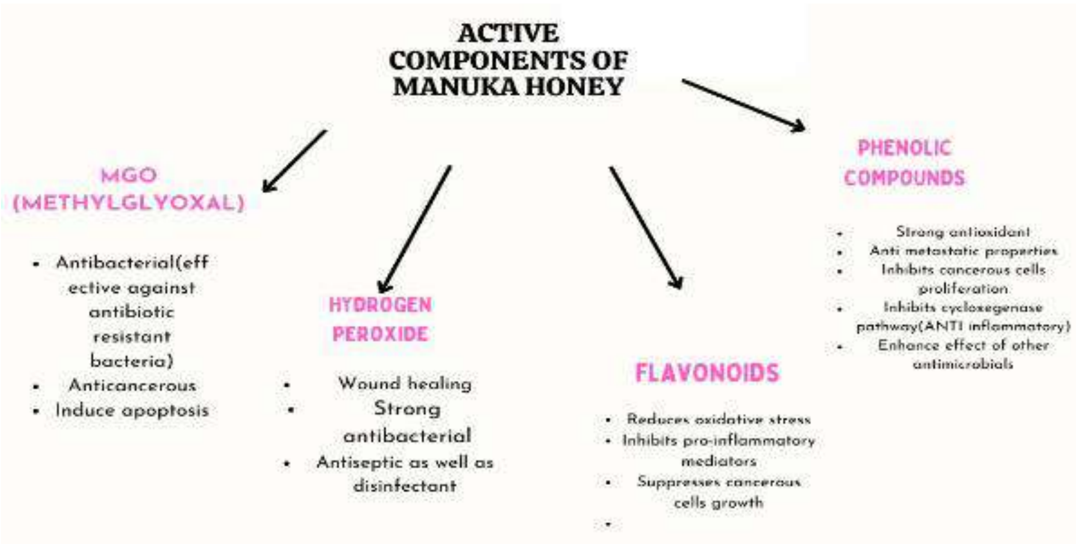

Fig.1: Summing up the composition of Manuka honey

This honey has its pronounced role in chronic and secondary bacterial infections and wounds treatments. Thus, due to its complex chemistry, it acts as broad-spectrum antimicrobial agent, topical wound applications and cancer remedies with efficient results, widely mentioned through researches in the literature (El-Senduny et al., 2021).

Manuka Honey and its Antibacterial Activity

Manuka honey and its importance as an antibacterial nectar has been stated in world's top literatures. It is widely accepted broad spectrum remedy in various primary and secondary bacterial infections. Manuka honey comprises of UNIQUE MANUKA FACTOR that include methglyoxal and phenolic compounds with the absence of peroxide. This UMF has great importance in providing antimicrobial effects especially against antibacterials effects (Johnston et al., 2018). Manuka honey is seen to be active against different streptococci species like *Streptococcus pyogenes* and *S. mutans, Pseudomonas aeruginosa, Proteus mariabilis, Enterobacter spp., S. aureus, S. epidermidis, E. coli,* and *MRSA* (methicillin resistant S*taphylococcus aureus*). In chronic wounds, bacteria exist with biofilms formation that makes antibiotics proliferation and activity difficult, and resistance may develop (Alvarez-Suarez et al., 2014). These problems can be mitigated by use of Manuka honey that can provide antibacterial effects by unique compounds present in it. It can restrict the growth of both types of bacteria by reducing their gene expressions showing high antibacterial, and anti-virulence effects (Al-Kafaween et al., 2022). It can provide anti biofilm pursuits *in vitro* when used in combination with other antibiotics like oxacillin and vancomycin etc. (Campeau et al., 2014)). Mode of action behind this activity is its interaction with translational activities of ribosomes (Packer et al., 2012).

Manuka Honey and *Pseudomonas aeruginosa*

Manuka honey is the potential inhibitor of *Pseudomonas aeruginosa. P. aureginosa* is most predominant and multi drugs resistant bacteria present in all kinds of wounds. It is a type of opportunistic pathogens, present in all kind of environments abundantly. It is most commonly involved to cause endocarditis, urinary tract infections, meningitis, pneumonia, and other wound infections especially burn wounds (Henriques et al., 2011). It has become resistant to most of the available antibacterials after using novel antibacterial interventions against its spread. Likewise, it is the need of hour to introduce new, effective and herbal remedies to combat antimicrobial resistance of harmful and predominant microbes (Nolan et al., 2020).

Manuka honey is bactericidal in its action against *Pseudomonas aeruginosa.* It affects this bacterium by altering its structure at genetic level. It works by contributing to cell wall distress via reducing oprF porin (outer membrane's major protein of *P. aureginosa*) expression (Roberts et al., 2012). The major contribution of manuka honey in its antimicrobial activity is permeabilization of bacterium's cell membrane via proton transport, and ultimately leading to cell lysis (Bouzo et al., 2020). Moreover, it can also reduce motility of *P. aureginosa* by inhibiting flagellar associated genes i.e., fliC (Flagellin protien), fleQ (Flagellar Regulator), flgK (Hook-associated protein), motA (Motor protein component A) and motB (Motor protein component B) that are very significant in regulation, and functioning of flagella (Roberts et al., 2015). Manuka honey can also inhibit the growth of this bacterium by suppressing siderophores (iron chelating compounds for iron sequestration) present on it (Kronda et al., 2013).

Manuka honey and *Escherichia coli*

Manuka honey has proven to be effective in variety of pathogenic bacteria. *E. coli* is a gram-negative bacterium which is abundant in water and food materials. It can produce protective layer called biofilm to increase its virulence and AMR. It has a virulent serotype *E. coli* O157:H7 which produce Shiga toxins 1 and 2, responsible for its resistance to wide range of antimicrobial drugs. So switching to other therapeutic regimes is the need of hour (Nolan et al., 2020).

Research conducted by Kim and Kang, (2020) has shown that manuka honey significantly inhibits the biofilm formation by virulent *E. coli* O157:H7. It also retarded the growth and viability of this bacterium in chronic wound conditions. So, anti-biofilm action of this honey treats most of the infections as resistance is lost to much extent.

Manuka honey and *Staphylococcus aureus*

Staphylococcus aureus is one of the most prevalent gram-positive bacteria which is declared as multiple drugs resistant bacteria in the world's scientific literature. The main example is methicillin resistant *Staphylococcus aureus*, commonly known as MRSA. It causes wide range of food borne infections, skin problems, mastitis, wound damage etc. It is present in all kind of environments. Jenkins et al. (2011) performed detailed research on effect of manuka honey against MRSA. They investigated that minimum inhibitory concentration of manuka honey ceases the cell division of this pathogen. They observed enlarged cells with septa that were exposed to honey and ultimately cells stop to grow. Further interesting remark from Jenkins et al. (2011) study is that there are some unknown components of manuka honey that causes changes and stop cell division in MRSA. So, it urges the researchers to explore the more unique properties of manuka honey which are unknown yet.

Wound Management and Manuka Honey

Honey is an oldest edible substance that has many other non-edibles uses too. Its many advantageous effects are seen in different fields of life sciences, medical sciences, and veterinary field. It has been used as a natural therapy for centuries in treating different kinds of wounds. Different wounds like burns, optic conditions, GIT problems, periodontal issues, as well as surgical wounds can be treated through the application of Manuka honey. Manuka honey is used in wounds healing because of its antimicrobial, anti-inflammatory properties, can stimulate tissues regeneration via epithelization, can help in moisture retention and reducing odor, and can also promote autolytic debridement (Kapoor et al., 2021). Manuka honey works by producing inflammatory cytokines that are mandatory for wound healing by stimulating the monocytes (Langemo et al., 2009). Different kind of honey dressings are available in the market to treat various wounds due to medical conditions like diabetes, obesity, and aging. Manuka honey has an immunomodulatory effect in wound healing because of the presence of assorted plant derivatives and bee derivatives that put a spurt on healing and regeneration (Martinotti et al., 2019). Manuka honey is anticipated as all-in-one cure for treating diabetic wounds. It is a fast and effective remedy due to its anti-inflammatory, anti-oxidant, and non-resistive anti microbials action (Alam et al., 2014). The nonresistant anti-microbial property of honey is due to presence of a unique compound in it called as Methylglyoxal, while immune stimulatory properties are due to propolis, flavonoids, phenolic acid, and esters (Patel et al., 2013). Manuka honey can be used to treat non healing, chronic wounds by neutralizing the alkaline pH of wound by its own acidic pH that helps reducing protease activity, and enhancing fibroblast activity and oxygen perfusion, that ultimately aids in wound healing (Gethin et al., 2008). Manuka honey can help in releasing immune mediators like tumor necrosis factor and interleukins by stimulating macrophages that plays very significant role in healing and curing wounds, and confining different microbial infections (Fernandes-Cabezudo et al., 2013).

Manuka Honey and Burn Wounds

In burn injuries, there is a blast of free radicals that accelerates the activity of xanthine oxidase, leading to extreme tissue damage, necrosis, and oxidation of organic compounds like proteins, lipids, and DNA in affected tissues and as well as in nearby tissues (Nakajima et al., 2013). Manuka honey can be helpful in treating burns by repairing the above damages through stimulating growth of the tissue, epithelization, providing anti-microbial effect, synthesizing collagen, retaining moisture, and minimizing tissue scar (Al-Wailli et al., 2018). These all effects are helpful in rapid healing of burns. Honey can have various other effects like it can deodorize the wound, helps in debridement of dead cells and tissues, can alleviate pain, and is an anti-inflammatory, and anti-bacterial substance (Vendamme et al., 2013). With these properties of manuka honey, burn injuries can easily be attenuated and managed.

Manuka Honey and Different Optic Wounds

Manuka honey has shown good results in treating different conditions and infections related to eyes, and different kinds of manuka honey treatment strategies are under research. Post operative corneal edema can be treated with antibacterial manuka honey. It contains sugars with low water content, having high osmolarity and acidic pH that helps in reducing edema and increasing epithelization (Albietz et al., 2015). Conditions with persistent epithelial defects like corneal abrasions, erosions, keratitis, or ulcers can be easily treated with manuka honey ointments (Alsarhani et al., 2023). Dry eyes can also be treated easily with manuka honey as it helps retaining moisture. Manuka honey is also used as an alternative treatment for malfunctioned glands of eyes (dry eyes) like meibomian gland dysfunction. Cyclodextrin complexed manuka honey has potential effect in treating eye infections particularly blepharitis caused by staphylococcus spp. and pseudomonas spp. with lower minimum inhibitory concentration and minimum bactericidal concentration (Craig et al., 2017).

Manuka Honey and Different GIT Injuries

Manuka honey has anti-inflammatory and anti-oxidant properties that has made it useful in healing injuries, wounds, and in skiving dead parts of tissues especially mucosal layers. Manuka honey is very conventional and widely known for managing and healing GIT disorders like peptic ulcers, gastritis, gastroenteritis, enteritis etc. Manuka honey can have anticipated effects in treating GIT issues and infections related to *Vibrio cholera* due to its antimicrobial properties with less risks of resistance (Hussain, M.B., 2019). Wounds of GIT are prone to different bacteria like *Escherichia coli* O157:H7, *Listeria monocytogenes, Cronobacter sakazakii, Salmonella enterica* serovar *typhimurium,* and *Pseudomonas aeruginosa*. Manuka honey can be used as an anti-infective or an anti-inflammatory oligosaccharide in healing these wounds (Lane et al., 2019). It is very valuable remedy in curing chronic infective wounds like duodenal ulcers.

Manuka Honey and Periodontal Wounds

As we are well aware about the anti-inflammatory, anti-oxidant, and anti-microbial properties of manuka honey, so we can imagine that how effectively and efficiently it can be used to mitigate the oral lesions and injuries. Different studies have proved that Manuka honey has very therapeutical effects in mouth infections, and periodontal infections like gingivitis, and periodontitis etc. The origin of these anomalies is plague formation due to bacteria present in oral cavity, and can exacerbate the injuries. Manuka honey has a factor known as UNIQUE MANUKA FACTOR that imparts anti-bacterial activities and is very beneficial for stopping the growth of dental plagues and injuries progression (Nayak et al., 2010). Moreover, manuka honey can alleviate the pain by providing soothing effect. Presence of methylglyoxal, and glyoxal can fasten the tissue regeneration and healing by enhancing immunomodulation (Niaz et al., 2017).

Anti-cancerous Effects of Manuka Honey

Honey is a conventional and complementary natural plant extract and is used therapeutically in different ailments for centuries. Manuka honey is seen to have very satisfactory effects in cancer patients as a palliative cure. Different attributes of manuka honey like its anti-proliferative properties, anti-metastatic properties, apoptic properties, radical scavenging and anti-inflammatory properties can help in therapeutically alleviating and anodyning different kinds of cancers (Afrin et al., 2020). Manuka honey is seen to be used in combination with 5-florouracil to improve the sequels of chemotherapy, to prevail over the resistance shown by cancerous cells to different chemotherapies, and to reduce the graveness of adverse toxins (Afrin et al., 2018). Manuka honey accomplishes its anti-tumor or anti neoplastic results by permeabilizing mitochondrial membranes, arresting the cell division, inducing apoptosis, and modulating stress by oxidation (Martinotti et al., 2020). Manuka honey can be consumed in colon cancers because it can inhibit the cancer cell lines activity and growth, can restrict proliferation, and can induce apoptosis. These inhibitory effects are due to phenolic compounds like quercetin, gallic acid, syringic acid, kaempferol, and luteolin present in Manuka honey (Afrin et al., 2018). Manuka honey can be a promising anti-cancer cure for hepatocellular carcinoma when used in combination with Doxorubicin as these can synergistically inhibit oncogenic factors involved by inducing apoptosis (Al-Rafaey et al., 2021).

Manuka Honey as Antioxidant

Oxygen is the most vital element for life but still it can cause illness and destruction of cells when ‘free radicals’ are formed following its metabolism. These free radicals increases and travel from cell to cell, causing disruption of cellular membranes and result in cellular damage (Blasa et al., 2006).

Honey contains various antioxidant components including ascorbic acid, organic acids, phenolic compounds, glucose oxidases, catalases and carotenoid derivatives (Blasa et al., 2006). Phenolic compounds (phenolic acids) play evident role in antioxidant property of honey. Alzahrani et al., (2012) has searched that manuka honey has the most abundant number of phenolic compounds than any other honey. It makes it efficacious in antioxidant action and other healing properties.

Conclusion

Due to increasing antimicrobial resistance to various bacteria, the world badly needs to switch to new remedies. Manuka honey is one of the highly powdered substances to be effectively use in many abnormal conditions. It has extreme biological importance due to multiple properties to combat stress, cancerous issues and wound injuries. It can be a promising product in many other non-curable defects in human and veterinary medicine. But there is lack of extensive research on it to clarify its exact mechanism of action in different ailments. Similarly, a collaborative work is needed to investigate its further components with their mode of actions which are hidden so far.

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Chapter 12

Pharmacological and Therapeutic Values of Turmeric

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ABSTRACT

Curcuma longa L., commonly known as turmeric, is a perennial herb belonging to the Zingiberaceae family, extensively cultivated in tropical Asian climates. Its rhizomes exhibit rectangular, ovate, and pyriform morphology and traditionally valued in the Indian culture as 'Haldi', are processed into turmeric powder. This powder is widely recognized as a flavoring agent and an essential constituent in curry dishes worldwide. Turmeric, employed as a spice for over 4000 years, has religious significance and has been integral to South Asian medical traditions. Turmeric comprises carbohydrates, proteins, fatty acids, minerals, moisture, and contains various beneficial compounds such as tumerone and curzerenone. It contains curcumin which consists of curcumin I (94%), curcumin II (6%), and curcumin III (0.3%), which gives it a distinctive yellow hue. With diverse traditional uses across global cultures, turmeric has been utilized in Italy, India, traditional Chinese medicine, and traditional Thai practices for addressing health issues such as stomach discomfort, wound care, and preventative measures against diarrhea and dysentery. Research has highlighted its potent antibacterial, antifungal and antiparasitic properties as well as its potential to combat severe bacterial infections. Furthermore, curcumin, a key component of turmeric, serves as a powerful antioxidant, demonstrating efficacy in preventing tissue damage and oxidative stress. Clinical investigations have revealed promising outcomes for curcumin in addressing various conditions including diabetes, cancer, arthritis, and Alzheimer's disease. Recent studies indicate that Curcuma oil exhibits promise as a treatment for conditions associated with oxidative stress, such as cerebral stroke. Its efficacy in improving neurological function, reducing tissue damage, and supporting nerve cell survival has been observed in rats with brain damage due to reduced blood flow. Moreover, turmeric oleoresin and essential oil have demonstrated the potential to reduce high blood sugar levels and decrease abdominal fat in obese, diabetic mice.

KEYWORDS		
Turmeric, Curcumin, Antimicrobial, Antioxidant, Anti-inflammatory	Received: 19-May-2024 Revised: 11-July-2024 Accepted: 21-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Turmeric (*Curcuma longa* L.) is a perennial herb classified within the Zingiberaceae family and extensively cultivated in the tropical climates of Asia. Typically attaining a height of up to 1 meter, it is characterized by a short stem and oblong, pointed leaves, and produces funnel-shaped yellow flowers. While this plant is indigenous to tropical and subtropical regions globally, it is predominantly cultivated in Asian nations, particularly India and China. In India, it is referred to as 'Haldi', and its rhizomes, which exhibit rectangular, ovate, and pyriform morphology and are generally short-branched, hold significant traditional value (Lal, 2012; Yadav and Tarun, 2017). The roots and rhizome of *C. longa* are processed into turmeric powder, widely esteemed as a flavoring agent and essential component in curry dishes worldwide (Jurenka, 2009; Wilken et al., 2011).

Turmeric has been a spice for 4000 years, spreading to China, East Africa, West Africa, and Jamaica. Marco Polo compared it to saffron in 1280. It has religious significance and has also been used in South Asian medical traditions for centuries. Turmeric comprises of carbohydrates, proteins, fatty acids, minerals, and moisture. It contains curcumin which consists of curcumin I (94%), curcumin II (6%), and curcumin III (0.3%) (Li et al., 2011) that give it the yellow color and other beneficial compounds like tumerone and curzerenone.

Turmeric has diverse traditional uses in different cultures, including Italy, India, traditional Chinese medicine, and traditional Thai practices. It is used for various ailments such as stomach discomfort, wound care, and preventing diarrhea and dysentery. The recommended preparations include consuming powdered turmeric for therapeutic benefits and preparing rhizomes for medicinal use (Gao et al., 2024).

Turmeric exhibits potent antibacterial properties and holds potential for addressing severe bacterial infections. Research has indicated that turmeric can impede the proliferation of detrimental fungi, bacteria, and parasites. Turmeric mouth rinse has been effective in preventing plaque and gingivitis and has shown a significant reduction in overall bacteria count (Wang et al., 2010). Additionally, curcumin, a compound found in turmeric, has been found to have modest effects against certain *Leishmania* species and *Plasmodium falciparum* (Chahal et al., 2024). Nano-curcumin has been observed to have bactericidal effects by disrupting bacterial cell walls.

Turmeric extracts act as powerful antioxidants and can help to prevent tissue damage and oxidative stress. Its antioxidant properties help to lower lipid peroxidation, antidiabetic activity, inhibition of platelet aggregation and thromboxane synthesis (Verma et al., 2018). Additionally, curcumin derivatives are useful in preventing and treating gallstones. Turmeric's ability to reduce blood glucose level in diabetic rats offers a constructive approach to lowering the risk of complications from diabetes (Farhadnejad et al., 2024).

According to research findings, curcumin demonstrates inhibitory effects on human cell enzymes, thereby mitigating the onset of inflammation. Its efficacy matches that of cortisone in managing acute inflammation, while turmeric effectively reduces inflammation-induced edema. Additionally, curcuminoids play a role in the inhibition of pro-inflammatory chemicals. Through its distinctive properties, curcumin is shown to lower inflammation within cells and diminish the synthesis of inflammatory mediators, as evidenced by scholarly investigations (Boroumand et al., 2018).

Turmeric is recognized for its multifaceted health benefits, encompassing cardiovascular protection, anticancer properties, hepatoprotective effects, potential in Alzheimer's disease, anti-inflammatory effects, neuroprotective activity, and gastrointestinal protection. Clinical investigations have indicated promising outcomes for curcumin, the bioactive compound, in managing conditions such as diabetes, cancer, arthritis, and Alzheimer's disease (Mishra and Palanivelu, 2008).

Recent research indicates that Curcuma oil shows promise as a treatment for cerebral stroke and other conditions related to oxidative stress. The oil has demonstrated effectiveness in improving neurological function, reducing tissue damage, and supporting nerve cell survival in rats with brain damage due to lack of blood flow. These benefits are attributed to the oil's ability to reduce the production of a molecule called inducible nitric oxide (NO) synthase (iNOS)-derived NO and its strong antioxidant properties. Additionally, another study highlights the potential of turmeric oleoresin and essential oil in reducing high blood sugar levels and decreasing belly fat in obese, diabetic mice (Honda et al., 2006).

Historical Background

Turmeric has a rich history as a culinary spice, with its origins dating back approximately 4000 years to India's Vedic culture. This spice holds religious significance and is believed to have reached China by 700 A.D., East Africa by 800 A.D., West Africa by 1200 A.D., and Jamaica in the 18th century. In 1280, Marco Polo likened turmeric to saffron. Moreover, South Asia has a documented history of utilizing turmeric for medicinal purposes within Sanskrit, Ayurvedic, and Unani traditions. Notably, Sushruta's Ayurvedic Compendium from 250 B.C. recommends the application of turmeric ointment in the treatment of food poisoning (Yadav and Tarun, 2017; Akilandeswari et al., 2020).

Taxonomic Classification

• Kingdom:	Plantae
• Subkingdom:	Tracheobionta -Vascular plants
• Superdivision:	Spermatophyta
• Division:	Magnoliophyta – Flowering plants
• Class:	Lilliopsida- monocotyledons
• Subclass:	Zingiberidae
• Order:	Zingiberales
• Family:	Zingiberaceae– Ginger family
• Genus:	Curcuma L.- curcuma
• Species:	*Curcuma longa* L.
• Scientific Name:	*Curcuma longa* L. (Chattopadhyay et al., 2024)

Chemical Composition

Turmeric is composed of carbohydrates (69.4%), proteins (6.3%), fatty acids (5.1%), minerals (3.5%) and moisture contents (13.1%). Steam-distilled essential oil of turmeric contains zingiberene, cineol, a-phellandrene, borneol, sesquiterpenes and sabinene. The yellow color of turmeric is attributed to curcumin (3–4%), which consists of curcumin I

(94%), curcumin II (6%), and curcumin III (0.3%) (Li et al., 2011). The chemical structure of Curcumin I, II, and II is shown in Fig. 1.The rhizomes have been found to contain beneficial compounds such as tumerone a, tumerone b, curzerenone, curdione, mono- and di-demethoxycurcumin (Meng et al., 2018).

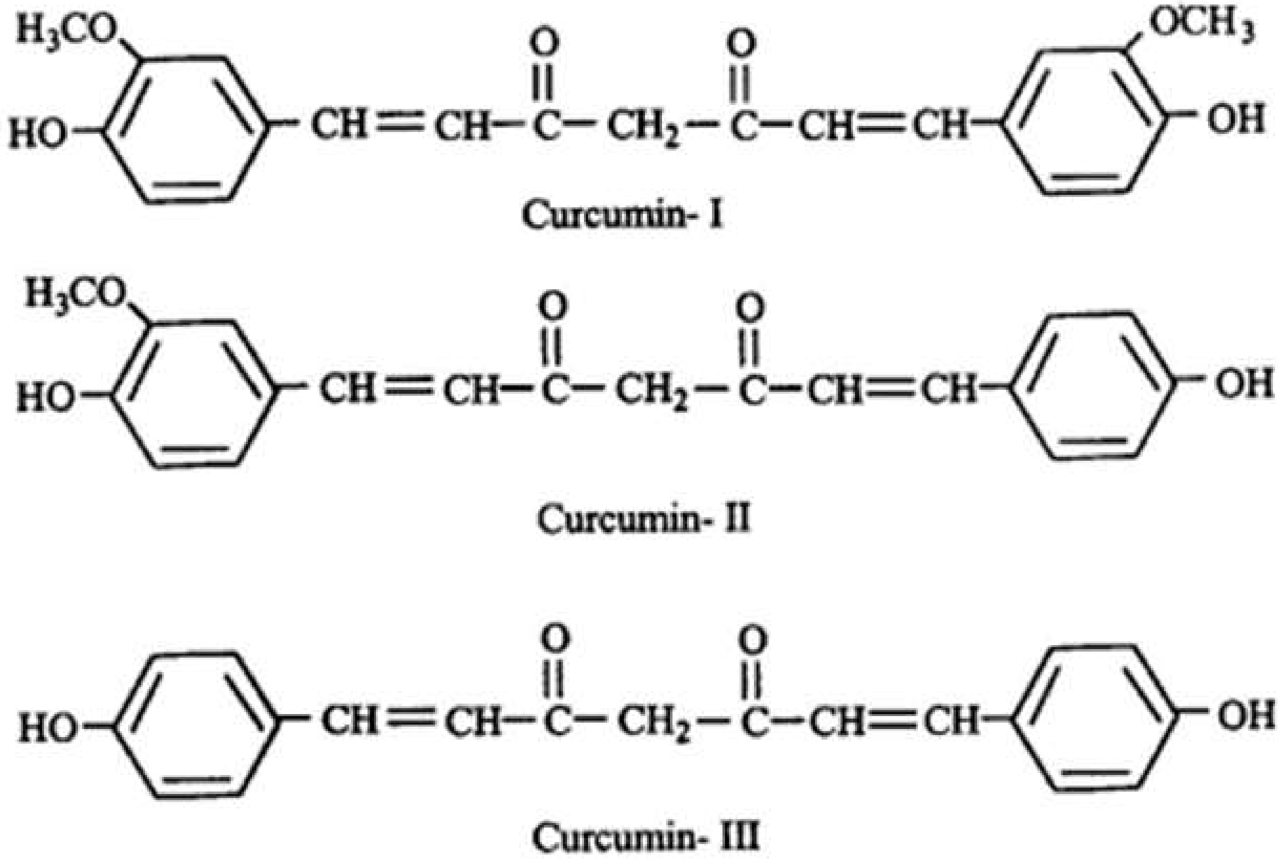

Fig.1: Chemical structure of Curcumin I, II and II (Nasri et al., 2014)

Therapeutic Properties of Turmeric

Turmeric exhibits various therapeutic and pharmacological activities. The following outlines the most important pharmacological and therapeutic properties of turmeric.

Antimicrobial Activity

Turmeric demonstrates potent antibacterial properties and holds promise for the treatment of severe bacterial infections. It has been demonstrated that turmeric inhibits the growth of some harmful fungi, bacteria, and parasites. One investigation using *Eimera maxima*-infected chicks showed that adding 1% turmeric to meals increased weight gain and decreased intestinal lesions (Kwon and Magnuson, 2009). In a different experiment on animals, guinea pigs treated topically with turmeric oil for a week showed reduced growth of harmful fungi and dermatophytes (Dujic et al., 2009). Additionally, it has been discovered that curcumin exhibits modest action against major *Leishmania* species and *Plasmodium falciparum* (Huang et al., 1998). Nano-curcumin has been observed to disrupt the bacterial cell wall, leading to complete bactericidal effects (Ji and Shen, 2014). Furthermore, the combination of EGCG and turmeric presents a potential avenue for preventing and treating *Acinetobacter baumannii* infections (Mythri et al., 2011).

The administration of essential oil derived from turmeric leaves effectively lowers fungal growth and the synthesis of aflatoxins G1 and B1 (Mythri and Srinivas Bharath, 2012). However, the clinical utility of curcumin is hindered by its low water solubility. *Acanthamoeba castellanii* poses challenges in eradication due to its resistance to antiamoebic medications. Examination of the amoebicidal efficacy of ethanol extracts derived from various plant species, including daffodil, groundnut, and turmeric, has been conducted to address *Acanthamoeba castellanii* cysts. The researchers have made a notable finding that the extract exhibits inhibitory effects on Acanthamoeba cyst reproduction, with the observed impact being contingent on both time and dosage (Harish et al., 2010). Furthermore, turmeric mouth rinse has demonstrated efficacy in the prevention of plaque and gingivitis and has also shown a significant reduction in overall bacteria count (Wang et al., 2010). In addition, turmeric displays the ability to restrict the development of *Bacillus subtilis* and *Escherichia coli* by impeding the assembly of temperature-sensitive Z mutants (Fts Z) and diminishing their polymerization (Yanagisawa et al., 2015). Moreover, curcumin exhibits a dose-dependent influence on infectivity and cell proliferation, notably reducing the cytotoxicity of *V. vulnificus* on HeLa cells by impeding *V. vulnificus* proliferation. Additionally, curcumin curtails bacterial adhesion and inhibits the binding of RTX toxin to host cells (Ahmad et al., 2020).

Antioxidant Properties

Turmeric extracts, specifically curcumin, demonstrate notable antioxidant properties due to their water and fat solubility. These antioxidant effects are comparable to those of vitamins C and E. Curcumin pre-treatment has been proven to efficiently mitigate the effects of ischemia on heart tissue. In an in vitro study utilizing bovine aortic endothelial cells, the impact of curcumin on endothelial heme oxygenase-1, an inducible stress protein, was assessed. Results indicated that curcumin treatment bolstered cellular resilience to oxidative damage following an 18-hour incubation period. Furthermore, curcumin exhibits preventive properties against the oxidation of lipids and hemoglobin. Its antioxidant effects serve to inhibit the generation of reactive oxygen species (ROS) by activated macrophages. Additionally, curcumin derivatives such as bisdemethoxycurcumin and demethoxycurcumin have been identified as valuable in the prevention and treatment of cholelithiasis (Akram et al., 2010; Velayudhan et al., 2012; Pawar et al., 2015).

Anti-inflammatory Activities

According to molecular research, curcumin has been found to impede the activation of certain enzymes or factors within human cells, thereby preventing inflammatory reactions. Orally administered curcumin has exhibited comparable efficacy to cortisone or phenylbutazone in the treatment of acute inflammation. When administered orally, *C. longa* significantly reduces inflammation-induced edema. One plausible rationale for the anti-inflammatory attributes of *C. longa* is its capacity to hinder neutrophil function during inflammatory conditions and suppress the production of inflammatory prostaglandins derived from arachidonic acid (Cronin, 2003).

Moreover, curcuminoids impede the activities of phospholipases, nitric oxide elastase, thromboxane, leukotrienes, prostaglandins, lipoxygenase (LOX), cyclooxygenase (COX), interferon-inducible protein, tumor necrosis factor (TNF), and interleukin-12. By inhibiting the lipoxygenase pathway, they concurrently curtail prostaglandin synthesis and leukotriene formation (Bundy et al., 2004).

Notably, studies conducted by Surh et al. 2001 have illustrated curcumin's capacity to suppress the expression and activity of cyclooxygenase-2 (COX-2) across diverse animal models and cell lines. Furthermore, the topical application of curcumin entails the inhibition of lipopolysaccharide (LPS)-mediated COX-2 expression. In this context, the effect of curcumin on increasing COX-2 levels in macrophages not activated by LPS may contribute to the reduced production of prostaglandin E2 (PGE2), independent of the catalytic inhibition of COX (Pu et al., 2013). As highlighted by Zhang et al. (2015) curcumin impedes the synthesis of PGE2 induced by TPA or chenodeoxycholate, alongside the repression of COX-2 protein and mRNA expression. These findings delineate the potential of curcumin as a modulator of inflammatory responses.

Cardiovascular and Anti-diabetic Effects

Turmeric's impact on cardiovascular health is primarily attributed to its antioxidant properties, which also lower lipid peroxidation, antidiabetic activity, and inhibition of platelet aggregation. Its effects on cholesterol levels may be linked to decreased gastrointestinal cholesterol absorption and enhanced hepatic cholesterol conversion to bile acids. Its constituents are thought to inhibit platelet aggregation through potentiation of prostacyclin synthesis and inhibition of thromboxane synthesis. Turmeric also lowers blood glucose level in diabetic rats and reduces the complications associated with diabetes mellitus. More research is required to discover the optimal doses for cardiovascular protection and cholesterol or glucose-lowering effects (Khajehdehi, 2012).

Anticancerous Effects

The impact of turmeric on the etiology of cancer has been the subject of several animal research. Curcumin has been shown in several studies (Sa and Das, 2008; Park et al., 2013; Shanmugam et al., 2015; Giordano and Tommonaro, 2019) to prevent the three phases of carcinogenesis, which are angiogenesis, tumor promotion, and tumor development. It was demonstrated that curcumin inhibited tumor development and cell proliferation in two investigations on prostate and colon cancer. Additionally, several common mutagens and carcinogens can have their action suppressed by turmeric and curcumin.

Turmeric and curcumin have been demonstrated to have anticarcinogenic qualities due to their direct antioxidant and free radical scavenging activities, as well as their indirect capacity to increase glutathione levels, which helps the liver detoxify pollutants and mutagens and prevents the formation of nitrosamines. It has also been demonstrated that curcumin prevents UV radiation from inducing mutagenicity (Aggarwal et al., 2003; Shpitz et al., 2007).

Hepatoprotective Properties

The combination of turmeric rhizome powder and amla juice has long been utilized as a traditional remedy for treating jaundice (Pandey, 2002). Within the turmeric rhizome extract, curcumin, the principal antioxidant, has demonstrated the ability to facilitate apoptosis in damaged hepatocytes. This protective action is implicated in the suppression of hepatic fibrogenesis and inflammation. Administration of the ethanolic extract of *C. longa* rhizomes at dosages of 250 mg/kg and 500 mg/kg has exhibited a notable and dose-dependent hepatoprotective effect. Moreover, the volatile oils and curcumin contained in *C. longa* exhibit potent anti-inflammatory properties (Salama et al., 2013).

Alzheimer's Disease

Researchers found that curcumin has the potential to reduce plaque formation in aging mice with advanced plaque deposits reminiscent of those seen in Alzheimer's disease. In Alzheimer's disease transgenic mice, curcumin demonstrated the ability to decrease oxidative damage and address amyloid pathology. Its powerful antioxidant and anti-inflammatory properties also showed promise in reducing oxidative stress and inflammation, both significant factors in Alzheimer's disease (Rao et al., 2012).

Arthritis and Turmeric

Curcumin, a dietary supplement used in Ayurvedic medicine, has shown promising results in treating inflammatory conditions such as arthritis. Funk et al. 2006 demonstrated that an extract of curcumin, free of essential oils, effectively reduced joint inflammation. Additionally, a hydroalcoholic extract of turmeric was found to dose-dependently suppress joint inflammation and periarticular tissue damage. According to recent research, oral curcumin treatment was successful in reducing the neutrophil inflammatory response in rats with zymosan-induced arthritis (Nonose et al., 2014). Furthermore, scholars suggest that curcumin therapy may serve as a dependable and secure substitute for addressing osteoarthritis (Panahi et al., 2014).

Neuroprotective Activity

Curcuma oil has been observed to effectively mitigate nitrosative and oxidative stress, thereby attenuating the adverse effects of ischemia. This suggests its potential to ameliorate the collapse of the mitochondrial membrane induced by ischemia. Furthermore, the administration of Curcuma oil has demonstrated a robust capacity to counteract the release of cytochrome c, modulate the Bax: Bcl-2 ratio, and activate caspases, culminating in the sequential induction of apoptosis. Consequently, compelling evidence supports the high efficacy of Curcuma oil in neuroprotection, indicating a broad therapeutic window for mitigating ischemic brain damage (Dohare et al., 2008).

Gastrointestinal Effects

Turmeric contains beneficial ingredients such as p-tolymethylcarbinol and sodium curcuminate, which offer protection to the gastrointestinal tract. Sodium curcuminate has been found to stimulate the production of pancreatic enzymes, secretin, gastrin, and bicarbonate, while also inhibiting intestinal spasm and p-tolymethylcarbinol. Moreover, turmeric has demonstrated the ability to prevent the formation of ulcers induced by stress, alcohol, indomethacin, pyloric ligation, and reserpine. In rat experiments, turmeric significantly increased stomach wall mucus (Pawar et al., 2015). In an open, phase II trial, 800 mg of powdered turmeric was given five times a day to 25 patients with confirmed stomach ulcers, leading to full healing in 48 percent of the patients after five months. The data did not indicate any negative reactions or blood abnormalities. Additionally, curcumin was observed to reduce mucosal damage in mice (Chanda and Ramachandra, 2019).

Ethnomedicinal Use

Turmeric is utilized for a variety of applications across the world. In Italy, it was used to protect the skin from sunburn (Scartezzini and Speroni, 2000). In India, turmeric is traditionally administered orally to alleviate symptoms of poor digestion, fevers, skin conditions, vomiting during pregnancy, and liver disorders. Externally, it is utilized to address conditions such as conjunctivitis, skin infections, cancer, sprains, arthritis, hemorrhoids, and eczema (Chopra and Chopra, 2006). Moreover, in certain practices, Indian women utilize turmeric topically to mitigate unwanted hair growth (Goh and Ng, 1987).

In traditional Chinese medicine, both the tuber and rhizome are utilized for various therapeutic purposes. They are commonly employed to address stomach discomfort (Araujo and Leon, 2001). According to traditional beliefs, the rhizome of turmeric is thought to possess analgesic properties and is considered to stimulate blood and Qi flow. Conditions such as jaundice, frozen shoulder, amenorrhea due to blood stasis, postpartum abdominal discomfort due to stasis, as well as chest and abdominal pain and distension, are commonly treated using turmeric rhizome. Additionally, it is used to heal wounds and injuries. Similarly, the tuber shares similar properties and is employed in the treatment of viral hepatitis. Notably, it is considered to have cooling properties, particularly beneficial during hot weather (Sahoo et al., 2021).

The utilization of turmeric in traditional Thai practices encompasses multiple therapeutic applications, as documented by Chokevivat and Chuthaputti, (2005). One such application involves using a combination of powdered turmeric and rainwater to treat ringworm, applied twice daily. Moreover, the rhizome of turmeric, when scraped and applied, has been found to alleviate irritation and inflammation resulting from mosquito bites. Alternatively, the topical application of a paste comprising powdered turmeric and water may be used recurrently to alleviate discomfort (Pondini et al., 2023).

Furthermore, the consumption of tablets containing powdered turmeric and honey three times a day has been purported to offer carminative attributes and therapeutic benefits for peptic ulcers (Alburyhi and El-Shaibany, 2023).

To help prevent diarrhea and dysentery, you can prepare the rhizomes by breaking them into tiny pieces and mixing them with warm water. Take two teaspoons of this mixture three or four times a day. Adding a bit of salt can enhance the flavor. Alternatively, you can roast the rhizome, break it into small pieces, soak them in lime water, and then drink one or two glasses of the liquid.

Wound care: bring powdered turmeric and coconut or fat to a boil until yellow oil is produced. Put the oil on any cuts or bruises. To cure wounds, either squeeze the juice from the turmeric rhizome or combine turmeric with a few milliliters of lime water, alum, or potassium nitrate, then apply it to the wounds. You may use this recipe to treat inflammations as well (Gritsanapan and Pothitirat, 2009).

Turmeric Oil

Turmeric, a well-known spice, possesses bioactive components that are responsible for its various therapeutic effects. Notably, the volatile oil found in turmeric plays a significant role in its medicinal properties. Studies have shown that turmeric oil effectively prevents Trichophyton-induced dermatophytosis in guinea pigs. Additionally, research conducted by Apisariyakul et al. (1995) revealed that turmeric oil exhibited inhibitory effects on 15 different dermatophyte isolates at varying dilutions. In contrast, curcumin, another component of turmeric, did not show the same inhibitory effects on the dermatophyte isolates.

Furthermore, investigations into the antiviral properties of zedoary turmeric oil spray in the respiratory tract have indicated promising results. According to a study by Huang et al. in 2007, the application of zedoary turmeric oil spray was found to slightly inhibit influenza virus, parainfluenza viruses I and III, respiratory syncytial virus, and adenoviruses 3 and 7. Interestingly, significant inhibition was observed specifically against parainfluenza virus II. These findings highlight the potential of turmeric oil in combating viral infections, particularly within the respiratory system.

The findings indicate that Curcuma oil exhibits potential as a therapeutic intervention for cerebral stroke and other oxidative stress-related pathologies. Notably, the research demonstrates the efficacy of Curcuma oil in ameliorating neurological impairments, reducing infarct and edema volumes, and enhancing neuronal survival rates in rats with ischemia-induced damage. These favorable effects are credited to the oil's capacity to attenuate the production of inducible nitric oxide (NO) synthase (iNOS)-derived NO and its robust antioxidant properties (Dohare et al., 2008). Additionally, the study proposes that Curcuma oil may mitigate delayed neuronal death through a caspase-dependent mechanism (Rathore et al., 2008). Furthermore, a distinct investigation underscores the potential of turmeric oleoresin and essential oil in mitigating heightened blood glucose levels and diminishing abdominal adiposity in obese, diabetic murine models (Honda et al., 2006).

Conclusion:

Turmeric is a perennial herb cultivated in tropical Asia. It is processed into turmeric powder and widely used in curry dishes. It contains beneficial compounds and has been traditionally used for various health issues. Research has highlighted its potent properties, including antibacterial and antioxidant effects, and its potential in addressing conditions such as diabetes, cancer, and Alzheimer's disease. Although there have been numerous studies on its properties, more research is needed to fully understand its therapeutic potential for managing diseases. Developing pharmaceuticals from turmeric is seen as a promising way to harness its medicinal properties. While raw extracts from the plant have shown effectiveness, modern pharmaceuticals require a thorough investigation of their pharmacological properties, bioactivity, mechanisms of action, and potential toxicities, along with standardization and clinical trials. Given the increasing interest in plant-derived treatments with traditional roots, there is a clear need to refine modern pharmaceuticals using turmeric, for effective disease management. A comprehensive evaluation of turmeric is necessary to uncover its clinical applications and maximize its benefits for humanity.

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Chapter 13

Unlocking Health Benefits: The Potential of Olive Leaf Extracts in Promoting Well-being

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ABSTRACT

Olive leaves are being used in traditional medicine due to their pharmacological effects. Olive leaves contain many therapeutic compounds like phenolic, alkaloids, and flavonoids. Oleuropein is the most abundant phenolic compound of Olive leaves, oil and fruit, the three structural subunits are hydroxytyrosol, elenolic acid and a glucose molecule. Oleuropein has many vital protective roles on orangs and organs system. It has also capability of antimicrobial, anticancer and antioxidant. It protects skin from UV radiations, protect nervous system from oxidative damages and down regulate the cardiotoxicity. A lot of reach has been searched regarding Oleuropein to provide the health benefit of this compound specially by adopting traditional Mediterranean diet as a model of healthy eating. The chapter also opens the windows for the new researcher to explore the multidimensional protective role of Oleuropein present in olive leaves extracts.

KEYWORDS
Olive leaves extract, Oleuropein, Anticancer, Antioxidant, Skin protection, Phenolic compound

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INTRODUCTION

Olive leaves are recognized for their numerous pharmacological benefits. Extracts from olive leaves possess antimicrobial, anti-inflammatory, anti-oxidant, anti-hypertensive, anti-hypercholesterolemic, anti-hyperglycemic, antithrombotic, diuretic, and anti-tumor properties. This book chapter highlights the extensive range of medical applications of olive leaves extracts, which can be utilized to address various health concerns (Sabry, 2014)

Olive leaves are a plentiful and economical source of bioactive components, such as triterpenes, lignans, flavonoids, and secoiridoids. Olive pruning produces an estimated each year, an olive tree produces 25 kilograms of leaves and twigs and only about 10% of olives make it to the mills. The oleuropein and hydroxytyrosol are two main substances present in olive leaves and possess numerous beneficial properties, including anti-tumor, anti-inflammatory and antidiabetic activities (Haque et al., 2018).

Oleuropein is abundant in raw olive fruit and leaves (Cavaca et al., 2020). Oleuropein concentration decrease and hydroxytyrosol concentration rise as a result of chemical and enzyme process that takes place during fruit maturation or as a result of olive processing (Leri, 2016). Hydroxytyrosol is the primary breakdown product of Oleuropein (Imran et al., 2018). Three structural subunits makeup the oleuropein molecule 4-(2-hydroxyethyl) benzene-1, 2-diol is a kind of polyphenol that also termed as hydroxytyrosol (HT) (Ventura et al., 2019), a secoiridiod known as elenolic acid (Grewal et al., 2020) and a glucose molecule (Omar, 2010). Oleuropein is a potent bio phenol that is commonly found in extra virgin olive oil, olive leaves, and some oleaceae family plants. Its potential antioxidant and anti-inflammatory actions are mostly responsible for its principle pharmacological benefits, which include anticancer, cardio protective, neuroprotective, gastroprotective, hepatoprotective radioprotective, anti-diabetic, and anti-obese among others (Hassen et al., 2020). Oleuropein, hydroxytyrosol, and tyrosol are the most abundant polyphenolic chemical found in olives (olea europaea L) and olive oils which play a significant role in the Mediterranean selection of food. The amount of phenolic material is influenced by the season of harvest, location and climate. The positive effects of oleuropein, including its antiviral (Bulotta et al., 2014), antibacterial (Himour et al., 2017), anticancer (Jin et al., 2018), anti-inflammatory (Omar, 2010) and antineuropathic capabilities (Gamli, 2016), have been demonstrated in experimental, clinical, and epidemiological research. Olive leaves, olive roots, virgin olive oil, and olive mill waste (vegetation and wastewater) all contain oleeuropein. (Leri, 2016).

The olive tree (olea europaea L.) an evergreen plant that has been domesticated since antiquity, is a common component of traditional medicine. Cardiovascular illnesses, cancer, inflammation and stroke have been shown to be less common in people who consume Mediterranean diet high in olives and their derivatives. In addition to olives and their oil, olive leaf and its many health benefits have recently captured the interest of many academics. Many of the positive effects of OLE are thought to stem from the potent antioxidant properties of its constituents, especially oleuropein and hydroxytyrosol. The literature has detailed numerous strong health benefits of olive leaf extract (OLE), including effects on the cardiovascular system (Covas, 2007), hypoglycemic effects (Omar, 2010) and antibacterial effects (Kermanshah et al., 2020).

Olive leaf and its extract's key phenolic component, oleuropein, gives olive fruits their distinctively bitter flavor (Ambra et al., 2017) and scent (Issaoui et al., 2021). The antioxidant properties of oleuropein and its hydrolyzed imitative have also been illustrate to have numerous benefits on human health. Numerous studies claims that olive leaf may benefit variables associated to diabetes and cardiovascular diseases through a variety of ways. Additionally, toxicology research indicates that olive leaf is generally harmless, even at high dose (Agagunduz, 2020). Oleuropein, the main phenolic substance in *Olae europaea L*., has attracted scientific attention for a number of health-promoting properties, including anticancer, anti-inflammatory, cardio-and neuroprotective. Oleuropein has been studied for its potential antioxidant and anti-inflammatory properties, also for its strange effect on autophagy and amyloid fibril growth (Nediani et al., 2019, Leri and Bucciantini, 2016). Despite the growing number of studies that have been published that examine the positive results of oleuropein, there are few clinical studies examining the benefits of this polyphenol as a human nutraceutical. and there are numerous issues with its bioavailability, bio accessibility and dosage that still need to be resolved (Nediani et al., 2019). Recent studies have linked OL and their extract to a wide range of advantageous health characteristics, including a significant antioxidant effect, antihypertensive action decreased body mass, fat storage (Ahamad et al., 2019) and hypoglycemic effects. Olive leaf extracts (OLE) have been shown in numerous investigations to exhibit antibacterial action against a variety of bacteria, fungi and viruses.

OLE has been linked to the activity of cells that contribute to the inflammatory response. Additionally OL has been said to have anticancer qualities that limit tumor necrosis factor production as well as anti-proliferative and pro-apoptotic effect. By delaying the lipid peroxidation process, the antioxidant chemical from OL can lengthen the shelf life of food products. In order to boost up the quality and stability of meat products and vegetable oils, olive leaf have been researched as an additional supplement. OL are abundant in bioactive chemicals such as sugars, triterpenic acids, and phenolic compounds (Medina et al., 2019. The main aim of this review is to provide a panoramic view of health benefits of oleuropein.

Structure and Sources

The most prevalent substance in OLE is oleuropein which is followed in abundance by hydroxytyrosol an oleuropein precursor and hydroxytyrosol's conjugated glucoside verbascoside and caffeic acid (De Bock et al., 2013). The substances responsible for the bitter flavor astringency and resistance to oxidation in olive fruit include tyrosol and hydroxytyrosol (Kermanshah et al., 2020).The structure of Oleuropein plays role in radical scavenging due to structural and bonding position (Hassanzadeh et al., 2014. DOI10.1016/j.foodchem.2014.05.015). It was claimed that the phenolic compounds in olives were influenced by the time of harvest and that the phenolic content varied depending on when the olives were harvested between September and December (Polari et al., 2020). It has been also reported that concentration of rutin, verbascodies, toxifolin and tyrosol increases in months of October to November then reduce as the plant grow and ripen (Reis et al., 2022).

According to reports, Ferulic and vanillic acid levels increased as harvest time progressed, but apigenin, cinnamic acid, p-coumaric, and 4-hydroxybiphenyl carboxylic acid amounts decreased among the phenolic compound found in sariulak olives (Gamli O F , 2016).

Oleuropein is phenolic secoiridoid glycoside made up of a glucose molecule, a secoiridiod called elenolic acid and a polyphenol called 4-(2-hydroxyethal) benzene-1, 2-diol, also known as hydroxytyrosol (Souilem et al., 2016). It is one of the most prevalent bioactive substances found in olive tree leaves (olea europaea). The variety organ, olive product, climate, ripeness of the olives at the time of the harvest, and the processing system all effect the amount of oleuropein present (Hassen et al., 2015).

Oleuropein is the substance that gives olives, olive leaves, olive pulp and olive seeds their bitter flavor. Oleuropein concentration in immature olives can grow up to 140 mg g^{-1} dry matter, while quantity in leaves typically ranges between 60-90mg g^{-1} dry matters (A.P.M. Antunes et al*.,* 2008). Depending on the kind of enzyme that breaks down oleuropein, the end product of this process may vary (Liu et al., 2018). Oleuropein aglycone or decarboxymethyl oleuropein aglycone is produced by the enzyme glycoside (EC 3.2.1.21) by the release of glucose, whereas esterase create glucosyl derivatives such as hydroxytyrosol, elenolic acid by hydrolyzing the ester bonds in oleuropein (Otero et al., 2021). Olive leaf dry matter has a very high Oleuropein concentration (6-14%). Although it is abundant in olive trees and leaves, this complex phenol is less common in olive oil varieties other than extra virgin olive oil. Oleuropein are more frequently converted by olive production procedures into hydrolysis products including hydroxytyrosol and tyrosol, which leads to a decrease in non-hydrolyzed oleuropein forms (Agagunduz, 2020).

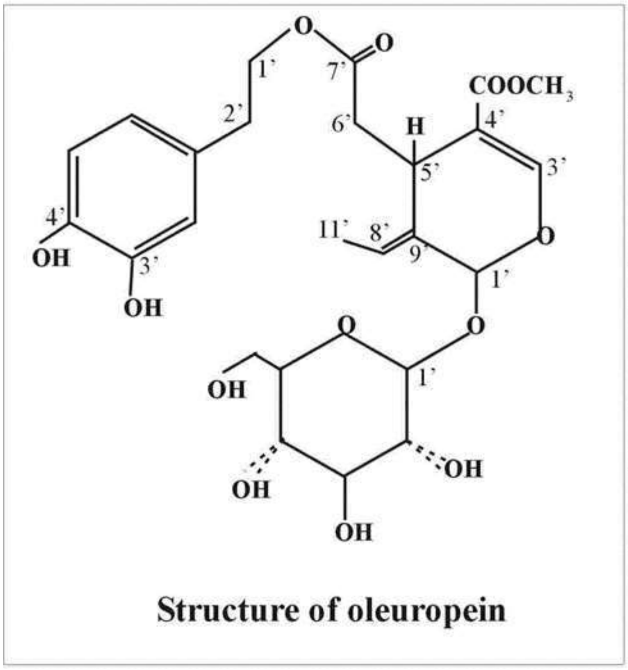

Fig. 1: Diagramic represention of Oleuropein

Protetive Effect on Different Organs

Protective Effect on Skin

Olive Leaf Extract (OLE) that down regulate the growth of tumors in mice chronically UVB irradiated, protect skin from carcinogenesis (Shamshoum et al., 2017) and UVB induced skin damages (Da Silva et al., 2019). It also increases the thickness of skin and reduce it elasticity (Wanitphakdeedecha et al., 2020a). The mechanism by which olive leaves reduces the incidence of tumor and tumor growth is by down regulating the expression of MMP-2, -9, -13 by decreasing amount of COX2 levels and expression of VEGF. OLE and its derivate protect skin from photo damage, photo aging and carcinogenesis induced by UVB (Kimura and Sumiyoshi, 2009). Oleuropein induction causes telogenic C57BL/6N mouse skin to develop anagenic hair growth. The stimulation of the Wnt10b/-castenin signalling pathway and an increase in the expression of the genes IGF-1, VEGF, HGF, and KGF in mouse skin tissues are linked to the influence on hair development in mice tissue (Tong et al., 2015). Oleuropein and its metabolite like hydroxytyrosol (HT) due to low permeability they penetrate skin barrier and shows cytoprotective effect by enhancing oxidative stress induced cytotoxicity in human skin fibroblast cells (Li et al*., 2022*), Similarly OLE cream has anti-inflammatory, antioxidant, anti-aging and photo-protective effects that lead to facial rejuvenation. The time period for improvement is 1 month after the treatment and it improve the skin texture, hydration and skin barrier function in 2 month period after the treatment (Wanitphakdeedecha et al., 2020b).

Protective Effect on Liver

The treatment reduced MDA generation, a byproduct of lipid peroxidation, and increased oxidative stress, NO levels, and protein carbonyl content, all of which are biomarkers of protein oxidation. Immunohistochemical labelling also demonstrated a decrease in iNOS and endothelial NOS (eNOS) expression in the liver. As a result, dietary supplementation of olives leaves extracts may be useful in lowering sensitivity to arsenic-induced lipid peroxidation. OLE mechanisms of HBV replication inhibition and anti-HBV action in vitro and in vivo protect the liver against viral harm (Yoon, 2018). They significantly (29%) lowered the increase of glucose in diabetic rats compared to diabetic rats that were not treated, and significantly (50,52%) decreased urea in diabetic animals that were not treated. Oleuropein decreases elevated levels of serum NO, MPO, urea, and creatinine in diabetic rats while also preventing leukocyte infiltration and glomerulosclerosis. The majority of diabetic injury, inflammation, and cancer pathogenic pathways involve oxidative stress (Ahmadvand et al., 2017). Protects HepG2 cells from PQ-induced necrosis by inhibiting Casp-3 cleavage while also serving as a pro-oxidant (Katsoulieris, 2016). In septic mice, OLE pretreatment reduces liver damage by down regulating several parameters such as alanine aminotransferase, lactate dehydrogenase, and aspartate aminotransferase (Alsharif et al., 2020). Free radical scavenging action, inhibition of interleukin 6, anti-inflammatory and hepatoprotective effects (Habibi et al., 2021). Nuclear transcription factor-B (NF- B) turns inactive by the nuclear transcription factor erythroid-derived 2-like 2 (Nfr2), which triggers the cellular antioxidant response. (Hsu et al., 2022), which prevents the cellular inflammatory response; and inhibition of the PERK pathway, which prevents EPR stress, autophagy, and lipogenic response (Soto-Alarcon et al., 2017). The protective effect of OLE is shown in the schematic diagram (Figure 2).

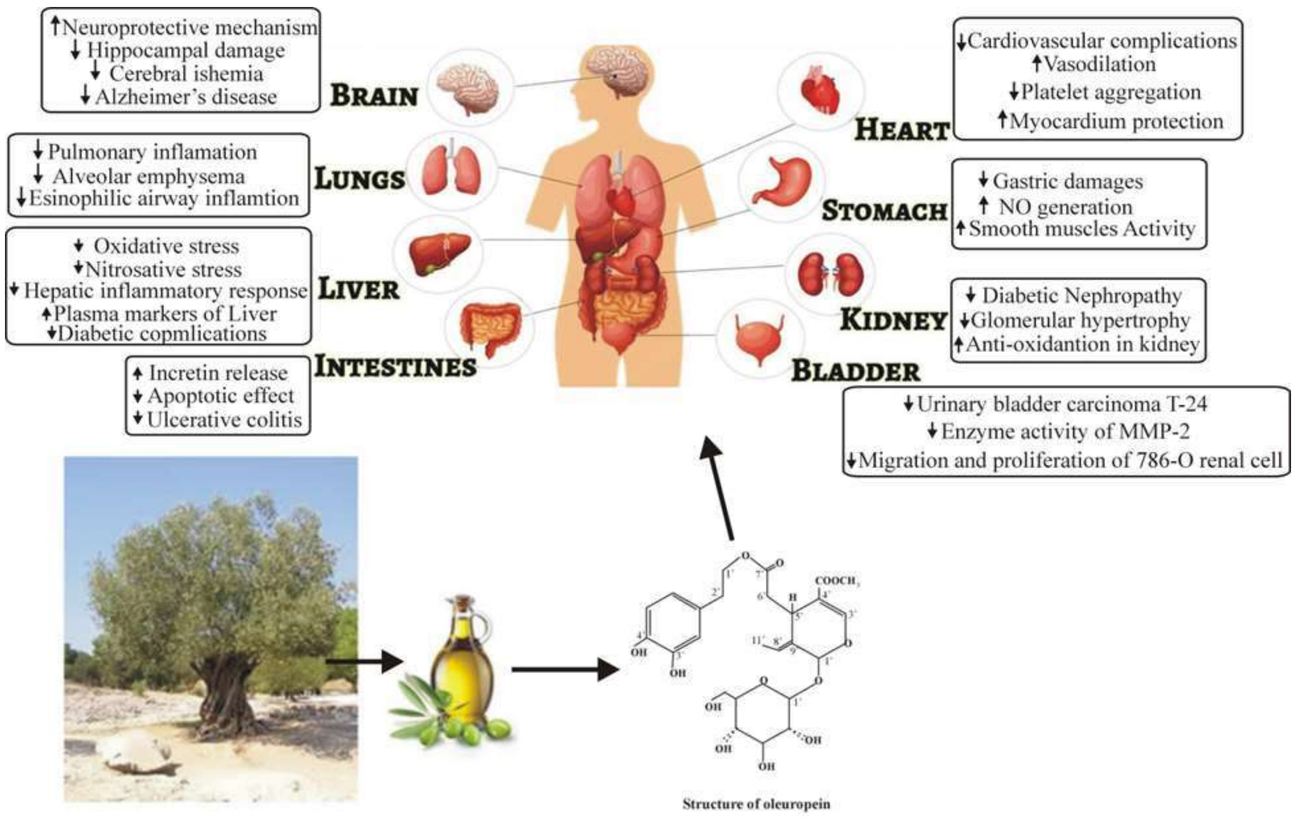

Fig. 2: Schematic diagram illustrating the various therapeutic effects along with underlying mechanism of action and highlight the application of OLE on different orangs

Protetive Effect on Different Systems
Effect on Cardiovascular System

The cardiovascular system is commonly known as circulatory system that is very vital for the healthy life of the individuals. The oxidative stress, inflammation effects this system very severely. Different strategies were being used previously like use of plant extracts. OLE has an antioxidant effect on cardiovascular system. It prevent Cardiac system from acute Adriamycin cardiotoxicity and hypolipidemic activities (Esmailidehaj et al., 2016). Oleuropein suppress copper sulphate induced oxidation of LDL and it prevents LDL cholesterol to accumulate in the arteries. Oleuropein stimulates HOCL, which affects apoB-100 by chlorination and acts as an initiating factor for LDL lipid peroxidation and this process prevent the arteries from cholesterol accumulation (Bulotta et al., 2014). It is a polyphenolic constituent with high antioxidant capacity comparable to a hydro soluble analog of α-tocopherol or vitamin E (Manna et al., 2004). Oleuropein cause better myocardial dysfunction following ischemic reperfusion injury. It also have vasodilatory, anti- inflammatory and anti-platelet aggregation effects (Esmailidehaj et al., 2016). This phenolic substance also reduces endothelial activation, which in turn reduces the lipopolysaccharide (LPS) driven production of vascular adhesion molecule-1 VCAM-1 in human endothelial cells. Oleuropein also act as direct cardioprotective phenolic compound because it prevent heart from cellular damage and oxidative stress by reducing the biomarkers of these abnormalities which are creatinine kinase, biomarker of cellular damage and glutathione which is marker of oxidative stress exposure of cardiac system (Bulotta et al., 2014).

Effect of Immune System

The immune system consists of cellular networks with various tissues and organs that protects body from the infections and diseases. The system consists of different immune gene that are regulated by various plant extracts. The OLE has protective effect immunity (Jin et al., 2018, Zhang et al., 2017, Vezza et al., 2019). It produces immunity by following mechanisms like It up regulate the antioxidant enzymes (mGCLC) (Alirezaei et al., 2012) and down regulate the enzymes of different parasites like (ldGCLC) (Sarbishegi et al., 2014). On the same time the Oleuropein has ability to increase the Th1 polarization and expression of immune genes like (INF- γ, TGF- β1, IL-10, IL-12β). In this immunomodullatory effect inhibit the IL-1β gene expression (Kyriazis et al., 2016).

Effect of Nervous System

OLE protect the brain (Sarbishegi et al., 2014, Shi et al., 2017) and spinal cord (Pourkhodadad et al., 2016) from oxidative stress (Alirezaei et al., 2012. DOI10.1007/s13105-012-0177-8). They played a role as neuro-protective against colchicine and protect form Alzheimer's disease (Omar et al., 2017) colchicine impaired the memory significantly due to oxidative stress (Pourkhodadad et al., 2016). Similarly OLE with hypothermia protect subcortical white matter by myelinating oligodendrocytes increasing the myelin density and up regulating oligodendrocyte from post hypoxia ischemia without producing any adverse effect on putamen or motor cortex neuron counts (Lee et al., 2021). OLE in high dose treat the Parkinson's disease by a mechanism like decreasing cell proliferation and cell growth, protection against the neurotoxin 6-hydrodopamine (6-OHDA), regulate the mitochondrial function (Elmazoglu et al., 2017) and also improve significantly cognitive function (Pantano et al., 2017).

Antimicrobial Effects of Oleuropein

Antibacterial Effect

A verity of antibacterial properties of Oleuropein has been explored in several research trails. The following is the order of antimicrobial activity of olive leaves against Bacillus cereus, candida albicans > E. coli > S. aureus > P. Aeruginosa. Additionally, no Gram-positive nor Gram-negative bacteria were selected for. This leaf extract has the power to denature proteins and alter the bacteria's cell membrane permeability. (Ghomari et al., 2019) Olive leaves contain oleuropein, which has potent antibacterial properties against both gram-negative and gram-positive bacteria as well as mycoplasma. By destroying the bacterial membrane and/or upsetting cell peptidoglycans, phenolic compounds that are comparable to oleuropein exert their antibacterial activity. Numerous researchers have looked into the relationship between oleuropein and membrane lipids using biophysical tests. Although the precise mechanism of oleuropein's antibacterial activity is still not fully understood, some writers have suggested that it is caused by the presence of the ortho-diphenolic system (catechol). The capacity of the glycoside group to pass through the cell membrane and reach the target location is modified, according to Saija and Uccella's 2001 hypothesis. It is also implied that the creation of amino acids that are essential for the development of particular microorganisms is in fact interfered with. Another mechanism put forth is the direct stimulation of phagocytosis, which is the immune system's response to all kinds of microorganisms. Oleuropein and its hydrolysis byproducts can prevent Salmonella enteritidis growth, Staphylococcus aureus enterotoxin B synthesis, and the germination and subsequent development of Bacillus cereus spores, development of Klebsiella pneumoniae, Escherichia coli and B. cereus is completely hindered by Oleuropein and other phenolic compounds (p-hydroxybenzoic, vanillic and p-coumaric acids) (Omar, 2010)**.** Antimicrobial properties identified in the extract are due to the high content of phenolic compounds present in the extract. Several human intestinal or respiratory tract pathogens, including Haemophilus influenzae, Moraxella catarrhalis, Salmonella typhi, Vibrio parahaemolyticus, Staphylococcus aureus, Vibrio cholerae, and Vibrio alginolyticus, have been shown to be inhibited by or grown more slowly by hydroxytyrosol and oleuropein, two other phenolic compounds. (Debib and Boukhatem, 2017). Gram-negative bacteria are less sensitive to polyphenols than Gram positive bacteria (Seow et al., 2014). Gram-positive bacteria are vulnerable to polyphenols because the hydrophobic polyphenol components interact with the bacterial membranes. The presence of hydrophilic cell wall is responsible for resistance of gram-negative bacteria to polyphenols (Calo et al., 2015)**.** A previous study showed that E. Coli motility was reduced by olive waste extract (Carraro et al., 2014)**.** To determine if OLE reduces L. monocytogenes cell motility, swimming experiments for cell motility were conducted. Because L. monocytogenes cells normally exhibited flagella without OLE treatment, but lost flagella when treated with OLE, OLE decreased the motility of L. monocytogenes. Cell wall damage was also observed. Changes in gene expression were also predicted using the genome model. Moreover, inhibition of biofilm formation in L. monocytogenes and S. Enteritidis was also done by OLE (Liu et al., 2017). Changes in the cytoplasmic membrane occur which lead to the disruption of the cell could envelop by the interaction of OLE and other compounds in olive oil with phosphatidylglycerol at the surface of the bacterial cell wall. Secretion of exoprotein produced by Staphylococcus aureus is effected by the olive's phenolic compounds aureus (Furneri et al., 2002)

Antifungal Effects

Antifungal activity of Oleuropein shows by mechanism like increasing the permeability of cell membrane, increase the apoptosis, inhibition of filament formation in fungus. 30 fungal strains were tested for activity of olive leave extracts which includes (*Alternaria alternata, Aspergillus chevoileri, Aspergillus chrysogenum, Aspergillus elegans, Aspergillus flavus* (four strains), *Aspergillus fumigatus, Aspergillus nidulans, Aspergillus niger (two strains), Aspergillus oryzae, Aspergillus parasiticus* (three strains), Oleuropein demonstrated the strongest antifungal activity of all the test substances (18 out of 30 fungi) Oleuropein's surface-active characteristics, which could alter the cell membrane's permeability, could provide an explanation for the substance's activity. (Korukluoglu et al., 2007).

Oleuropein's in vitro antifungal activity against *Candida albicans* revealed a minimum inhibitory concentration (mic) value of 12.5 mg/ml-1 with sub-inhibitory concentrations, with apoptosis being the main method of cell death. Antifungal medications target virulence factors that are crucial for the development of the fungal infection. Oleuropein influences the morphogenetic conversion of Candida albicans and inhibits filamentation. The cellular enzymes saps, which are released by C. albicans and are thought to be associated with the pathogenicity of the fungi, are inhibited by oleuropein. Oleuropein significantly reduced the cellular surface hydrophobicity (csh) of Candida albicans, a factor linked to adherence to epithelial cells, in both aerobic and anaerobic conditions, according to the hydrophobicity experiment. Moreover, the decrease in total sterol concentration in the membrane of C. albicans cells is another mechanism contributing to the antifungal activity. (Zoric et al., 2016)**.**

Olive leaf extract, of which oleuropein is the main constituent, packaged in chitosan nanoparticles exhibits in vitro antifungal action that inhibits both germination and growth. Electrostatic contact between the amine group of chitosan and the negatively charged components of the fungi's cell membrane (phospholipids, proteins, and amino acids) is necessary for germination, could be the proposed mechanism of action.cytotoxic activity exhibited by oleuropein is responsible for its antifungal activity (Muzzalupo et al., 2020). cell death by apoptosis as well as morphological changes inside nucleus are caused by oleuropein (Alfahdawi and Alsewuidi, 2022).

Anti-viral Effects

The salmonid rhabdovirus viral hemorrhagic septicaemia virus (VHSV), which causes hemorrhagic septicemia, was blocked from replicating in vitro by olive tree leaf (Olea europaea) and its primary constituent, oleuropein (Ole). Before infection, virus incubation with LExt or OLE lowered the infectiousness of the virus to 10 and 30%, respectively. Additionally, when applied to cell monolayers 36 hours after infection, LExt significantly reduced VHSV titers and viral protein accumulation (virucidal impact) in a dose-dependent manner. On the other hand, interactions with the viral envelope were suggested by the ability of both the LExt and Ole to prevent cell-to-cell membrane fusion brought on by VHSV in uninfected cells. (Micol et al., 2005). Oleuropein inhabit the Human Immune deficiency virus by blocking the viral entry, integration and replication into the host cell while in influenza virus it inhabit the hydroxytyrosol that causes abnormalities in the surface of virion envelope. Olive leaf extract rich with ethanolic acid reduce the metabolic activity and inactivate the neuraminidase activity (Salamanca et al., 2021).

Olive leaf extract produce anti-HIV activity and change the gene expression of HIV. OLE effect the HIV by targeting gp-41 envelope protein. The oleuropein and its metabolites like elenolic acid, aglycone, hydroxytyrosol all effect gp-41 by producing hydrophobic pocket on it Due to hydrophobic activity the the N terminal of gp 41 core N36 trimer is effective binding site (Bao et al., 2007. Olive leafs rich of phenolic compounds has been reported effective against SARS-CoV-2 in different in-vitro studies. It not only in-activate the virus but also produce anti-inflammatory, antipyretic, immunomodulatory and analgesic effect on same time. Oleuropein show in silico against (Mpro/3Clpro), blocking the ACE2 receptors and increasing the in-vitro virucidal activity simil, olive leafs and fruits decrease platelet's aggregation, prolonged the prothrombin time and finally prevent intravascular coagulation similarly, the phenolic products like hydroxytyrosol and maslinic acid produces anti-inflammatory and immunomodulatory activity by decreasing Intraleukin (IL-1β), (IL-5), (IL-6), (IL-13), (IL-17), TNF-α and inducible nitric oxide synthase (iNOS) in that way they inhibits sytokine strom and are effective for treatment of asthma and cough for COVID-19 patients (Abdelgawad et al., 2022).

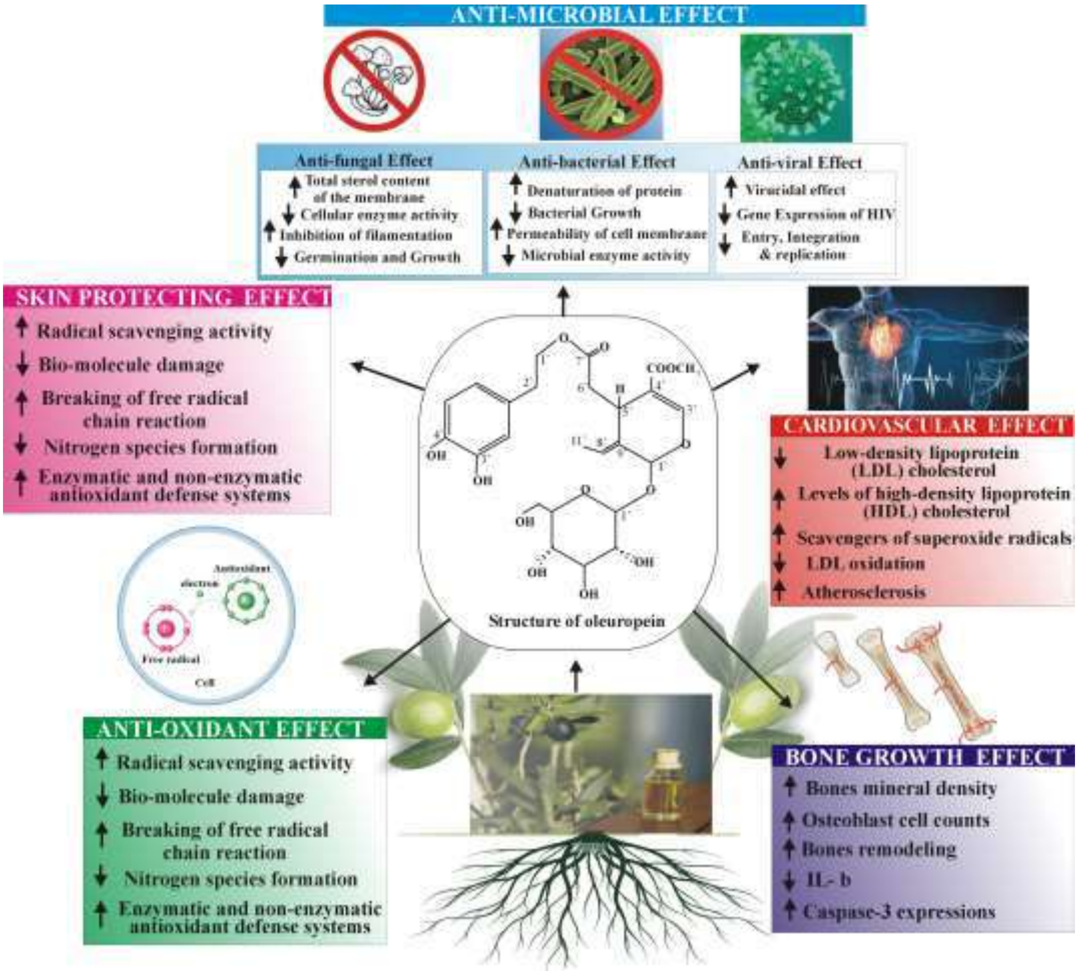

Fig. 3: Schematic representation of biological effects of Oleuropein for improvement of health disorders

Tables of Olive Leaves Extract Medicinal Effect

References	Type of collection	Dosage	Model	Mechanism of action
ANTI MICROBIAL				
(Martín-García et al., 2022)	olive leaves	28.1–49 mg g−1	Different Bacterial Stains	↑ denaturation of protein ↓ bacterial growth ↑ permeability of cell membranes
(Himour et al., 2017)	olive leaves powder	5 g	Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and Staphylococcus aureus	↑ inhibiting of bacterial colony ↑ antimicrobial potential ↓ side effects
(Lee and Lee, 2010)	olive leafs extracts	5.0 g	Gram positive (B. cereus, B. subtilis and S. aureus), Gram negative bacteria (P. aeruginosa, E. coli and K. pneumoniae) and fungi (C. albicans and C. neoformans)	↓ rate of growth of pathogens ↓ microbial growth
(Borjan et al., 2020)	olive leaves	-	E. coli, K. pneumonia, S. aureus C. albicans and C. neoformans	↓ microbial several enzymes activity ↑ damage to cell membranes
ANTI OXIDANT EFFECT				
(Czerwińska et al., 2012)	virgin olive	1 to 50 μM	Blood cells	↓ biomolecule damage ↓ formyl-met-leu-phenylalanine (f-MLP) ↓ phorbol– myristate–acetate (PMA) ↓ nitrogen species formation ↑ lipopolysaccharide (LPS) and Monocytes
(Irakli et al., 2018)	Olive leaves	250 mg	Chemicals	↑ radical scavenging activity (RSA)
(Lee and Lee, 2010)	Olive leaves	1 Ml	Chemicals	↑ radical scavenging ability ↑ nitrite-scavenging ↑ breaking the free radical chain reaction
(Martínez-Martos et al., 2014)	Oleuropein compound	25 μL	Male adult Wistar rats	↑ enzymatic and non-enzymatic antioxidant defense systems ↓ lipid peroxidation and protein oxidation levels ↑ thiobarbituric acid-reactive substances
BONE DISEASES				
(Díaz-Curiel et al., 2020)	Virgin Olive Oil	100 μL/day to 200 μL/day	Ovariectomized Rats	↑ bone mineral density ↑ recovery of bone elasticity ↑ recovery fractal dimension (complexity of bone) ↑ bone remodeling
(Alethari et al., 2021)	Olive Leaf Extract	45 mg/kg	Albino Rats	↓ level of TNF a ↓ IL- b ↓ RF ↓ MDA ↓ Albumin ↓ Bilirubin
(TASKAN et al., 2019)	Oleuropein	24 mg/kg/day	Wistar rats	↑osteoblast cell counts ↓ TRAP-positive osteoclast ↓ Inflammatory cell counts ↓ caspase-3 expressions
(MN Horcajada, M Beaumont et al. 2022)	Olea extracts	125 mg olf	Guinea pigs	↓ MAPK signaling pathway ↓ NF-Kb signaling pathway
CARDIOVASCULAR				

(Ruiz-Canela and Martínez-González, 2011)	virgin olive oil (VOO)	3.6 – 54.1 g/day	Human Beings	↓ low-density lipoprotein (LDL) cholesterol ↑ levels of high-density lipoprotein (HDL) cholesterol ↑ scavengers of superoxide radicals ↓ LDL oxidation ↓ atherosclerosis
ANTI-VIRAL EFFECT				
(Salamanca et al., 2021)	Olive leaf extract rich with ethanolic acid	-	Madin-Darby canine Kidney (MDCK-SIAT1) Cells	↓ viral entry ↓ viral integration ↓ replication ↓ Viral metabolic activity ↓ Neuraminidase activity
(Abdelgawad et al., 2022)	Oleuropein	20 µg/ml	In vitro study	↑ Virucidal activity ↑ Blocking ACE2 receptors in SARS-Cov-2
(Abdelgawad et al., 2022)	olive leafs and fruits	-	In vitro study	↓ IL-5,6,13,17 ↓ TNF-α ↓ Sytokine strom
SKIN PROTECTING EFFECT				
(Ichihashi et al., 2000) (Carrara et al., 2021)	super virgin olive oil	-	Mice	↓ ROS ↓ UV induced lipid peroxidation ↓ Skin tumors
(John et al., 2019)	Oleuropein	p 3: 10 mg/kg	Mice	↓ duration of skin carcinogenesis ↓ oxidative stress ↑ Chemoprevention

Other Protective Effects

Anti-Oxidant Effect

Olive leaf extract are sources of anti-cancer and anti-oxidant agents. Olive extracts are experimentally used against breast and hepatocellular carcinoma cells. The Reactive oxygen species that causes damage to DNA are severely suppressed by the olive leaf extract result in decrease the susceptibility to cancer and oxidative stress (Rashed et al., 2022.

Human dental pulp stem cells (DPSCs) cells were able to avoid MG-dependent glycative stress thanks to oleuropein, the main bioactive component of olive leaves. By increasing the activity of glyoxylase 1, the main MG detoxifying enzyme, through a mechanism involving the redox-sensitive transcription factor Nrf2, it reduces MG-induced glycative stress and DPSC impairment. (Monache et al., 2021).

Olive waste methanol extracts had the highest free radical scavenging activity and the lowest EC50, according to antioxidant assays, which were followed by ethyl acetate and petroleum ether extracts. Antioxidant activity was seen in all results, and it was dose dependant. Oleuropein's ability to scavenge free radicals and reduce phytotoxicity are both strongly correlated with the availability of hydroxyl groups in phenolic compounds, according to studies linking the efficiency of olive extracts to phenolic content. It is well known that phenolic chemicals act as an antioxidant to protect biomolecules from oxidative damage. Oleacein (di-aldehyde form of decarboxy-methyl linoleic acid), an oleo derivative, is one of the most prevalent elements of olive oil. Results revealed that oleacein was a more effective HOCL scavenger than oleuropein at inhibiting neutrophils, oxidative burst, and myeloperoxidase release. The Mediterranean diet's phenolic components, which are based on olive oil, guard against chronic degenerative disorders. (Czerwinska et al., 2012).

↑: Increase ↓: decrease f-MLP: formyl-met-leu-phenylalanine PMA: phorbol– myristate–acetate NSF: nitrogen species formation RSA: radical scavenging activity NSA: Nitrite-scavenging activity TNFα: Tumour necrosis factor α IL- β: Interleukin β MDA: Malondialdehyde TRAP: Tartrate resistant acid phosphatase, caspases: cysteine aspartic proteases, MAPK: Mitogen activated protein kinases NF-Kβ: Nuclear factor- kβ, LDL: low density lipoprotein, HDL: High density lipoprotein, ACE: angiotensin converting enzyme, SARS: severe acute respiratory syndrome, UV: ultraviolet

Conclusion

Olive Leaves extract produces many protective roles in experimental animals like antimicrobial, anti-inflammatory, anti-oxidant, anti-hypertensive, anti-hypercholesterolemic, anti-hyperglycemic, antithrombotic, diuretic, and anti-tumor properties. It has also radical scavenging capabilities, decreasing the tumor growth, increasing the permeability of cell membrane of bacteria; down regulate the glucose level in diabetic patients, protective role on skin, cardiac system and nervous system. There are many bioactive components, such as triterpenes, lignans, flavonoids, and secoiridoids. Olive leaf and its extract's key phenolic component, oleuropein.Due to wide range of therapeutic properties the Oleuropein used as medicinal purpose in different clinical trials. After exploring different published research, we found Oleuropein to provide the health benefit of this compound specially by adopting traditional Mediterranean diet as a model of healthy eating. However, several mechanisms are still not revel and are waiting for new researcher to explore them.

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Chapter 14

Ozonated Preparations: Ozonated olive oil as alternative of aseptic bactericidal germ-destroying drugs

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ABSTRACT

Bacterial infections are the most commonly occurring infections in all kinds of living beings, either humans or animals. Commonly, anti-bacterial drugs (antibiotics) are used for the treatment of these infections. With modernization and development in all fields, secondary infections have also progressed. Ozonated preparations are evolutionary therapeutic agents that have many characteristics: anti-microbial effects, wound healing, gastrointestinal ulcer treatment, and antifungal agents. Research has proven that ozone therapy is the most effective treatment for microbial infections. The preparation of ozonated products required an ozone generator, ozone gas, and oil. The main aim of using ozonated preparations, especially ozoanted oil, is to prevent AMR (anti-microbial resistance), which has been a global issue for decades.

KEYWORDS		
Ozonated olive oil, Antibacterial, Antifungal, Biocompatible, AMR, Wound healing	Received: 15-June-2024 Revised: 11-July-2024 Accepted: 15-August-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Bactericidal agents are antibacterial agents that have the capability to kill bacteria, while bacteriostatic agents retard bacterial growth. Antiseptics are antibacterial substances that reduce the chances of infection and are non-damaging to living tissues. Bacterial pathogens cause different infectious diseases in living beings [Table 1]. Organic or inorganic antiseptic agents are combined with biomaterials to induce antibacterial activities [Fig. 2]. The effectiveness of an antibacterial agent depends upon the strain of bacteria and their respective mechanisms (Saidin, 2021)

Ozone (O3) is an inherently unstable gas molecule that forms spontaneously from oxygen (O2) when electrical discharges and UV rays interact with the atmosphere. Ozone consists of three oxygen atoms arranged in a cyclic pattern. Ozone gas has a brief half-life, meaning it has a limited duration of existence. As a result, it cannot be kept and must be utilized immediately. Ozone generators produce it by a high-voltage gradient [Fig. 1]. Ozone possesses the ability to eradicate viruses, bacteria, and fungi. The oxidizing capabilities of ozone allow it to destroy the cytoplasmic membrane, cell walls, and lipid molecules in capsids (Donato et al., 2023).

Ozone therapy is a commonly employed method for promoting wound healing by addressing the issue of antibiotic resistance. Ozone therapy is commonly used to promote wound healing and provide antimicrobial effects (Borges et al., 2017). Ozonating the oil promotes the development of formulations that possess enough stability of ozone derivatives. The National Centre for Scientific Research has officially certified OLEOZON®, vegetable ozonated oil, as a pharmaceutical product in Cuba. This product is approved for both oral and topical medicinal use. When ozonated oil is used on wounds, it triggers a prompt response and involves a larger number of cells in the healing process. It also promotes better formation of new blood vessels (angiogenesis) by increasing the levels of vascular endothelial growth factors and cyclin D1 expression. Multiple research publications have shown that ozonated oil is beneficial for facilitating the healing of skin lesions. Ozone is an effective treatment for tissue repair due to its ability to induce wound healing and its possession of antibacterial, immunological, antioxidant, and oxygenating properties whether given topically as a gas or integrated into oils. Ozonated oil can be an effective supplementary therapy for the treatment of tissue lesions and wound healing. (Anzolin et al., 2020).

Fig. 1: Ozone generator

Fig. 2: Inorganic and Organic antibacterial agents

Table 1: Bacterial agents and their associated infectious diseases

Escherichia coli (E. coli)	Gastrointestinal and urinary tract infections
Staphylococcus aureus (S. aureus)	Wound and Skin infections, bacteremia, nosocomial pneumonia, endocarditis and toxic shock syndrome
Streptococcus pneumonia (S. pneumonia)	Otitis, Upper respiratory infection, sinusitis, pneumonia, and meningitis
Mycobacterium tuberculosis (M. tuberculosis)	Tuberculosis
Pseudomonas aeruginosa (P. aeruginosa	Bacteremia, Nosocomial pneumonia, and burn infections
Klebsiella pneumonia (K. pneumonia)	Hospital acquired pneumonia infection and bacteremia

Wounds treated with ozonated oil has considerably higher collagen content, tensile strength, and superoxide dismutase activity than wounds treated with a vehicle. Skin from the excised wound region that had been treated with ozonated oil had greater healing activity, according to histopathological investigation. Ozonated oil has the potential to be used therapeutically to treat wounds (Pai et al., 2014).

Antimicrobial resistance is the capacity of bacteria to remain unaffected in response to antibiotics given in a defined dosage. According to microbiologists, bacteria have a mechanism which controls a higher minimum inhibitory concentration (MIC) than the wild bacteria. Bacterial resistance to a specific antibiotic can be a natural property of the bacteria or a secondarily acquired mechanism. Bacterial cell have ability to survive the effect of antibiotics. The use of high doses of antibiotics in all sorts of infections can also be the possible reason for antimicrobial resistance. Antimicrobial resistance (AMR) is considered as a global problem (Acar, 2001).

Preparation of Ozonated Products

Ozonation is mostly conducted on unsaturated fatty acids derived from various oils, with olive oil being the most commonly utilized. Ozonized products are created by the use of ozone gas and specific ingredients such as saline for ozonated saline preparation or oil for ozonated oil preparation. Ozonated (ozonized) olive oil is produced by passing a mixture of ozone and oxygen gas through pure olive oil until it hardens. Ozonation, facilitated by an ozone generator, induces alterations in the chemical makeup of oil and generates novel biological characteristics. Therefore, the production of ozonated oil is a straightforward procedure. Ozone reacts with the double bonds of an unsaturated oil to create an unstable primary ozonide. This ozonide then breaks down to make ozonized derivatives, such as cyclical trioxolane, which is one of the active therapeutic ozone compounds (Chung, 2019) [Fig. 3]

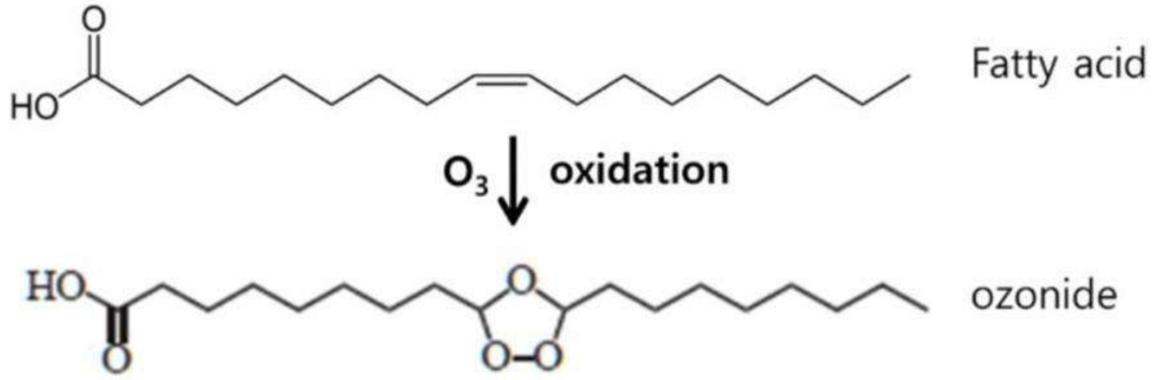

Fig. 3: Process of ozonation in fatty acid chain of oil (Chung, 2019).

Ozone and their Mechanism of Action

Ozone possesses two distinct properties: antimicrobial and antioxidant actions. It finds application as a clinical therapeutic agent for treatment of inflammatory conditions either acute or chronic, burn wounds, and diabetic ulcers. It also elevates tissue oxygenation and metabolism, influencing the delicate balance between oxidants and antioxidants. Through this mechanism, ozone can effectively regulate an imbalanced oxidant/antioxidant situation, reducing and adjusting levels of H_2O_2 and antioxidant molecule respectively. Moreover, ozone-generated peroxides contribute to the improved oxygen release and availability by modulating antioxidant molecules such as SOD and G6PH in red blood cells. This, in turn, promotes the metabolism and release of cytokines, autacoids, and growth factors, working in conjunction with its antimicrobial properties. Hence, it promotes wound healing more rapidly (Pivotto, 2020) [Fig. 4]

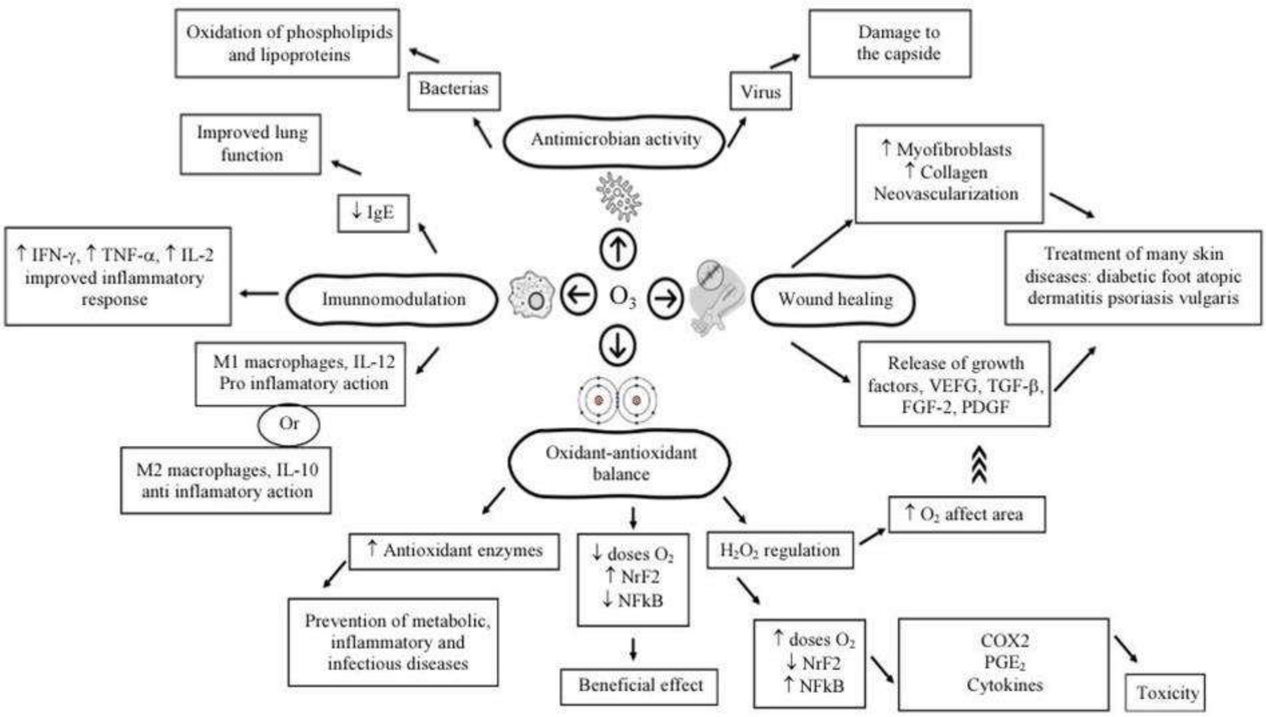

Fig. 4: Mechanism of ozone therapy (Pivotto, 2020).

Ozone has killing action against bacteria, viruses, fungi and protozoa. The bactericidal characteristic of therapeutic ozone concentrations indirectly activates components of cellular and humoral immunity as well as the non-specific defense system, which involves phagocytosis activation, enhanced synthesis of cytokines (interferons) and interleukin tumor necrotic factor (Pivotto, 2020).

Ozonated Olive Oil as Antimicrobial

Ozonated olive oil has following properties:

- Antimicrobial
- Anti-inflammatory
- Immuno-stimulant
- Angiogenetic properties

The features of ozonated olive oil are linked to its status as a non-antibiotic therapy, which aids in the reduction of antibiotic overuse in bacterial illnesses. The antibacterial efficacy of ozonized oil is assessed using the agar diffusion method. The oil hinders the proliferation of the majority of microbial strains, including bacteria and fungi. The process of ozonation of olive oil results in the creation of several harmful substances (hyperoxides, ozonides, aldehydes, peroxides, diperoxides, and polyperoxides) that are responsible for the antibacterial properties. Different strains of bacteria (*Staphylococcus, Streptococcus, E.coli, Pseudomonas, K. pneumonia, S. typhimurium*) respond differently when treated with ozonated olive oil (Ford, 2010).

Ozonized oil exhibits substantial inhibitory effects on the proliferation of mycelia. The activity of this substance can be ascribed to its ability to oxidize fungal cells, leading to the oxidation of lipids in the cytoplasmic membranes. This has a detrimental impact on genetic material, enzymes, intracellular proteins, and spore envelopes. The ozone molecule interacts with certain molecules found in cellular components, such as those with double bonds, sulfhydryl groups, and phenolic nuclei. This interaction enables ozone to pass through the fungal wall and disrupt the cell. As a result, damage occurs to membrane phospholipids, intracellular enzymes, and genomic materials (Fitzpatrick et al., 2018). The effect of ozonated oil on the fungal growth varies by specie and dose rate. It may also change the color of fungal specie, lysis of fungal cells, and process of sporulation of fungus.

Administration of Ozonated Oil

Ozonated oil commonly used by applying on the skin (topical route) but oral administration is also used as a recent therapeutic route. Use of ozonated oil has been increasing during recent years. Further may include; intramuscular, intravenous, subcutaneous, intravaginal or intra-rectal routes [Table 2].

Table 2: Ozonated preparations along with their route of administration

Ozonated Preparations	Routes of administration
Enteral ozonated oil and water	Ingestion/ PO*
Parenteral ozonated oil	Intramuscular, subcutaneous, IV*
Parenteral ozonated saline	Intra-tumoral
Routes systemic	Autohemotherapy
Topical ozonated oil	Inhalation
Topical ozone gas	Ozone bagging therapy

*PO= Per-oral
*IV= Intravenous

Topical Application of Ozonated Oil

Topical application of ozonated oil/saline is the most common therapy method. It is easy to use and absorb quickly by large a surface area. Blood supplies to the skin also help the more absorption of topical ozonated saline and oil respectively (Hussain et al., 2020). Table 3 shows the topical use of ozonated oil in different medical problems.

Table 3: Application of ozonated oil

Topical application of ozonated oil	Wound washing and healing Intestinal irrigation Mouth washing Sinus irrigation

Ozonated Olive Oil

Several liquid oils, after ozonation, can treat a variety of diseases. Olive oil has a green color. When olive oil is ozoned with ozone gas accurately, it loses its original color and looks colorless. The mechanisms of oxidizing the anti-oxidants and polyunsaturated fatty acids by ozone in the blood make the process of using ozoneated oil in the treatment of various pathologies easier. Ozonated oil helps patients with intractable fistulae or wounds heal effectively. Ozonated olive oil [Fig. 5] has a stable bactericidal effect, which may decrease to some extent if stored for 8 years. In some European countries, ozonated olive oil is not only used to treat skin diseases by being applied topically but is also used for disinfecting the skin lesions and promoting their healing mechanisms (Fitzpatrick et al., 2018).

Topical ozone exhibits significant antibacterial properties, favorable immunologic advantages, enhanced oxygenation capability, and a commendable safety profile, rendering it an attractive therapeutic option for both acute and chronic wounds. When comparing the effects of ozonated olive oil and pure olive oil on wound healing, it was found that wounds treated with ozonized olive oil had much smaller sizes compared to wounds treated with pure olive oil. A study revealed that wounds treated with ozonated water exhibited significantly reduced wound size in comparison to wounds treated with ozonated sunflower oil. Ozonated saline and oil offer advantages such as accelerated wound healing, increased reduction in wound size, and enhanced clinical indications of wound healing. Determining the concentration of oil in ozonation is crucial as a higher amount of oxidation does not always result in an improved therapeutic benefit (Hussain et al., 2020).

Fig. 5: Ozonated Olive Oil

Indications for Ozone Therapy

Ozone therapy is a cheap method and does not produce resistance to antimicrobial drugs. Ozone therapy has a wide range of benefits and treatment protocols in various infections and diseases.

Some of the indications for ozone therapy have been listed below:

- Arterial circulatory diseases,
- External ulcers and skin lesions
- Supportive therapy in cancer and rheumatoid arthritis
- Dental medicine including extraction of tooth and buccal infection
- Inflammatory conditions
- Post-operative reduction of inflammation, bacterial infections and enhancing blood circulation

Veterinary Field; Use of Ozonated Preparations

Over the past few decades, the field of veterinary care has increasingly embraced alternative medical approaches, including ozone therapy. Ozone therapy is a treatment technique used in integrated medicine where ozone is given to an organism to treat or improve certain diseases. The utilization of ozone therapy in the medical field has been reported for the past century, but its documentation in the veterinary field dates back only two decades. The initial application of ozone was as a disinfectant; however, the FDA has granted approval for the utilization of ozone therapy as an antibacterial agent in the food industry (Hawkins, 2006).

Veterinarians dealing in cattle medicine have expressed significant interest in utilizing ozone therapy to enhance and update traditional treatment methods. In veterinary medicine, ozone therapy is mostly utilized as a substitute for antibiotics in the treatment of several reproductive problems like as:

- Metritis
- Retention of fetal membranes
- Mastitis
- Infections of female reproductive tract
- Improving the reproductive efficacy in dairy

Ozone therapy in musculoskeletal disorders has two main directions:

1. Orthopedics
2. Spinal injuries both in large and small animals (Hawkins, 2006)

Ozone therapy used for relieve of chronic pain in muscular disorders, osteoarthritis, nerve damage, disc herniation, and osteomyelitis. In horses, ozone has excellent results in the treatment of chronic laminitis, ozone therapy showed satisfactory results in degree 1, 2 of lameness in equines. In canines, ozone therapy helps in relieving of pain due to spinal injuries and osteoarthritis. Hence, in small and large animals' use of ozonated preparation play a very key role and also ease the veterinarian clinical practices. With the use of ozonated products, it is very convenient for a veterinary doctor to restrict the irrational uses of antibiotics and play a role in decreasing the resistance due to antibiotics or other antimicrobial drugs. Ozonated preparations used intraarticular, exhibit exceptional results in horses by reducing the inflammation of joints, suppresses the complications with rheumatoid arthritis (Imani et al., 2013).

In clinical practice, ozonated water is used for its bactericidal and anti-inflammatory effects in dental diseases. Ozone gas therapy combined with O_2 cab is used in the treatment of the fistulas, bedsores and ulcers of the limbs. In addition, major autohemotherapy (auto transfusion with a large volume of blood treated with pure ozone gas) can be used for the treatment of herpes infections, hepatitis, blood circulation disorders, rheumatoid diseases and allergic diseases (Fitzpatrick et al., 2018). Minor autohemotherapy (intramuscular injection of a small volume of blood treated with ozone gas) is also used in the treatment of inflammatory disease, rheumatoid diseases and mild arterial circulatory disturbances. Rectal insufflation with ozone gas and local application of ozonated oil can be used for the treatment of inflammatory diseases and wound healing in veterinary field (Laku et al., 2021).

AMR and Role of Ozonated Products

Ozone demonstrates a synergistic effect when used with some antibiotics. Indeed, the application of O3 to Bacillus subtilis spores resulted in an increased susceptibility to heat and osmotic stressors as a consequence of damage to the inner membrane. Ozone is employed to mitigate the impact of antibiotic resistant bacteria (ARB) and antibiotic resistant genes (ARGs). Ozonated preparations have the ability to hinder the growth of multiple strains of bacteria and are responsible for their bacteriostatic activity. In addition to its bacteriostatic effect, it may also play a role in the eradication of bacterial species. Ozone (O3) enhances the antibacterial effectiveness when used in conjunction with chlorhexidine (Nasar et al., 2016).

In the same manner, ozonated oil and saline also have the characteristic of anti-viral and anti-fungal activities. Ozone can deactivate the virus activity and hence, reduce viral damage to living beings. In viral infection, there will be no specific treatment only supportive therapy adopted. With the help of ozonated preparations, it is easy to combat the different strains of virus and hence, prevention of the secondary bacterial infection. Retardation of fungal growth and inhibition of spore formation can be possible with the help of these ozone containing products. Ozone (O3) also functions by inhibiting the synthesis of enzymes necessary for the interactions between fungus and its host, as well as between different fungi. These enzymes are typically created to promote the growth and proliferation of the fungi within the host. Managing fungal infections in veterinary medicine is a complex task. However, with the advent of ozonated medicines, it has become feasible to treat such diseases with ease and efficacy. The efficacy of O3 against protozoa has been proven in laboratory settings, utilising ozonated oil and ozonated water, with several parasites including Leishmania, Giardia, Cryptosporidia, and Microsporidia (Bakoji et al., 2013).

Conclusions

The therapeutic efficacy of ozonized oil is ascribed to its antibacterial, antifungal, antiviral, and anti-parasitic characteristics. The high concentration of ozone in the oil contributes to its potent antimicrobial properties. The synergistic effect of ozone and its derivatives, such as ozonized molecules, make them potential alternative antimicrobial agents. Further scientific research is needed to understand the mechanisms of action and determine effective concentrations against various microbes, particularly in the context of the global Covid-19 pandemic. Therefore, the use of ozonated oil as a substitute for antimicrobial medications effectively decreases the likelihood of antimicrobial resistance (AMR) and contributes to addressing the global problem.

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Chapter 15

Medicinal Benefits of Copper Nanoparticles and its Toxicities

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ABSTRACT

Copper is an important metallic element that is found abundant in nature. Copper nanoparticles have promising therapeutic applications such as cancer disruption. The study emphasizes occupational exposure dangers, particularly the inhalation threats encountered by workers in companies that produce copper nanoparticles. Copper is vitally important for metabolic processes and contributes to lipid and iron metabolism, binding of tissues, and electron transport in both humans and animals. The chapter focuses on the relationship between copper and several diseases, including neurological disorders like Alzheimer's disease and Parkinson's disorder, emphasizing the need to maintain appropriate copper levels in the brain. It also investigates copper's effects on diabetes, cardiovascular disease, and the immunological response. Recognizing the possibility of medicinal advantages, the study closes by emphasizing the need for integrated investigations to better understand the health effects of copper nanoparticles, given their growing use in medical applications and possible hazards to both humans as well as the environment.

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INTRODUCTION

Polymeric pieces formed from synthetic or natural polymers, known as nanoparticles, are spherical. Their diameters range from 10-500 nm due to their large surface area to volume ratio and circular shape (Berry and Curtis, 2003). Rapid advancements in nanoparticle technology have made it possible to treat an extensive spectrum of ailments, including neurological conditions like Parkinson's and Alzheimer's disease. Nanoparticles attempt to manage these characteristics by adjusting their physicochemical properties (Sindhwani and Chan, 2021).

Copper, silver, platinum, gold, magnesium, zinc, alginate, and manganese are used to create nanoparticles of metal oxide (NPs), which are a type of nanomaterial. Copper and copper oxide nanoparticles stand out among nanomaterials as potential prospects for a wide range of medical applications. Applications of nanoparticles include treatments of various diseases (Dubchak et al., 2010; Chang et al., 2012). Furthermore, it is worth noting that there is a significant level of retention of metal oxide nanoparticles in the natural environment and food chain, and persistent consumption of them may have adverse impacts on individuals (De Berardis et al., 2010).

Human Exposure

There are four main ways that humans might come in proximity to manufactured nanoparticles: by consuming food, optical exposure, penetration through the skin, and inhalation. Depending on the fundamental particle size, nanoparticles have been demonstrated to settle in both the lower and upper respiratory tracts (Madl and Pinkerton, 2009). Compared to larger particles, the ability to stay in lung tissue for longer durations causes increased oxidative stress and an inflammatory response because of hypersensitivity and irritation (Madl and Pinkerton, 2009). Because of their minuscule size, single copper nanoparticles possess the ability to travel through the cell membranes and travel via tissues between cells (Lee et al., 2016). Over time, these particles find their way into the bloodstream (Lee et al., 2016). Occupational workers are the most probable cohort population to be exposed to Copper Nanoparticles by inhalation. For instance, when rubber and asphalt are produced, industrial facilities exude copper nanoparticles (Midander et al., 2009).

Copper as an Essential Metal

Both humans and animals need copper, which is an essential metal, for metabolic activities (Bhattacharya et al., 2016). It is required for lipid and iron metabolism, and additionally for the binding of connecting tissues, though at high exposure quantities, it becomes toxic (Siddiqui et al., 2013). Within the natural environment, fundamental copper can be found with zero valency configuration as a metal Cu^0, as an artificial nanoparticle CuNP, or as Cu^{1+} or Cu^{2+} in ionic form (Georgopoulos et al., 2001). Copper is an element with a number in the atomic structure i.e. 29, and an atomic weight of 63.54 a.m.u, that occurs naturally (WHO, 1998). Each copper compound exerts various levels of cytotoxicity in living beings. Cu in our environment may originate from an array of sources, including mineral deposits in the earth's crust and unintentional emissions from factories (Kim and Fergusson, 1994). Copper's distinctive chemical and mechanical characteristics allow it to be valuable throughout an extensive variety of domains (Ren et al. 2009; Zhang et al. 2014). Copper's mechanical characteristics encompass minimal rusting, potent conductivity in both heat and electricity, and a high degree of flexibility. Copper is often described to be 'chemically inactive' because it typically melts with acids with the aid of a specific oxidative source. Nonetheless, cationic copper bonds with a variety of biological molecules and has the potential to interfere with natural ecological and biological reactions. The ions of Cu^{1+} and Cu^{2+} are found in many enzymes and amino acids, and their presence has been linked to the movement of electrons across the pathway of electron transport in mitochondria (Georgopoulos et al., 2001). Copper serves as a naturally produced metal that plays a variety of roles in basic biological processes and is found in all domains of life. The function of copper metal being a biogenic metal is that it's found in low amounts in the environment. Adolescents obtain copper through food as well as water, both of which are essential for growth. Copper consumption in infants is limited because metal is supplied bundled up in protein found in milk rather than free. The protein ceruloplasmin is the major protein for transportation within the human system, having a substantial amount of storage of 6 copper atoms for each protein; nevertheless, it can also be coupled with different proteins, like albumin. Copper's biological activity includes the transfer of electrons catalysts in the production of proteins; fat, iron, and glucose conversion; hemoglobin, and muscle and tissue development (Malkin and Malmstro, 1970; Georgopoulos et al., 2001).

Nanotechnology is defined as studying and developing technology that involves the atoms, molecules, as well as macro-molecular levels (Poole Jr, 2003). Nanoparticles are particles that have at least 1 dimension and are not larger than 100nm. The quantum dots might have no dimension at all (Hudlikar et al., 2012). Nanoscale compounds are used in a wide range of applications, including electrical, magnetism and biological, medicine, beauty products, vitality, ecology, and catalysts, among other materials (Rathod et al., 2011). The main highlight is the importance of guaranteeing broader socioeconomic reforms and long-term growth (Kelsall et al., 2005). The field of nanotechnology is the 21st century's intellectual change, it is developing fast as a result of global expansion and research (Sivakumar et al., 2011). NPs of Cu_{12} have potential uses in optical science, medical technology, and the production of nano-fluids (Din and Rehan, 2017). Metallic nanoparticles made of copper (Cu NPs) have certain features that have incredible sensibility, heating, and anti-bacterial capabilities because of quantum interactions and a large ratio of surface to volume (Wang et al., 2000).

Copper Nanoparticles usage

Copper nanoparticles used as a sewage sterilizer (Ruparelia et al., 2008). They possess an excellent attraction for membrane-active parts of microbes and are being used to treat *Bacillus subtilis* (Ruparelia et al., 2008). Medicines that have copper as a basic ingredient are commonly utilized to disrupt cancers and malignant cells. Cu NPs may be employed in testing for hemoglobin disorders such as beta-thalassemia as they aggregate with a human erythrocyte mutation (Hokita et al., 2015).

Medicinal Properties of Copper

The ions of copper are widely recognized as a possible medicinal ingredient in numerous ailments. The innate antibacterial property of Cu^{+}, the one that they can confer on their metal complexes, is the driving force behind this method (Dalecki et al., 2017; Djoko et al., 2015). Complexes of metallic substances have demonstrated sensitivity in transporting or removing Cu from diseased tissues (Szymański et al., 2012). Cu has just been revealed as a vital part of the intrinsic defense system, which serves as the initial line of protection against invading pathogens. Most pathogenic bacteria have conserved metallic material acquisition, stability, and defense mechanisms (Solioz et al., 2010). Disruption of these routes frequently reduces survival as well as pathogenicity (Djoko et al., 2015).

Diseases Related to Copper Deficiency/Excess

Copper Linked with Pathology of Cancer

The use of copper is attributed to the abnormalities of several diseases, including malignancies and tumors, neurological degenerations and disorders (White et al., 2015), tumors in blood vessels (Urso and Maffia, 2016), and, more recently, infections caused by microbes (Djoko et al., 2015). The copper ions are emerging as both an appealing pharmacological target and a promising tool for accelerating the creation of innovative probing for pharmacological treatments (Denoyer et al., 2015). In clinical trials, modifying tissue levels of copper i.e., treatment with chelation or using the ions of copper on specific targets (Toor, et al., 2024) has proven effective in cancers or neurological disorders (Al-Hakkani, 2020).

Copper and Neurogenerative Diseases

Cu is an essential element of amino acids that are required for brain function. Cu, on the other hand, has been linked to the development of neurological disorders that include Parkinson's (PD), Alzheimer's (AD), and fatal motor neuron disease known as Amyotrophic Lateral Sclerosis (Ameh et al., 2019). AD causes synaptic breakdown, and elevated levels of copper, iron, and zinc, with increasing deposition of amyloid β proteins in tissues of the brain. The protein that makes up the amyloid precursor gene molecule, which is believed to be related to early symptoms that appear in Alzheimer's disease, has a site that binds copper (Aschner, 2009).

Alzheimer's Disease (AD)

AD is a complicated condition characterized by numerous impacted processes within the cell, including chronic oxidative stress, inflammation of the brain, abnormalities in the breakdown of energy, and others. Senile plaques and tangles of neurofibrillary cells are the most common tissue abnormalities linked with Alzheimer's disease (Biswas et al., 2005). A normal healthy grownup brain is believed to contain 7 to 10% of the body's overall Cu, which is present in the liver, considered the main organ responsible for copper regulation. Cu is especially abundant in the regions of the hippocampus and black nucleus of the adult brain of an individual (Hung et al., 2013). According to recent research, altering the normal balance of biological ions made up of metals such as Fe, Zn, Al, and Cu performs a significant role in the development of AD. Copper homeostasis has been studied extensively (White et al., 2015). Interestingly using oxidative activity of copper in Haber Weiss/Fenton processes increases the formation of hazardous ROS reactive oxygen species. As a result, the contradictory property of Cu is necessitated (Hung et al., 2013).

Wison's Disease (WD) and Menke's Disease (MD)

Two rare hereditary disorders, MD and WD, precision management for keeping the ideal balance and spread throughout the human brain while avoiding unwanted interactions with other regions of the cell clearly define the importance of copper and its toxic effects. WD is genetically recessive and Menke's disease is linked to X-chromosome, these are the best-known and understood homeostatic copper syndrome. ATP7A and ATP7B produce copper-transporting ATPases that are membrane-bound (Emerich et al., 2003). WD is a hereditary ailment of the metabolism of copper that causes cirrhosis of the liver and/or neurological disability. WD patients diagnosed with severe chronic liver disease develop symptoms late and experience more hepatic problems than those suffering from chronic or acute liver failure, as well as a lesser cumulatively free time from hepatic problems or mortality. Targeting tumor cellular Cu with the harmless chemical DSF inhibits proteasomal function, which results in selective death activation within cancerous cells (Fulton et al., 2023). MD is a syndrome that is X-linked hereditary syndrome that results from an alteration within the ATP7A genes. ATP7A gene produces a Cu-carrying ATP enzyme called ATPase. Disorders within this region cause deficiency of copper and ailments such as hypo-thermic neurological breakdown, cognitive impairment, anomalies in scalp hairs known as steel wool, breaking of the bone, and ruptured aortas. Even when flowing concentrations of copper are adjusted by injectable Cu treatment, a malfunction of ATP7A function in the blood-brain barrier causes a malfunction in Cu discharge via barrier cells (Brewer, 2003 a, b). Wilson syndrome is an autosomal regressive hereditary condition caused by mutations in both copies of the ATP7B gene. It oversees Cu transport to the endocrine route and released into the liver's bile (Brewer, 2003). Clinical symptoms include complications with liver function and brain impairment. The eye cornea is damaged, resulting in the Kayser Fleischer ring, a distinctive brown darkening of the cornea that is extremely peculiar to neuronal WD (Gaetke et al., 2003).

Diabetes

The condition of diabetes mellitus is frequently encountered in people with aceruloplasminemia. Diabetes is currently assumed to be an unfavorable outcome of elevated Iron ion buildup in the pancreas caused by a deficiency of ferroxidase functioning within tissues (Ghonimi et al., 2022). Whereas modified Cu absorption may either significantly or insignificantly affect the balance of glucose. Diabetes can also disrupt copper consumption (Ghosh, et al., 2015). The existence of Cu^{+} in the blood can accelerate the synthesis of more complex glycosylated final products. In diabetes, it is linked to the development of subsequent issues. Blood plasma contents in diabetic people appear to be greater than in non-diabetics. Plasma Cu was significantly greater in diabetic patients causing problems like retinal degeneration, high blood pressure, and cardiovascular issues (Halevas et al., 2018).

Cardiovascular Disease

In the world, most deaths are caused by cardiovascular disorders. In 2008, around 17.3 million people died because of cardiovascular issues, accounting for almost 31% of cases. This figure is expected to rise to 4.23 million by 2030, with these diseases accounting for 35% of all deaths. Most Asian countries have 2 to 5 times higher stroke fatality rate than in the West. Deficiency of experimental copper has been found to substantially increase the vulnerability of lipoproteins and heart tissue to peroxidation of lipids, thus raising the probability of coronary failures (Percival, 1998). The cardiac arteries and heart are sensitive to inadequate levels of Cu. Cardiovascular changes in physiology encompass larger myocytes, myofibril degeneration, broken basal laminae at capillary myocyte junctions, development of mitochondria, edema, and segmentation (Hordyjewska et al.,2014). Having insufficient copper results in anemia because the enzyme cytochrome oxidase is essential to produce blood. Copper reduction examinations reveal anomalies in blood pressure levels and stenosis of the aorta (Hu et al., 2018).

Response of Immune System

It's been proven that fibrotic and inflammation-related cytokines depend upon copper metal. Cu consumption changes during the inflammatory process, causing serum levels to rise. Cu is critical for immunological response, particularly, the production of IL-2 by active lymphocytes increases the functionality, and efficacy of humoral immunity along with cell immunology primarily affecting T cells (Mallick et al., 2021).

Toxicity of Copper

Toxicity of copper is typically a life-threatening condition caused by copper pollutants in food and water (Pohanka et al., 2019). Symptoms include feeling nauseous, throwing up, abdominal discomfort, migraines, a rapid heart rate, difficulty in breathing, and hemolytic anemia. As stated by Rajeswari et al. (2014), most susceptible individuals experience the effects at a concentration of 3 mg/l. Some researchers have speculated that chronic intake of contaminated water with high levels of copper may be harmful to vulnerable populations, such as newborns, and young children.

Toxicokinetic

The nose and throat tract are a particularly prevalent channel of NP contact. Nonetheless, the digestive system is also a possible way. NPs of copper can enter the alimentary canal by drinking water and eating food or by means of the mucociliary evacuation of the breathing tract, which is absorbed after swallowing (Rajput et al., 2018). When copper nanoparticles access the gut, they react with acid produced by the stomach, disperse within villi, or move throughout the intestinal tract. The epithelial cells of the intestine transfer copper nanoparticles to other parts of the body via circulation (Chang et al., 2012). Copper nanoparticles are gathered in the kidneys, liver, and spleen, causing abnormalities and damage to the organs (Rajput et al., 2018). It is believed that the copper nanoparticles' high surface area boosts their ability to react with H+ ions present in stomach fluid, solubility is allowed to the ionic form of copper which leads to excessive Cu absorption into the cells. Excessive Cu^+ within the liver cells interrupted the healthy functioning of the liver, slowing the breakdown of nutrients and triggering conjunctivitis and kidney tube deterioration. In rats, the toxicokinetic (TK) parameters of copper nanoparticles were investigated after just one dose of 500 mg/kg (Lee et al., 2016). The toxicity of CuNPs can have various effects on the body when the body is exposed in the route of exposure. The size of particles determines their deposition in the airways (Chang et al., 2012). Solubility in acid is what determines particle disintegration in the gut. The ability of particles to diffuse into tissue cells, which is influenced in part by their outermost charge, determines their overall dispersion (Chang et al., 2012). The toxicity effects of copper nanoparticles are enlisted in Table 1.

Table 1: Copper Nanoparticles Toxicity Effect

Cu NPs	Testing Body	Application Route	Outcomes of Cu NPs	Ref
CuO	Mussels	Ambient water	Increased susceptibility of mussels to infection by *Vibrio tubiashii,* causes sensitivity and cellular toxicity	{Torres-Duarte et al., 2018}
CuO	Mice 57BL/6	Intranasal	Pulmonary inflammation, fibrosis	{Lai et al., 2018}
CuO	Rats	Intranasal	Alveolitis, lung inflammation, damage of the epithelium	{Gosens et al., 2016}
Cu	Female rats	Intraperitoneal	Uterus weight reduction, apoptotic process	{Hu et al., 2019}
CuO	Rats	Oral gavage	Bone marrow, stomach, and liver damage	De Jong et al., 2018}

Human Exposure to Cu-based NPs

Individuals may be confronted with metallic nanoparticles of oxide from a variety of natural and industrial sources. Natural occurrences, such as volcanic eruptions, can produce nanoparticles, as the processes in industries that emit a lot of metal vapors, such as machining, grinding, melting point, molding, and soldering. Metallic nanoparticles are also purposefully used in retail goods that include medications, sunblock, dental products, and petroleum items, resulting in greater human susceptibility to them. The nanoparticles cause cell cycle detention, resulting in genetically planned cellular death. On the contrary end, excessive use of Copper NPs increases the risk of poisoning in human beings, other organisms that exist, and the surrounding environment. Furthermore, integrated research and investigations of copper-based nanoparticles in medical use, including hazards, health inspections, and benefits, are critical (Midander et al., 2009).

Conclusion:

Numerous approaches to cancer treatment use metallic nanoparticles. It has been demonstrated that nanoparticles can exhibit either immediate anti-tumor properties or intermediate hyperthermic antitumor effects, in culture and animals. Furthermore, nanoparticles can function as a traditional chemotherapeutic treatment, lowering the side effects and the necessary dosage. Considering chemotherapeutic perspective of metallic nanoparticles, there are still limits due to the cell-to-cell diversity utilized in each cancer environment, which impedes comparative investigations. Another constraint is the development of protein corona following nanoparticle binding to blood cells and proteins in the plasma, which affects in vivo clearing and dispersion. New research initiatives will allow the synthesis of novel forms of metallic nanoparticles. Copper nanoparticles, for example, have better and specific antitumor behavior, increased biological compatibility and bio-distribution, and are relatively harmless for healthy cells and tissues.

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Chapter 16

Medicinal use of *Nigella sativa* (KALONJI OIL)

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ABSTRACT

Black cumin, (*Nigella sativa*) is famous for the wealth of its medicinal qualities used worldwide by cultures since ancient times. *N. sativa* also known as black seed or black cumin; however, it originates from Southwest Asia, commonly people Middle East, Mediterranean basin and Southern Europe grow this. Black cumin has a significant historical and religious background with its roots in Islamic and Greco-Arab medicine. The seeds chemically contain various substances such as proteins, saponins, fixed oil alkaloids among others. Many of these compounds have medicinal properties but the major one being thymoquinone which exhibits antioxidant activity alongside anti-inflammatory effects besides being anticancerous also. The seeds also include essential fatty acids minerals together with vitamins all packaged within themselves naturally. Black cumin has been extensively researched upon regarding its pharmacological potential as an immunomodulatory agent against cancer cells; it could act as painkiller too. Black seed plant extracts show potent antimicrobial actions in vitro tests done so far proved this point beyond reasonable doubt. Moreover, based on different findings obtained during scientific investigations possible applications may include: diabetes management through insulin secretion enhancement anti-cancer activity due to interference with cell division processes at various stages anti-metastatic effect by blocking tumor spread into surrounding tissues antibacterial properties against Gram-positive bacteria like Staphylococcus aureus and Streptococcus pneumoniae antifungal activity towards Candida albicans. There's more in addition to what has already been mentioned above about its potential uses against different diseases black seed oil extract was also found effective against parasitic infestations such as roundworms and hookworms.

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INTRODUCTION

Kalonji, a common herbal treatment sometimes called black cumin or black seed, has several medical uses. Various degenerative conditions are treated with this seed. It's a wonderful herb with a long religious and historical background (Alam and colleagues, 2023). Approximately 20 species make up the tiny genus *Nigella*, commonly referred to as fennel flower, which is a member of the Ranunculaceae family (Niu et al., 2021). For thousands of years, *Nigella sativa* has been used as a spice, food preservative, and protective and therapeutic treatment for a variety of illnesses. It has long been believed in Islam that blackseed may cure every kind of illness, although it cannot stop aging or death (Sultana et al., 2015). Numerous studies have been conducted on this plant. Its chemical composition and biological properties have been thoroughly investigated due to its numerous historical applications. Numerous investigations on animals have already been conducted to determine the diverse effects of *N. sativa* oil on various elements of the metabolic syndrome, such as blood pressure and blood glucose (Najmi et al., 2008). Native to Asia, *N. sativa* is an annual flowering plant that is grown throughout the Middle East and Mediterranean region, South Europe, Syria, Turkey, Saudi Arabia, Pakistan, and India. People in Asia, the Middle East, and Africa have been using *N. sativa* extensively for ages in folk treatments, both as an oil and as herb. It is considered by Muslims to be among the best kind of medicinal treatment accessible. Black seed and oil have been characterized as a stimulant in several illnesses and as a useful treatment in hepatic and digestive disorders in the Greco Arab/Unani Tibb medical system (Shrivastava et al., 2011).

RESEMBLANT

The plant's seeds are referred to as "Black cumin" in English; in Arab nations, they are called "Habba Al-Sauda" or "Habba Al-Barakah." This plant is known by the common name "Kalonji" in Urdu. In Persian and Turkish, it is referred to as "Siyah Danch" and "Cork out," respectively. According to Sultan et al. (2012), the plant is also known by the names Love-in-a-mist, Habatul Barakah, Sonez, Krishana, Jiraka, and Sidadanah.

Table 1: Scientific classification of the plant (Hira Ijaz et al., 2007)

Kingdom	Plantae
Sub -Kingdom	Tracheobionata ;that is vascular Plant
Supervision	Spermatophyte
Order	Ranunculates
Family	Ranunculaceae Butter Cup Family
Genera	Nigella
Species	Sativa

A novel approach in contemporary clinical medicine is the use of natural substances to treat resistant illnesses. Natural products are being employed as alternative treatments for a variety of ailments due to their good clinical efficacy and minimal toxicity. Among them is *N. sativa,* also referred to as black seed (seed of capsulated plant), which has religious and historical significance, in Tibb-e- Nabawi it is recommended on daily basis (Prophetic Medicine). Hazrat Abu Hurairah said ‘’I have listened from Rasool Allah (PBUH) that there is cure for all diseases in black seeds except death and black cumins are shooneeze’’ (Hira Ijaz et al., 2017). One of the most well researched plants in terms of phytochemistry and pharmacology is *N. sativa.* Patients have used *N. sativa* seed extracts to treat polio, diarrhea, flatulence, suppress coughs, dissolve renal calculi, delay the onset of cancer, manage abdominal pain, diarrhea, and flatulence, and have anti-inflammatory and antioxidant properties (Al-khalaf et al., 2013). Furthermore, studies have demonstrated the anthelminthic, antischistosomal, antiviral, and antibacterial properties of essential oils. Furthermore, a range of pharmacological actions, including respiratory stimulation, hematological hepatoprotective, hypoglycemic, antioxytocic, antinociceptive, and immunopotentiation effects, are produced by the crude oil derived from the seeds (Godinho et al., 2014). The positive benefits of *N. sativa* oil on rheumatism, associated inflammatory disorders, headache, flatulence, and blood homeostasis anomalies seem to be related to these latter pharmacological characteristics. In addition, the seeds are used to treat eczema and bronchial asthma since they are thought to have carminative, stimulatory, and diaphoretic qualities (Gali-Muhtasib et al., 2006).

Vitamins, carbohydrates, mineral elements, lipids, and proteins—among which are eight or nine important amino acids—are the nutritional components of *N. sativa*. In addition, black cumin seeds include alpha hederine, saponin, and trace amounts of carvone, limonene, and citronellol. They also offer reasonably good levels of several vitamins and minerals, including Fe, Ca, K, Zn, P, and Cu. Most of the pharmacological effects are caused by the quinine component, of which TQ is the most prevalent. TQ exhibits anticonvulsant, antibacterial, antifungal, antioxidant, and anti-inflammatory properties. (Ahmad and Associates, 2013).

Chemical Constituents

Numerous investigations were conducted to determine the components of black cumin seeds. *N. sativa* seeds contain proteins, fixed oil, alkaloids, saponins, and essential oils. Additionally, the seeds of *N. sativa* contain saponin, a possible anticancer agent, and alpha-hederin, a water-soluble pentacyclic triterpene. Thymoquinone is the most prevalent quinine component, and it accounts for the majority of *N. sativa's* pharmacological characteristics (Sultana et al., 2015). Moreover, the essential oil has a notable 10% concentration of fatty acid ethyl esters. Thymoquinone produces dithymoquinonene and other oligocondensation products when stored. A fatty oil high in unsaturated fatty acids is also present in the seeds; it primarily consists of linoleic acid (50–60%), oleic acid (20%), eicodadienoic acid (3%), and dihomolinoleic acid (10%) (Phulwaria et al., 2019).

The fixed oil (32-40 %) contains: unsaturated fatty acids which includes: arachidonic, eicosadienoic, linoleic, linolenic, oleic, almitoleic, palmitic, stearic and myristic acid as well as beta-sitosterol, cycloeucalenol, cycloartenol, sterol esters and sterol glucosides.

Volatile Oil

Saturated fatty acids are present in the volatile oil (0.4-0.45%), which includes nigellone, which makes up the sole component of the oil's carbonyl portion, carvacrol, α and β-pinene, d-limonene, d-citronellol, and p-cymene. The seed's volatile oil also includes longifoline, 4-terpineol, t-anethole, carvacrol, and p-cymene (Forouzanfar et al., 2014). There are two distinct types of alkaloids found in black cumin seeds: pyrazol alkaloid, which contains nigellidine and nigellicine, and isoquinoline alkaloid, which contains nigellicimine and nigellicimine n-oxide (Forouzanfar et al., 2014).

Fatty Acids

GC-MS can be used to identify the various fatty acid types present in NS. The most common fatty acid is linoleic acid, which makes up 56%. The second-highest fatty acid found (24.6%) is oleic acid (Babayan et al., 1978). NS seed oil also contains trace levels of palmitic acid, stearic acid, eicosadienoic acid, linolenic acid, and a few additional acids. Fatty acids were found to make up 8% of all compounds found. But several of these compounds have demonstrated the ability to modulate the way that the sodium pump and cardiac glycosides interact (Hossain et al., 2021). The oil of N. sativa seeds has been highly studied, showing predominance of linoleic acid (1) (50–60%), oleic acid (2) (20%), myristic acid (3) (30%), and palmitic acid (4) (12.5%) (Tiruppur Venkatachallam et al., 2010; Kooti et al., 2016). Nigella seed oil from Morocco also showed that the major fatty acids were linoleic acid (1) (58.5 and 56.5%), oleic acid (2) (23.8 and 24.9%) and palmitic acid (4) (13.1 and 11.9%) using cold press and solvent extraction, respectively (Gharby et al., 2015). The major compounds were like those found in N. sativa seeds from other Mediterranean countries. These fatty acids were also reported as major compounds from the seed oils, extracted by n-hexane, of different N. sativa genotypes from India (Saxena et al., 2017).

Minerals such as potassium, phosphorus, calcium, and iron are included in *N. sativa* along with smaller levels of zinc, magnesium, manganese, selenium, and copper. There are also trace levels of alkaloids such nigellimine, nigellidine, and nigellicine. Significant amounts of phytosterols, including as β-sitosterol, avenasterol, stigmasterol, campesterol, and lanosterol, have been found in black cumin. (Amin et al., 2016).

Phytochemical Profiles

Black cumin's phytochemical makeup varies according to its growing region, maturity stage, processing procedures, and isolation methods. Black cumin's bioactive phytochemicals, which include major and minor secondary metabolites, have been divided into several chemical classes, such as phytosterols, alkaloids, polyphenols, terpenes and terpenoids, and tocols (Hannan et al., 2021). Depending on the producing region, maturation stage, processing method, and oil extraction methodology, *N. sativa* has a variable phytochemical makeup. Black cumin's bioactive phytochemicals are primarily found in the seeds (85%), bark (8%), and sprouts (7%). These phytochemicals include primary and secondary metabolites that fall into various chemical classes, such as terpenes and terpenoids, phytosterols, alkaloids, tocols, polyphenols, and other constituents. Additionally, there are two types of components: terpenic chemicals, which are volatile, and flavonoids, phenolic acids, tannins, and fatty acids, which are non-volatile (Derosa et al., 2024).

N. sativa seeds contain two types of alkaloids: isoquinoline alkaloids, which include nigellicimine and nigellicimine-N-oxide, and pyrazol alkaloids, or indazole ring bearing alkaloids, which include nigellidine and nigellicine. Additionally, the seeds contain α-hederin, a water soluble pentacyclic triterpene, and saponin, a potential anticancer agent. Trace amounts of other compounds, such as carvone, limonene, and citronellol, were also detected. The seeds of *N. sativa* also contain protein (26.7%), fat (28.5%), carbohydrates (24.9%), crude fiber (8.4%), and total ash (4.8%) (Ahmad et al., 2013). The seeds also contain a good number of various vitamins and minerals, such as Cu, P, Zn, Fe, and carotene, which is converted by the liver into vitamin A (Shafodino et al 2022).

The terpene and terpenoid family are the major chemical group of black cumin, to which belong TQ and its derivatives, such as carvacrol, 4-terpineol, α-pinene, thymol, t-anethol, thymohydroquinone (THQ), dithymoquinone, p-cymene, sesquiterpene, longifolene, and several other compounds. The wide range of black cumin pharmacological properties is mainly due to quinine components, the most prevalent of which is TQ (Derosa and associates, 2024).

Phytosterols lower total cholesterol and low-density lipoprotein levels, and are becoming more and more popular in the human diet due to their nutraceutical and medical effects (San Mauro-Martín et al., 2018). According to estimates from several researchers, the total sterol content of black cumin seed oil ranged from 18 to 42% of the unsaponified substance (Cheikh-Rouhou., 2007). The principal sterols detected were 5-avenasterol, stigmasterol, campesterol, and β-sitosterol (Matthaus, B., and ÖzCaN, M. M., 2011) It is thought that tocopherols suppress lipid peroxidation by having appealing free radical scavenging capacity. Black seed oil was found to contain a total of 9.15 to 27.92 mg/100 g of tocopherol, according to reports from a variety of sources. α- and γ-tocopherol and β-tocotrienol are among the most well-known tocopherols found in black cumin seeds. (Yimer et al., 2019).

Naturally occurring antioxidants, tocopherols prevent lipid peroxidation in biological membranes by scavenging free radicals. Tocopherols come in four different isomers, called alpha (α), beta (β), gamma (γ), and delta (δ), depending on where the methyl group is located on the chromanol ring. Out of all the tocopherols, γ-tocopherol has the highest level, varying between 8.57 and 34.23 parts per million (Kiralan et al.,2014). The extraction techniques used may have an impact on the tocopherol isomers' composition. Variations in the cultivated areas, maturity period, and storage conditions can all lead to variations in the tocopherol isomer concentration of black cumin (Hannan et al., 2021).

Nigella sativa seeds were found to contain 19 different polyphenols. These included caftaric acid, gentisic acid, caffeic acid, chlorogenic acid, p-coumaric acid, ferulic acid, sinapic acid, cichoric acid, hyperoside, isoquercitrin, rutin, myricetin, fisetin, quercitrin, quercetin, patuletin, luteolin, kaempferol, and apigenin. Quercetin and kaempferol were the most prevalent among them. Strong polyphenol antioxidants, kaempferol and quercetin, guard against oxidative cell damage and various illnesses like osteoporosis, lung cancer, and cardiovascular events. Additionally, by preventing platelet aggregation and LDL oxidation, kaempferol inhibits arteriosclerosis (Derosa et al., 2024).

Pharmacological Properties

Many pharmacological characteristics, such as those that are carminative, anti-inflammatory, analgesic, diuretic, emmenagogue, galactagogue, and expectorant, are shown by *N. sativa*, according to traditional Unani literature. *N. sativa* has been the subject of numerous phytochemical, pharmaceutical, and clinical investigations, which have shown off a few of its potential benefits, including anti-diabetic, anti-cancer, immunomodulator, analgesic, antimicrobial, anti-inflammatory, bronchodilator, renal protective, gastro-protective, and antioxidant qualities. *N. sativa's* exceptional therapeutic potential makes it one among the best-rated evidence-based herbal remedies. Most of the essential oil's therapeutic properties are attributed to thymoquinone, which is its primary bioactive ingredient (Alam et al.,2023).

Anti-cancer Properties

The black seed oil is an enhancer of the NK cells, which is a potential applicability in immune therapy. However, the components in oil may induce antioxidative–induced prooxidant effects thus the carcinogenetic effect (Khalife et al., 2016). Numerous processes evaluated by (Alam et al., 2023) highlight the anti-proliferative, pro-apoptotic, antioxidant, cytotoxic, anti-mutagenic, and anti-metastatic properties of *Nigella sativa*. Black seed oil has the potential to be used in immune therapy since it stimulates NK cells. However, the elements in oil may have prooxidant effects that are generated by antioxidants, which would result in the carcinogenetic effect. The primary component of black seed essential oil, thymoquinone, exhibits anti-neoplastic properties in many tumor cell lines both in vitro and in vivo. *Nigella sativa* methanolic extract, which was applied to SiHa human cervical carcinoma, demonstrated an 88.3% suppression of the cancer cells' ability to proliferate. It might be a different source of medication for the treatment of cervical cancer. (Islam et al., 2017).

Nigella sativa might also be used as an effective chemopreventive agent against breast cancer. In our current study, Nigella sativa seed was used for biological synthesis of AgNPs (Rohini et al., 2019).

Antimicrobial Activity

Antibacterial Effect

The volatile oil of *Nigella sativa* contains thymohydroquinone, which exhibits a highly significant effect on gram-positive bacteria, such as Staphylococcus aureus. It was found that *N. sativa's* diethyl-ether extract inhibited gram-positive bacteria in a concentration-dependent manner. Gram-negative and S. aureus bacterium Escherichia coli and pseudomonas aeruginosa (Ahmad et al., 2021). It functions synergistically with streptomycin and gentamycin and additively with spectinomycin, erythromycin, tobramycin, doxycycline, chloramphenicol, nalidixic acid, ampicillin, lincomycin, and co-trimoxazole. It works similarly to mupirocin topical. It can fight off resistant microbes, such as a lot of multidrug-resistant gram-positive and gram-negative bacteria. (Sowunm et al., 2023). *N. sativa* extract showed nearly identical outcomes to topical antibiotic mupirocin in the treatment of newborns with staphylococcal pustular skin infections (Rafati et al., 2014). When it came to numerous gram positive and gram-negative bacteria that were resistant to multiple drugs, such as S. aureus and P. aeruginosa, N. sativa showed encouraging results (Ahmad et al., 2021). Neem 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.(Badger et al., 2021).

Antifungal Effects

The oil content of NS is thought to contain oleic acid and β-sitosterol, which are responsible for its antifungal properties (Asdadi et al., 2014). Furthermore, NS inhibits the growth of certain pathogenic yeasts, including Dermatophytes, C. albicans, C. dubliniensis, C. glabrata, and C. krusei. *Trichophyton rubrum* is *trichophyton mentagrophytes*. A study conducted in vivo on mice revealed that the aqueous extract of NS seeds exhibited antifungal efficacy against the Candida albicans that causes candidiasis (Gaspar et al., 2020). According to a different study, nitric oxide (NO) is necessary for the candidacidal pathway in mouse neutrophils. It's possible that the plant extract's active ingredient(s) may encourage monocytes and granulocytes to produce nitric oxide, which will have strong antifungal effects and ultimately kill Candida albicans (Shokri et al., 2016). (Nadaf et al., 2015) There is more anti-dermatophytic activity in NS essential oil. Additionally, four species of Trichophyton rubrum and one each of *Trichophyton interdigitale*, *Trichophyton mentagrophytes*, *Microsporum cani*, and *Epidermophyton floccosum* were shown to exhibit some antifungal activity against dermatophytes in an ether extract of NS seed and its active component TQ. In 2005, Aljabre et al. found the NS and TQ ether extracts had minimum inhibitory concentrations (MICs) of 10–40 mg/ml and 0.125–0.25 mg/ml, respectively, which prevented 80–100% of the development of fungi. When applied at concentrations of 0.1% and 0.15%, NS oil completely suppressed non-dermatophytic filamentous fungus such F. moniliforme, Alternaria alternative, and Drechslera hawiinesis. (Hossain et al., 2024).

Antiparasitic Activity

According to studies, NS has strong anti-parasitic (anti-helminth, anti-cestodal, and anti-schistosomal) qualities. Significant anticestodal activity was demonstrated by NS seeds. Children with roundworm and tapeworm infestations can be safely treated with these inexpensive, readily cultivated native plant-based medications. The most effective oral doses were 40 and 50 mg per kg of body weight with no significant side effects. The most potent synthetic medication, chloroquinone, exhibited an 86% suppression rate against *Plasmodium yoelii* infection, compared to a 94% suppression rate with the methanolic extract of NS seeds (1250 mg/kg) (Akhter at al., 1991). Rabbits with coccidiosis were treated with oil emulsions and aqueous suspensions of NS seeds at a dose of 400 mg/kg. Higher amounts of the alkaloid nigellicine, which is lethal to parasites, are present in the emulsion. (Okeola et al., 2014). Both the total number of ova that accumulated in the colon and the liver, as well as the amount of *Schistosoma mansoni* worms in the liver, were successfully decreased by NS oil. Additionally, studies have demonstrated its efficacy against *Hymenolepis nana* and other helminths (Ayaz et al., 2007). NS was evaluated against mature *Schistosoma mansoni* worms, miracidia, and cercariae. NS shown potent biocidal activity against all stages of the parasite and an impact on the adult female worms' ability to lay eggs. The molecular mechanisms behind NS's biocidal activity on parasites, however, have not yet been fully explored (Mohammad et al., 2005).

Anti-inflammatory Characteristics

TQ and the oil derived from *N. sativa* are mediated by several pathways, including cytoprotective, immunomodulatory, antioxidant, and inhibitory effects on inflammatory mediators. The basis of the inflammatory response linked to infectious and autoimmune disorders is the activation of neutrophils, eosinophils, mast cells, lymphocytes, and macrophages in response to antigen exposure and/or host cell damage. amplification of immunological responses mediated by T cells and natural killer cells, (Bahrami et al., 2021). Due to its anti-inflammatory properties, *N. sativa* may be helpful in treating a range of chronic illnesses, including as diabetes mellitus, solid tumors, hematological malignancies, and cardiovascular disorders.10, 30 Pro-inflammatory enzymes and cytokines24, such as interleukin (IL)-1α, IL-1β, IL-6, IL-10, and IL-1831, are among the molecular targets responsible for many of the advantageous characteristics of *N. sativa* extracted oil and TQ. It has also been demonstrated that fresh and stored extracts from *N. sativa* exhibit distinct modulation patterns. (Bordoni et al., 2019). Additionally, it has been demonstrated that *N. sativa* oil extract decreases the expression of pro-inflammatory cytokines, such as cyclooxygenase-2 (COX2), inducible nitric oxide synthetase, tumor necrosis factor-α (TNF-α), prostaglandin (PG)-E2, and lipoxygenase, which are released by damaged or activated host cells within an inflamed joint. For these reasons, it may be beneficial in the management of rheumatoid arthritis and osteoarthritis.10,32 TQ has been demonstrated to elicit clinical and radiographic suppression of rat models of arthritis at dosages of 2.5–5 mg/kg/day (Shad et al., 2021). Even if therapy for encephalomyelitis began after the onset of the first clinical symptoms, *N. sativa* may be utilized as a preventative measure or a support system (Manoharan et al., 2021).

Antioxidant Activity

Nigella sativa decreases the production of superoxide (O2), hydrogen peroxide (H2 O2), and hydroxyl (OH) radicals. Several studies have carried out in different species shown the antioxidants activities of *Nigella sativa* when supplemented to animals' rations and human diets. Leong et al. (2013) investigated antioxidant and antinematodal effects of *Nigella sativa* and *zingiber officinale* supplementations in ewes. They found increase of the antioxidant activity in serum. El-Far et al., (2014) These antioxidant effects of *N. sativa* seeds might be due to the active constituents like thymoquinone, carvacole, anethole and 4- terepinol (Islam et al., 2021). According to a study done on broilers using 3, 5, and 7% black cumin, *N. sativa* boosted the activity of many enzymes, including glutathione, catalase, myeloperoxidase, and adenosine deaminase, and lowered hepatic liver peroxidation (Sogut et al., 2008). In a different study, black seed oil strengthened the antioxidant defense system in rats given CCl4 and decreased the lipid peroxidation activities of liver enzymes (Mohammed et al., 2016). Propylthiouracil (PTU)-induced oxidative damage to brain tissue caused by hypothyroidism can be prevented by N. sativa. In comparison to the PTU group, *N. sativa* extract (400 mg/kg) and vitamin C (100 mg/kg) enhanced the amount of time in the target quadrant and decreased the time latency. Animals treated with *N. sativa* extract (100, 200, and 400 mg/kg) and vitamin C had greater serum thyroxine concentrations than the PTU group. (Beheshti et al 2017).

Therapeutic Effects

Pulmonary System

Studies have also demonstrated that TQ has anti-asthmatic properties, working through a similar mechanism to anti-inflammatory medications used to treat asthma (Sarkar and others., 2021). When 15 asthmatics were given doses ranging from 50 to 100 mg/kg of boiled *N. sativa* extract, the results showed that it greatly improved forced expiratory volume and peak flow measurements of pulmonary function, though not as much as theophylline. (Fatima and associates., 2021). At the doses utilized, the boiling extract's antiasthmatic activity was somewhat comparable to that of theophylline syrup. The boiling extract's antiasthmatic effect started off similarly to theophylline syrups. Thirty minutes after delivery, theophylline syrup and boiling *Nigella sativa* extract started to have an antiasthmatic effect. (Boskabady et al., 2010). According to reports, *N. sativa* oil and nasal spray help patients with allergic rhinitis by lowering their IgE levels and nasal mucus congestion (Nikakhlagh et al., 2011). It has also been demonstrated that thymoquinone inhibits leukotriene C4 synthase and 5-lipoxygenase, two additional mediators of pulmonary inflammation (Dajani et al., 2016).

Gastrointestinal Tract

One of the primary active ingredients in *N. sativa*, thymoquinone (TQ) is primarily in charge of the plant's medicinal properties. According to reports, *N. sativa* inhibits the generation of stomach acid and preserves the mucosal membrane's permeability, making it a promising treatment for gastrointestinal diseases (GID) (Shakeri et al., 2016). Numerous researchers have examined the effects of *N. sativa* seeds, oil, and extract in different GID cases, and they have discovered that these substances are useful both on their own and in conjunction with other active agents. To accomplish several objectives, including targeted transport to the colon and regulated release, *N. sativa* extract has also been effectively added to a number of nano formulations, including nanostructured lipid carriers (NLC) (Zakir et al., 2022).

Male albino rats were used to test the effects of TQ (10 mg/kg body weight, orally) and *N. sativa* oil (10 mL/kg body weight, orally) against acute alcohol-induced stomach mucosal damage (Kanter et al., 2005). The results demonstrated that *N. sativa* oil reduced the ulcer index and MDA level and aided in the repair of gastrointestinal injuries as well as the levels of SOD, GSH, and GST. Similarly, TQ exhibits some protective action against stomach lesions, albeit not as much as *N. sativa* (Zakir et al., 2022). TQ produces new gastroprotective mechanisms by suppressing the proton pump, acid secretion, and neutrophil infiltration and enhancing mucin secretion and nitric oxide generation (Perera et al., 2021).

Nervous System

Neurotoxicity caused by *N. sativa* and its components, particularly its primary ingredient (TQ). Numerous research' findings have demonstrated that the *N. sativa* seed has positive benefits on a variety of central nervous system conditions, such as memory loss, epilepsy, and neurotoxicity. Additionally, based on the current review, it is determined that the principal ingredients of *N. sativa* seed benefited nervous system ailments by inhibiting AChE activity, raising GABAergic tone, and having special antioxidant properties. (Khazdair and others, 2015) Moreover, *N. sativa* can lessen acetylcholineesterase (AChE) activity and oxidative stress of the brain tissue in rats, as well as avoid harm to spatial memory following scopolamine treatment (Hosseini et al., 2015). *Nigella sativa* and its components' preventive effects against neurodegeneration and Alzheimer's disease (AD) (Cascella et al., 2018). The impact of *N. sativa* oil (NSO) on amino acid neurotransmitter alterations (epilepsy) brought on by pilocarpine (380 mg/kg, intraperitoneally) was studied. Following pilocarpine injection, aspartate, glutamate, GABA, taurine, and glycine levels increased dramatically in the cortex while aspartate and taurine levels decreased in the hippocampal regions. The aberrations caused by pilocarpine were not significantly improved by *N. sativa* oil (4 mL/kg) (N. A. Noor et al., 2012). The effectiveness of an aqueous *N. sativa* extract (40 mg/kg) in lowering the frequency of seizures in children with epilepsy (age 13) was assessed in a clinical experiment (J. Akhondian et al., 2007).

Effect on the Blood pressure and Heart Rate

Numerous studies have demonstrated the beneficial benefits of *N. sativa* on increased blood pressure and heart rate, and that consuming it is linked to a reduction in these conditions. It was discovered that *N. sativa* consumption helped the rats receiving cadmium treatment return to normal heart rate. In contrast, *N. sativa* was found to be useful in lessening the heart rate abnormalities caused by diabetes in rabbits that received an alloxan injection. (H. Shafiq et al., 2014).

Toxicological Properties

Lethal dose 50 (LD50) values for the active ingredients in black cumin seed, TQ, have been reported to be 2.4 g per kg of body weight in Swiss albino mice. The immediate behavioral changes observed at two and three g per kg of body weight of the composite were hypoactivity and breathing difficulties, while the late toxicities included a significant reduction in the virtual organ weight and glutathione distribution of the cardiovascular, hepatic, and renal systems. After two weeks of treatment with 6.4 g/kg of N. sativa aqueous extract (AqE) administered daily to mice for six weeks, one mouse died. However, after receiving 21 g/kg and 60 g/kg of the extract, respectively, mice 2 and 3 died at the 3rd and 5th week. Otherwise, according to K. Bensiameur et al. (2017), no additional deaths were reported because of applying any other doses. Furthermore, no mortality or toxicity signs were observed in the subchronic toxicity study conducted in mice given 30, 60, and 90 mg/kg/day of TQ for 90 days. However, there was a significant decrease in fasting plasma glucose levels, and there was no alteration in the toxicological significance of the body organs and histological investigation (O. A. Badary et al., 1998). When the fixed oil of black cumin was administered orally to mice and intraperitoneally to rats, the LD50 values were determined to be 28.8 ml/kg and 2.06 ml/kg, respectively. Chronic toxicity was also tested in rats administered daily with an oral dose of 2 ml/kg for 12 weeks' black cumin oil, but abnormalities in essential liver enzyme levels and histological modifications (heart, liver, kidneys, and pancreas) were not observed (Yimer et al., 2019). Two cases of allergic contact dermatitis were documented for two individuals who developed maculopapular eczema following topical application of pure *N. sativa* oil. The oil was ironically advertised as a treatment for "disorders of skin dysfunction, inflammation, acne, and eczema." Essential oils used in cosmetics and perfumes have been linked to incidences of contact dermatitis in the past. Topical corticosteroids were effective in treating these instances (Steinmann et al., 1997; Zedlitz et al., 2002). Validated most recently when it was demonstrated that giving rats oral doses of *N. sativa* fixed oil at a rate of 10 mL/kg for up to 12 weeks did not result in any mortality or appreciable changes to the main liver enzymes (Zaoui et al., 2021). Two cases of allergic contact dermatitis were documented for two individuals who developed maculopapular eczema following topical application of pure *N. sativa* oil. The oil was ironically advertised as a treatment for "disorders of skin dysfunction, inflammation, acne, and eczema." Essential oils used in cosmetics and perfumes have been linked to incidences of contact dermatitis in the past. Topical corticosteroids were effective in treating these instances (Steinmann et al., 1997; Zedlitz et al., 2002). TQ is helpful in shielding animals from the nephrotoxic effects of cisplatin. The decreased toxicity associated with linked nephropathy can be attributed to TQ's strong antioxidant capacity. (Hossain and associates, 2021). Specific dosages, such as 12.5 mg/kg given intraperitoneally, may function as effective antioxidants and protective agents against liver damage caused by chemicals. On the other hand, greater TQ dosages may cause oxidative stress and liver damage. Future research should, in fact, focus more on defining any potential toxicity for both the active components and the entire extract and oil of *N. sativa*, in particular (Salem et al., 2005). The autoimmune skin condition vitiligo is brought on by the death of skin melanocytes, which are responsible for producing skin pigment. An RCT comparing the effectiveness of applying fish oil and NS oil twice daily for six months to vitiligo lesions found that the former was more successful than the latter in shrinking the lesions. A highly bothersome form of papulovesicular dermatitis that significantly lowers a patient's quality of life is hand eczema. examined how NS ointment, betamethasone, and eucerin affected the patients' quality of life and the severity of their hand eczema (Tavakkoli et al., 2017).

Conclusion

In conclusion, *N. sativa* is an incredible herbal remedy that has been widely used for its medicinal properties due to its rich historical and religious background. It contains a variety of bioactive compounds including thymoquinone which is known to be responsible for most of its pharmacological effects. According to studies done on this plant so far it may be used as a possible treatment against various degenerative diseases because of its antioxidant, anti-inflammatory and anticancer activities. It has also shown promise in terms of being an anti-diabetic, immunomodulatory, analgesic as well as antimicrobial agent. In addition to this, black cumin has proven itself quite efficient when it comes to fighting against different types of parasites such as helminths or cestodes among others thus making them potentially valuable natural remedies for parasitic infections. Therefore not only could *Nigella sativa* serve as one among many therapeutic agents applicable across multiple health conditions, but more research needs to be conducted in order to fully understand what exactly these are and how they work in practice.

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Chapter 17

Use of *Moringa oliefera* in Veterinary Medicine

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ABSTRACT

Moringa oleifera has many fat soluble vitamins. *Moringa* also contains vital minerals that include: Magnesium, Copper and many such minerals. This plant also contains natural anti-oxidants. Death of the animals can occur sometimes due to poor quality roughages without supplementation, particularly during the dry season. It occurs because such fodders cause considerable weight losses. In chickens feed, Moringa meal can be used, because it causes excessive good production of animal body weight, so it is used without any restrictions. This plant increases the activity of goats when used as part of their diets. In animals, Moringa plays a great role in milk production increase, improves the affected growth and it has no effect on iron status. *M. oleifera* plant has been checked for antibacterial activity against different Clostridial infections. For this different isolates of its toxin related to its genotypes and has been compared with different commercial antibiotics in the field of veterinary medicine.

KEYWORDS		
Moringa Oleifera, Plant extract, Different animals, Veterinary Medicine, Good production	Received: 23-Jun-2024 Revised: 25-Jul-2024 Accepted: 01-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

M. oleifera has many fat soluble vitamins. *Moringa* also contains vital minerals that include: Magnesium, Copper and many such minerals. This plant also contains natural anti-oxidants. The flowers, leaves, pods, seeds, gums and bark of *Moringa* help in relieve of mineral and vitamin deficiencies stimulate normal blood-glucose levels, main a healthy cardiovascular system (Abdull-Razis et al., 2014).

Animal production major constraint in developing countries is the scarcity, quality of the whole year feed supply and fluctuating quantity of feeds. Death of the animals can occur sometimes due to poor quality roughages without supplementation, particularly during the dry season. It occurs because such fodders cause considerable weight losses. During the dry seasons, farmers can use shrubs and fodder trees for increasing availability of feeds and the quality fodders. A good and cheaper source of protein and micronutrients. *M. oleifera* leaves contain protein, fat, moisture and carbohydrates on a dry matter basis (Meel et al., 2018).

Moringa oleifera use in Chickens

In chickens feed, Moringa meal can be used, because it causes increase in the weight of animals, so it is used without any restrictions (Ramirez-Rojas et al., 2022). *M. oleifera* is an herbal plant and it has many therapeutic effects such as it has antiviral properties in equines. As we know that Influenza is a very communicable respiratory disease which causes high morbidity and mortality (Ashraf et al., 2017).

***Moringa oleifera;* use in Goats**

The nutritional status, health of ruminant animals and growth performance can be enhanced by *M. oleifera* leaves. This plant increases the activity of goats when used as part of their diets. It has also been estimated that if we dilute the commercial supplements with Moringa (Yusuf et al., 2018).

Comulative effect of *Moringa oleifera* in Animals

In animals, Moringa plays a very important role in increasing milk production, improves the growth and it has no effect on iron concentrations in animals. Moringa is used as a supplement in animals feed (Brar et al*.,* 2022). Moringa acts as a feed particle in the modern production of poultry (Castillo et al., 2018). *M. oleifera* helps in the control and treatment of dysentery causing parasites in livestock. *M. oleifera can be* used because it is used as immune enhancer effect and it also has contents which has antioxidant bioactive compounds which make animal's immunity strong (Elbarbary et al., 2023).

Use of *Moringa oleifera* against Clostridial Infections in Cattle, Sheep and Goats

Clostridium is most important pathogen that can cause severe and fatal infections in different livestock animals and hosts. For this different isolates of its toxin related to its genotypes and has been compared with different commercial antibiotics in the field of veterinary medicine. These pathogens are more prevalent in all livestock animals and different antibiotics can be used against these pathogens, but *M. Oleifera* is very effective against all these pathogens (Ibrahim and Altammar, 2024).

***Moringa oleifera* use as Leaf Meal in Starter Broilers**

Natural herbs applications for enhancing performance of production and health have been used to increase production of poultry (Onu and Aniebo, 2011). Its meal fulfills the need of all antibiotics for egg and meat production. The meal of this plant has great medicinal value and is using in almost all animals including livestock poultry and even in lab animals and experimental animals also (Mahfuz and Piao, 2019).

***Moringa oleifera* Use as Antioxidant in Feed of Dairy Cattle**

We can use Moringa as an anti-oxidant in the feeds of dairy animals because it has the property to neutralize the oxidants which are harmful for animal's metabolism and can effect as silage of Moringa in the feed of animals is given as a substitute for maize silage, so, it improves the health responsible traits of animals and improves the milk production in dairy cows (Cohen-Zinder et al., 2017).

***Moringa oleifera* Use in Liver Damage**

M. oleifera has efficacy against many respiratory pathogens. It is used in feedlot calves to decrease the prevalence of respiratory infections. It contains many such chemicals which are affective against liver diseases. With liver it also protects from many infections related to kidneys. Many molecular studies show its very beneficial effects on animal's health because it is effective against many *Mycoplasma* and *Salmonella species*. Moringa use for cure of diabetes and cancer and Moringa fortification in commercial products in now very common. We can use this in many medicines (Gopalakrishnan et al., 2016).

Use of *Moringa oleifera* in Rats for Colitis

For different pharmacological actions, *M. oleifera* has been using worldwide. We can use this plant in the treatment of peptic ulcer in adult rats (Abou-Zeid et al., 2021). The pathological changes due to different developmental stages of larvae of internal stomach worms. For extermination of intestinal helminths *M. oleifera* derivatives as this plant Seed oil of *M. oleifera* have high activity against the helminths as compared to leaf extract of *M. oleifera* (Saba, 2015).

Use of *Moringa oleifera* in case of GIT Parasites of Equines

As we know, as a means of transportation in rural areas of different countries in equines are used for draft purpose act against GIT parasites. Throughout the world, this animal has an important role in increasing the economy of people and improves the livelihood. Because of all these uses, the animal's welfare is very important and their health is poor. The reason behind all these the major problems are infection of GIT caused by parasites. The powder that is obtained from the leaves of this plant is used as a source to improve growth rate of meat as improves the quality of muscles and quality of meat of the pig in different areas of the world (Chen et al., 2021).

Use of *Moringa oleifera* in case of Goats Along with Sunflower Cake

The nutritional supplement contents present in meat of goats have been increased due to use of *M. oleifera* in animals. These things improve the milk and meat composition in goats as well as other small ruminants (Qwele et al., 2013). It helps in development of new antimicrobials. This plant is also used as a vegetable. It is beneficial in many diseases such as: wounds, tumors, and scurvy, inflammation and helminths diseases. Its Seeds are bitter, acrid, anti-inflammatory, antipyretic, purgative and ophthalmic.

They are beneficial in neurological disorders, inflammation reduction, to reduce different forms of fevers and disorders related to eye. Bark of this plant is used against the ascorbic acid deficiency disorders, and it shows sometimes red gums that are used for diarrhea. *M. oleifera* contains some compounds which decreases pathogens microbial growth and organisms' spoilage are phytochemical compounds. This plant's antimicrobials characteristics fulfill the needs of consumers who today are looking for healthy and safe products free from different preservatives. *M. oleifera* is very useful plants that can be easily used against the microbes found in whole Asia. Through researches, it is searched out that various parts of this plant are particularly important for microbes' growth. This plant can be used as feed additives in food industry, for synthetic antibiotics it can be used as a medicine and replacement of water cleaner agent for environmental protection (Mangundayao and Yasurin, 2017).

Moringa oleifera Use in Meat Animals

M. oleifera is used to determine the physical and chemical properties of chevon in crossbred goats. The consumer's sensory score influenced the chevon used in diet from goats supplemented with Moringa meal. The chevon will have higher first bite, flavor, aroma and juiciness. If we give supplements to crossbred goats with Moringa meal diet, it produces chevon with the high physical and chemical characteristics and sensory scores of consumers are good (Moyo et al., 2014).

If wound treatment is not done it will cause such infections that cause decrease in livestock production. As fast as the healing process occur, secondary infections will not develop and severity can be controlled by Moringa. Various treatments on clinics and clinical cases in field and many medicines are used that contain Moringa extracts, helps to control and speed up the wound healing process. But its use is not known by many farmers and practitioners (Balami et al., 2021).

Some substances that are active ingredients of *Moringa* that can be used to hasten the process of healing in animals. These plants have effects on all systems diseases in humans and livestock. There are some phytochemicals present in Moringa leaves that act as: antioxidant, antimicrobial activities and anti-inflammatory that can help the healing process of wound (Ijaz et al., 2016). So, we have explained enough about Moringa leaves that have their medicinal function in livestock (Waqiah et al., 2023).

Effect of *Moringa* on Production of Lambs

The leaves of Moringa have a good impact on productive performance of animals. The quality of sheep products improves M. oleifera. Livestock industry good feed consumption, which can be used as supplements of feed because it has high protein content and it is free of compounds that are important for secondary infections. *M. oleifera* can be used in place of maize meal in plans of livestock supplementation (Damor et al., 2017).

Moringa effect can be checked by orally administration of this plant daily to the animals. M. oleifera seed extract can be given for weeks and blood tests of animals can be performed to check different blood values either Moringa is affected or not. As we know, excess of everything is bad, so if Moringa extract is given in high quantity it will lead to health problems in animals (Hamzah and Dawood, 2023).

Moringa Leaves use for Milk and Serum in Animals

In many developing countries, Moringa has medicinal value and has been used against various infections as well as to increase milk production and to improve blood serum contents. It is used in feed of animals, particularly in dry regions, because there is poor quality of different feed sources (Al-Juhaimi et al., 2020). Animals are given the feed which contains crop products that can be used by farmers and hay of low quality is used that lacks important minerals but high in other contents that result issues related to digestibility and also effects energy levels may be due to deficiency of protein and that can result, improper growth and less milk production and quality. Therefore, instead of cheap protein sources are needed with a balanced quantity of that under dry conditions can be both fast produced and abundant (Malik et al., 2019).

Some of the cheap and good alternative protein sources are fodder, shrubs and trees that are very used effectively in all animals. Plant has different species and it has been used for different purposes in animals. These trees are economically important and have industrial importance because these are fast growing things and very good source of animal feed. Countries of East and Africa have widespread cultivation of these trees (Olugbemi et al., 2010).

This plant that has a property to cure diseases and is a good source of protein in animals feed. *M. oleifera* can be used in the feed of animals during dry seasons and it has many advantages which includes the property to be grown under different conditions. It has good quantity of protein and mineral contents that helps to make its utilization in the synthesis for microbes. It contains high amount of naturally present antioxidants and it also has a very less amount of anti-nutritional compounds (Minaiyan et al., 2014).

Many researchers have studied *M. oleifera* in the improvement of goat production; these studies are done on different animal breeds. Leaves are cultivated in whole world which are rich in amino acids, fiber and minerals contents due to high nutrition. *Moringa* has the ability for grow in dry climatic conditions. Therefore, we investigate the use of dry *M. oleifera* leaves has a good impact on milk and serum quality of goat (Alwaleed et al., 2020).

Effect of Dry *Moringa oleifera* Leaves on Broiler Chicken Performance

In the poultry industry high mortality is due to poor quality of feed. Therefore, natural sources which are chemicals for growth. Phytobiotics are used in place of Moringa for increasing growth of chicken; among the market phytobiotics. For growth of broilers, the addition of *M. oleifera* in broiler diets is used at different levels (Fouad et al., 2019).

Pharmacological and nutritional benefits for humans of *M. oleifera* leaves are numerous; they have benefits for livestock when used in feed of broilers. It has different properties between compounds present in *M.oleifera* leaves act on different animal's body parts. *M. oleifera* leaf meal effect on growth performance, gut integrity and or carcass yield, nutrient utilization efficiency as an alternative protein source or its extract is used alone or in combination with extracts of other plants (Nkukwana et al., 2014).

***M. oleifera;*-Benefits in Mice Reproductivity**

Leaves of *M. oleifera* have many protective activities. The extract of Moringa has six carbon compounds that increase the reproductive potential of male mice. If we add something, then we can say that hormone is used as supplements. So, hormones help in improvement of maturation rate in sheep. Different internal components of reproductive structures can be treated by using this plant's leaves.

Improvement in reproduction plays an important role in the survival of this little creature. Affective livestock production is playing role in regulating reproductive performance by using advanced reproductive technology is very important in all animals. Some nutraceuticals made from natural plants, that include some important agents and that have very good impact on animal reproduction. Though, we have very little information that if we give Moringa in diet to check the effect of Moringa powder on different blood parameters. These parameters indicate its effect on gene expressions in mice, thus to determine its role in animal reproduction is necessary (Rizk et al*.,* 2023).

Livestock sector in the whole world and trade of animals if checked, *Babesia* and *Theileria* discussion is first priority, these parasites affect blood and by ticks are transmitted. So, this can effect and these parasites affect blood cells. These infections can result in heavy economic losses in livestock and other animals. The symptoms of these diseases are: sickness, hemoglobinuria, lethargy, jaundice, and mortality. The prevalent of parasitic infections in cattle are *Babesia bovis* and *B. bigemina*. In horses, the main causative agents of the disease are different (Zeng et al., 2019).

But, no laboratory animals are available for cattle or equine infections. Moringa is effective against all these parasites. Presently Moringa is used against different internal as well as external parasites. So, Moringa is used as an alternate of antipiroplasmic drugs. In this way, the opposite to piroplasm efficiency of *M. oleifera* extract is considered very much. *M. oleifera* is the most widely distributed plant. It has an extensive range of medicinal and dietary uses all over the world. In fact, Moringa is rich in such natural compounds which can be used against the cancer. And it is also considered a very good source of micronutrients and macro. Moringa is effective against all types of infection. But, up till now there is no research on the efficacy of this plant extracts that they can be used against piroplasm. So, as a result, we can see this plants effect against all types of parasites (Mendieta-Araica et al*.,* 2011).

In tropical livestock production systems, one of the most important limitations is underfeeding. This happened due to limitations in both quantity and quality of animals feed. This is mainly marked throughout the dry season, because in dry season, mature and dry pastures are natural pastures. Therefore, we have a low nutritive value of animal diets that can be fulfilled by using Moringa. Most of the areas in tropics, Elephant grass creates the basal diet for dairy cows. Though, due to the relatively low quality of this grass, it is a quick source to provide a protein-rich feed supplement (Bashir et al*.,* 2016).

Conclusion

M. oleifera leaves contain protein, fat, moisture and carbohydrates on a dry matter basis. During the dry seasons, farmers can use shrubs and fodder trees for increasing availability of feeds and the quality fodders. In chickens feed, Moringa meal can be used, because it causes increase in the weight of animals, so it is used without any restrictions. This plant increases the activity of goats when used as part of their diets. *M. oleifera can be* used because it is used as immune enhancer effect and it also has contents which has antioxidant bioactive compounds which make animal's immunity strong. *Clostridium* is most important pathogen that can cause severe and fatal infections in different livestock animals and hosts. The meal of this plant has great medicinal value and is using in almost all animals including livestock poultry and even in lab animals and experimental animals also. It contains many such chemicals which are affective against liver diseases. With liver it also protects from many infections related to kidneys. Though, due to the relatively low quality of this grass, it is a quick source to provide a protein-rich feed supplement.

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Chapter 18

Therapeutic Benefits of *Berberis vulgaris* in Veterinary Medicine

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ABSTRACT

As the problem of antimicrobial resistance is increasing, there is more focus on the use of traditional natural products. *Berberis vulgaris* is one of these natural products which is N alkaloid known as berberine present within, responsible for its efficacy against different bacterial, viral, and parasitic infections of the animals. It grows in many regions of the world. One of its amazing features is that it can grow in regions with low water and high salt content. It is also resistant to seasonal variations. Its side effects are negligible. It is not rapidly absorbed in the body, but once absorbed gives valuable results. It has anti-parasitic, antifungal, and antibacterial properties thus improving health of the animals. Its methanolic ethanolic, fruit, leaves, water, and root extracts are being used. Currently, we are using *Berberis vulgaris* against *Leishmania*, *E. coli,* and *Candida* infectious agents. However, its exact mechanism of action is not known to us. So, there is a need for further research to find its exact mechanism of action so that it can be effectively used in the treatment of a range of anti-parasitic, antifungal, and antibacterial agents. In this way, we will be able to deal with antimicrobial resistance efficiently.

KEYWORDS		
Berberis vulgaris, Resistance, Antiparasitic, Antifungal, Antibacterial	Received: 17-May-2024 Revised: 20-Jul-2024 Accepted: 13-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

The medicinal plants have been used by the nations for a long period, probably from thousands of years ago (Bahmani et al., 2014). Despite the emergence of synthetic drugs, they have a great significance because of their safe use and low side effects as compared to synthetic drugs (Rahimi-Madiseh et al., 2017). The *Berberis vulgaris* is one of them. It is commonly known as barberry (Imenshahidi and Hosseinzadeh, 2016). It is a yellow-colored shrub and berries are its fruit farm. It is a common ingredient used in homeopathic medicine (Arayne et al., 2007). It belongs to the genus *Berberis* (Mokhber-Dezfuli et al., 2014). An alkaloid, known as berberine is a main component of *B. vulgaris* that is responsible for the development of its efficacy (Ni et al., 2015; Končić et al., 2010). It can survive even in the harsh environment because it reproduces through both sexual and asexual reproduction (Peterson et al., 2005). Iran is the major producer country (Sun et al., 2021). Traditionally, it is being used in the treatment of various ailments (Rad et al., 2017). Until the new therapeutic agents are developed using *B. vulgaris*, we can focus on its available component berberine for the treatment of various disorders (Imenshahidi and Hosseinzadeh, 2019). It does not show absorption from the gut of animals and accumulates in the intestines. The best route for its administration is the intraperitoneal route. Through this route, it is rapidly absorbed in the body. Once it gets absorbed in the body, it is distributed in all parts of the body equally. Meanwhile, it also increases the bioavailability of other therapeutic agents (Habtemariam, 2020). Sterols, phenols, tannins, and triterpenes are also its major components (Mokhber-Dezful et al., 2014). In veterinary medicine, it has broad roles. Some of these roles include antifungal, antiparasitic, and antibacterial effects in different species of animals. These are described in detail in this chapter.

Antiparasitic Effects of *B. vulgaris* in the Animals

According to several studies, berberine's antioxidant activity protects animal's splenic, hepatic, renal, and testicular tissues from the organ damage caused by *Schistosoma mansoni* (Dkhil, 2014; Dkhil et al., 2014; Al-Quraishy et al., 2013). Similar preventive effects have been demonstrated in cases of malaria caused by *Plasmodium chabaudi*, which causes splenic damage (Dkhil et al., 2015). In an *in-vitro* setting, berberine and *B. vulgaris* methanolic extract alone have shown strong scolicidal effects against protoscoleces of hydatid cysts at low doses and short intervals of exposure (Mahmoudvand et al., 2014a), thus treating cystic echinococcosis in animals. In an *in vitro* model, the ethanolic extract of *B. vulgaris* fruits also demonstrates a strong leishmanicidal action against *Leishmania tropica* (Mahmoudvand et al., 2014b). It also reduces the infection load of *Giardia lamblia, Entamoeba histolytica,* and *Trichomonas vaginalis* and causes structural changes in them. Similarly, when it is used with another compound known as pyrimethamine, then it significantly reduces the burden of malaria, more effectively than the other antibiotics such as the tetracycline class. In another research, it reduces the lesions in the animals caused by *Leishmania braziliensis* and *Leishmania donovani* (Mahmoudvand et al., 2014c). The *B. vulgaris* ethanolic extract reduces the size of cutaneous leishmaniasis (Fata et al., 2006). Similarly, mice afflicted with cutaneous leishmaniasis have demonstrated strong suppressive effects (90 percent recovery) using a lotion made from *B. vulgaris* root bark extract (Salehabadi et al., 2014). Another study suggested its exact mechanism of action against leishmaniasis. It caused an increase in the reactive oxygen species within a parasite, leading to the depolarization of membrane potential, ultimately leading to the depletion of ATP, and death of the parasite occur (De Sarkar et al., 2019). In short, it can be said that *B. vulgaris* has good effects against *Leishmania tropica, Leishmania donovani,* and *Leishmania braziliensis* (El-Saber Batiha et al., 2020). The significant scolicidal activity of the *B. vulgaris* methanol extract suggested that it would be useful in killing the protoscolices of hydatid cysts (Sohrabi et al., 2018; Rouhani et al., 2013). Similarly, when toxoplasmosis infection was inoculated into the mice as experimental animals, it was obvious that it limits the life cycle of *Toxoplasma gondii* by arresting its tachyzoites (Mahmoudvand et al., 2017).

Effects of *B. vulagris* on Bacterial Species of the Animals

It has been demonstrated that *B. vulgaris* possesses antibacterial properties against a range of microorganisms, including *Streptococcus agalactiae* (Peng et al., 2015). Additionally, berberine effectively inhibits the development of *Staphylococcus epidermidis* and is a potential therapy for periprosthetic infection (Wang et al., 2009a; Wang et al., 2009b). A cell protein known as FtsZ is the mechanism of action of berberine for antibacterial effects according to the latest research (Boberek et al., 2010). Different classes of antibiotics show synergistic effects with berberine. These antibiotics include linezolid, erythromycin, and cefoxitin. So, it means that the problem of antimicrobial resistance can be resolved by the application of berberine with these antibiotics (Wojtyczka et al., 2014). Its antibacterial efficiency is determined by a technique known as agar diffusion method (El-Zahar et al., 2022). Further details of its antibacterial effects in different animal species are summarized in Table 1.

Antifungal Effects of *B. vulgaris* in the Animals

There are different causative agents of dermatophytosis such as *Epidermophyton*, *Trichophyton,* and *microsporum*. In this disease, the hooves, nails, hairs, feathers, and skin of different animals are affected (Mahmoudvand et al., 2014c). Today, imidazoles are a class of antifungal agents that are most commonly used to treat fungal infections in animals. But there lies a need for great care while using it because there is reported toxicity and side effects of it (Adimi et al., 2013). So, there is a focus on the use of naturally available products such as *B. vulgaris* (Mahmoudvand et al., 2014c). The *B. vulgaris* has potential antifungal effects against *Candida* species of fungi (Freile et al., 2003). Its methanol extracts show the maximum efficacy against *Candida* species, however, the exact mechanism of action is not known (Ghaderi and MalekiNejad, 2006). One research suggests that berberine present within *B. vulgaris* shows the inhibitory effects of *B. vulgaris* against *Candida* species by inhibiting the biosynthesis of both the sterol and cell wall biosynthesis (Mahmoudvand et al., 2014c). Similarly, when *B. vulgaris* is applied in combination with amphotericin B, then the synergistic effects are obvious against the resistant strains of *Candida (*Han and Lee, 2005). The therapeutic benefits of *B. vulgaris* in veterinary medicine are summarized in Table 1.

Future Perspectives

Today, the world is facing the problem of antimicrobial resistance. We have to rely on the natural products for the treatment of microbial diseases. Currently, *B. vulgaris* is a natural product that we are using for the treatment of some bacterial, viral, and fungal infections in animals. However, its exact mechanism of action is not known to us. So, there is a need for further research to find the exact mechanism of action against these microbial agents and also there should be given a focus on using these agents against a range of fungal, bacterial, and parasitic infections as currently we are using them against only a few infectious agents such as *Leishmaniai, E. coli,* and *Candida* species. In this way, we will be able to combat the problem of antimicrobial resistance thus improving the health of animals and reducing the treatment costs as *B. vulgaris* is easily available because it grows in many regions of the world. Also, being a natural product, it has low side effects as compared to synthetic drugs. We will also be able to use it with the synthetic drugs to achieve the synergism. All these approaches will ultimately help to reduce the problem of zoonosis and antimicrobial resistance.

Table 1: Therapeutic benefits of *B. vulgaris* in veterinary medicine

Function	Reference
Protects the animals from hepatic, renal, splenic, and different organ damage caused by *Schistosoma mansoni*	Dkhil, 2014; Dkhil et al., 2014; Al-Quraishy et al., 2013
Prevention of malaria caused by *Plasmodium chabaudi in animals*	Dkhil et al., 2015
Scolicidal effects against protoscoleces of hydatid cysts, thus preventing the infection of cystic *Echniococcus*	Mahmoudvand et al., 2014a
A strong leishmanicidal action against *Leishmania tropica*	Mahmoudvand et al., 2014b
Reduces the infection load of *Giardia lamblia, Entamoeba histolytica,* and *Trichomonas vaginalis*	Mahmoudvand et al., 2014c
Prevention of malaria in animals when used in combination with pyrimethamine and shows good effects as compared to tetracyclines	Mahmoudvand et al., 2014c
Reduces the lesions in the animals caused by *Leishmania braziliensis* and *Leishmania donovani*	Mahmoudvand et al., 2014c
Reduces the size of cutaneous leishmaniasis	Fata et al., 2006
Prevents and treats cutaneous leishmaniaisis	Salehabadi et al., 2014
Good effects against *Leishmania tropica, Leishmania donovani,* and *Leishmania braziliensis*	El-Saber Batiha et al., 2020
Scolicidal activity against the protoscolices of hydatid cysts	Sohrabi et al., 2018; Rouhani et al., 2013
Causes the death of a parasite in an animal by the depletion of ATP within a parasite	De Sarkar et al., 2019
Prevents the toxoplasmosis caused by *Toxoplasma gondii* by arresting its life cycle stage known as tachyzoites	Mahmoudvand et al., 2017
Prevents dermatophytosis in animals	Mahmoudvand et al., 2014c
Replaces the available antifungal agents	Mahmoudvand et al., 2014c ; Adimi et al., 2013
Antifungal activity against *Candida*	Mahmoudvand et al., 2014c; Ghaderi and MalekiNejad, 2006; Freile et al., 2003
When used in combination with antifungal agents such as amphotericin B, then it shows synergistic effects against *Candida*	Han and Lee, 2005
Antibacterial activity against *Pseudomonas aeruginosa*	Končić et al., 2010; Kosalec et al., 2009
Antibacterial activity against *Bacillus subtilis*	Končić et al., 2010; Kosalec et al., 2009
Improves the intestinal health of broilers	Dibamehr et al., 2023; Yazdani et al., 2013; Rajain et al., 2006; Rajaian et al 2003
Causes an increase in the concentration of probiotics such as *Lactobacillus* in the gut of broilers	Zhang et al., 2013
Causes a reduction in the developemnt of *E. coli* in broilers	Zhang et al., 2013
Causes an increase in the concentration of probiotics such as *Lactobacillus acidophilus* and *Bifidobacterium adolescentis*	Čerňáková and Košťálová, 2002
Suppression of the growth of harmful microorganisms in the gut of animals	Čerňáková and Košťálová, 2002
Can be used in the treatment of gastrointestinal disorders in animals	Zhang et al., 2021
Limits the growth of *E. coli* and *Staphylococcus aureus*	El-Zahar et al., 2022
Shows a synergism when used in combination with different classes of antibiotics such as eryhtomycin and cefoxitin for the treatment of diseases	Wojtyczka et al., 2014
Antibacterial effects in animals	Boberek et al., 2010
Effectively inhibits the development of *Staphylococcus epidermidis*	Wang et al., 2009a; Wang et al., 2009b
Possesses antibacterial properties against a range of microorganisms, including *Streptococcus agalactiae*	Peng et al., 2015
Improves intestinal immunity, thus helping an animal combat with various gastrointestinal disorders	Gong et al., 2017
Prevents heat stress in animals	Sahin et al., 2013
Show antihistaminic and antiinflammatory effects	Akbulut et al., 2009
Antiparasitic, antibacterial, and antifungal effects in the animals	El-Zahar et al., 2022
Low side effects in animals as compared to synthetic drugs	Rahimi-Madiseh et al., 2017
Low toxic effects in animals as compared to synthetic drugs	Pang et al., 2015
Inhibits ion loss from the animal's body	Alzamora et al., 2011
Increase in the bioavailability of other therapeutic agents	Habtemariam, 2020

Conclusion

The *B. vulgaris* belongs to the genus *Berberis*. Its growing history is as long as human history. It grows in many regions of the world, including the United States, Europe, and Asia. In Iran, people use it in their daily life. As its side effects are negligible, it has not lost its importance despite the development of synthetic drugs. Although its bioavailability is quite low, once it is absorbed into the body, it gives us promising results. Also, it increases the bioavailability of other drugs. The berberine, an alkaloid, is responsible for the development of its antifungal, antiparasitic, and antibacterial properties. It has been used in human medicine for a long period. But now there is a focus on its use in veterinary medicine. If we talk about its antiparasitic activity, then experimentally, it has been found active against *Giardia lamblia*, *Entamoeba histolytica, Schistosoma mansoni, Trichomonas vaginalis,* and *Leishmania* species such as *Leishmania tropica, Leishmania donovani, Leishmania brazilensis*. Moreover, it can also be used against resistant malarial species. It is also improving the health of the animals. It improves the performance of animals by acting on their gut microbiota because it increases the concentration of good bacteria while reducing the effects of harmful bacteria. It improves the broiler's performance by improving the structure of its intestinal villi. Moreover, it also reduces the burden of *Staphylococcus* and *Streptococcus* species. When it is used with antibiotics, then it shows the synergism. It is also effective against *Candida* species of the fungi. It can be topically applied along with the oral administration. However, there is a need for further research to find out whether it can be used against other microbial diseases of the animals, and if can be used then what will be its mechanism of action, what will be the preferred mode of administration, and what will be the preferred dose. In this way, we will be able to reduce the use of antimicrobial agents, ultimately leading to a decline in antimicrobial resistance both in animals and humans.

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Chapter 19

Botanical Therapy as an Anticancer Mode of Treatment

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ABSTRACT

Phytochemicals found in plants, known for their antiviral, antibacterial, and anticancer properties, play a crucial role in treatment. Current estimates indicate that more than half of all cancer patients turn to complementary and alternative medicine following their diagnosis, with a significant preference for herbal medicine. Utilizing medicinal plants is crucial for warding off illnesses, particularly cancer, and the second most prevalent cause of death worldwide. Currently, certain cancer therapies involve the use of plant-based products containing phytoconstituents. However, specific mechanisms behind the positive impacts of medicinal plants remain largely unclear, hindering their progression to clinical trials and pharmaceutical development. It's worth noting that there is limited clinical evidence available regarding combination therapy involving chemotherapy drugs and herbal medicines. Despite significant advancements in managing and controlling cancer progression, there are still numerous gaps and unexplored opportunities. Consequently, this chapter underscores the importance of medicinal plants use as herbal extract or nano particles in promoting human health and highlights various phytochemicals derived from medicinal plants that hold promise in cancer treatment.

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INTRODUCTION

Cancer is a multifaceted illness marked by numerous abnormal signaling pathways due to genetic disturbances occurring at molecularlevels. It is a complicated, diverse illness, often not diagnosed in its early stages (Chandrashekar et al., 2022). Cancer, ranking as the second leading cause of death in the US, represents a significant global public health concern. The likelihood of developing cancer rises with age, with 80% of all cancer diagnoses in the United States occurring in individuals aged 55 and above. The American Cancer Society gathers contemporary information regarding cancer occurrence and results from population data, providing annual estimates of new cancer cases and deaths in the US. Approximately 2,81,550 new cases of invasive breast among women, 45,230 individuals are expected to be diagnosed with rectal cancer and 1,04,270 with colon cancer are projected to be diagnosed among women in the US in 2021. Renal and hepatic cancer is anticipated to cause the deaths of 13,780, and 30,230 individuals respectively (Siegel et al., 2021a). In 2022, approximately 6,09,360 individuals in the United States are expected to succumb to cancer, which equates to around 1,700 fatalities every day. Lung, prostate, and colorectal cancers in men and lung, breast, and colorectal cancers in women account for the majority of cancer-related deaths (Siegel et al., 2021b). It is anticipated that in 2023, there would be about 59,610 new cases of leukemia identified in the US, leading to 23,710 deaths from the illness. Pancreatic cancer is expected to lead to the deaths of 50,550 individuals (Siegel et al., 2023). In the United States, 611,720 deaths from cancer are projected to occur in 2024(Bray et al., 2024).

Plants with therapeutic qualities and the secondary compounds they produce have been known to man for ages, and they have been used in cooking ever since. Utilized in both traditional and contemporary medical systems, herbal medicine has established a vital scientific basis that guarantees health and safety across a wide range of global cultures (Farzaneh and Carvalho, 2015). Certain foods, such as vegetables and fruits high in polyphenols, are becoming more and more acknowledged for their potential health benefits as the body of research linking nutrition and health expands. Plants, known for their high fiber and phenolic content, have long been thought to contain biological qualities that make them good for improving health (Veiga et al., 2020).Botanicals are comprised of a diverse blend of compounds and demonstrate medicinal properties through the interplay of numerous phytochemicals (Fimognari et al., 2012). There is a widespread trend these days to use natural phytochemicals as a form of anticancer therapy. Various components within a botanical extract may exhibit mutually enhancing or complementary effects, potentially offering advantages in the realm of cancer treatment. Another potential benefit of utilizing whole botanical extracts involves the possibility of reducing negative side effects. Current chemotherapy medications derived from plants are often linked with high levels of toxicity (Vickers, 2002). The importance of incorporating anticancer plants in medicine is increasing, as they hold promise in alleviating the side effects of medical therapies and improving the quality of life for patients (Lee et al., 2018). The aim of this chapter is to compile data on current phytochemicals used in treating cancer, as well as promising candidates, primary mechanisms of action, and documented constraints.

Harnessing Botanical Agents for Cancer Therapy

Anticancer drugs have interfered with the normal functions of normal cells, as evidenced by research into cell toxicity, which has demonstrated their capacity to induce substantial apoptosis and DNA damage. With mounting concerns about the safety of these synthetic chemical drugs, there has been a growing focus on the utilization of bioactive substances in recent times (Chen et al., 2023).

Berberine, a natural compound derived from several medicinal plants like *Hydrastis canadensis* and *Berberis vulgaris*, is a small isoquinoline alkaloid. Othman et al. (2022) carried out research aimed at evaluating the effectiveness of selenium nanoparticles (SeNPs) synthesized through green methods, employing Ber as an anticancer treatment, and explored the mode of action through which these substances counter Ehrlich solid tumors (ESTs). The findings indicate that both Ber and SeNPs-Ber exhibit anticancer characteristics, evidenced by a notable reduction in the tumors' mass and dimensions. In mice treated with SeNPs-Ber, the study demonstrated the apoptotic effects by upregulating caspase-3 and Bax expression and downregulating Bcl-2 expression.The apoptotic influence of Ber is closely linked to the caspase signaling transduction and its dependent pathway and its signaling mechanism, which entails elevating the ratio of Bax to Bcl-2 along with the involvement of the tumor suppressor p53 as shown in Fig. 1. Consequently, the cytotoxic impact of SeNPs-Ber may stem from cellular apoptosis (Othman et al., 2022).

For an extended period in Eastern Asia, extracts derived from *Prunus mume* (Rosaceae) have been utilized in various cooking and medicinal applications. Extracts from *P. mume,* like MK615, consist of recognized anticancer compounds, predominantly ursolic acid and oleanolic acid. These are extensively studied pentacyclic triterpenes known for their strong anticancer properties. The way *P. mume* extracts work is a complex system. The natural combination of anticancer substances, including lupeol, ursolic acid, oleanolic acid, and other components, alters the progression of the cell cycle, inhibits cell growth, and frequently triggers autophagic or apoptotic death in tumor cells. Several proteins, including RAGE, Bcl-2, Id-1, and Aurora kinases (AK), were observed to be inhibited in cancerous cells treated with MK615. Treatment with MK615 shows potential for significantly reducing PD-L1 and NFκB expression in lung metastases associated with melanoma cells, offering promising clinical implications as shown in figure 1. It may help reduce the chemoresistance-induced PD-L1 expression and restoreT cells cytotoxicity against tumor cells (Bailly, 2020).

Ipomoea carnea belongs to the Convolvulaceae family. This plant has a variety of phytochemicals, including alkaloids, fatty acids, glycosides, tannins, alcohol, reducing sugars, flavonoids, and esters. The leaf extracts exhibited notable suppression of proliferation in a breast cancer cell line. The results from the assay(MTT) indicated that the apoptotic effects of Ipomoea carnea extracts were specific to MCF-7 cells. This extract induces cell shrinkage, cytoplasmic membrane blebbing, and the condensation of cells into smaller membranes. The Rho effector protein (ROCK I) triggered the blubbing of the membranes of cells, which promotes the myosin light chains phosphorylation, increasesATPase activity of the myosin, and facilitatesactin-myosin filaments linkage to the cell membrane. During apoptosis, it undergoes cleavage to produce an active form. ROCK proteins are essential and capable of causing the formation of membrane blebs, as well as the relocation of fragmented DNA into the apoptotic bodies and membrane blebs as shown in Fig. 1. The distinctive characteristics of morphological alterations indicated that *Ipomoea carnea* extracts triggered initial apoptotic alterations observed in breast cancer cell lines (MCF-7). The ability to effectively scavenge free radicals and demonstrate potent reducing power is the basis for the anti-tumor effect, which is associated with the existence of polyphenols and/or non-phenolic compounds. These components trigger diverse cellular mechanisms associated with inhibiting cancer growth and inducing apoptosis. Additionally, this plant induces programmed cell death or apoptosis in breast cancer cell lines via a pathway that relies on caspase activation (Dubey et al., 2022).

For centuries, silymarin, (*Silybum marianum*) extracted from the seeds of milk thistle, has been utilized in the treatment of liver-related diseases. For those with chronic liver conditions caused by oxidative stress (alcoholic and non-alcoholic fatty liver disorders), as well as hepatic toxicity induced by drugs or chemicals, antioxidant therapies like silymarin could provide advantageous outcomes. Liver cirrhosis and steatohepatitis elevate the probability of developing hepatic carcinoma. Silymarin exhibits membrane-stabilizing and antioxidant characteristics, which support the regeneration of hepatocytes. Moreover, it reduces inflammatory reactions and hinders the formation of liver fibrosis. Extended use of silymarin notably prolonged the survival period of individuals diagnosed with liver cirrhosis caused by alcohol. Silymarin demonstrates the capability must significantly decrease the multiplication of tumor cells. It can contribute positively to the equilibrium between apoptosis and cell viability by influencing cytokine activity. In certain cases of cancerous diseases, silymarin may be prescribed as adjunctive treatment (Fehér and Lengyel, 2012).

Malva sylvestris L., alternatively referred as common mallow that is widely acknowledged in Europe, Pakistan, Iran, and India. Malva extract contains a variety of compounds, including phenolic derivatives, flavonoids, catalase enzymes, vitamins

C and E, terpenoids and fatty acids (such as omega-3 and omega-6). These constituents exhibit both antioxidant and anti-inflammatory characteristics. Silver nanoparticles (AgNPs) were designed with the help of Malva sylvestris extract for studying their potential anticancer properties. AgNPscan trigger apoptosis by modulating the expression of key genes, including p53, either increasing or decreasing their activity as shown in figure 1. Exposure to silverAgNPsis responsible for the arresting of mitosis of cells at sub-G1 stage and apoptosis in many cancer cells. The efficacy of silver nanoparticles obtained from sylvestris extract against human renal cell carcinoma in various carcinoma cell lines is credited to their antioxidative characteristics. The presence of these silver nanoparticles resulted in a decrease in the viability of the human renal cell carcinoma cell line, which was dependent on the dosage. These results underscored the therapeutic benefits of these silver nanoparticles in treating renal cell carcinoma (Wang and Luo, 2023).

Ziziphus spina-christi belongs to Rhamnaceae family, has extensive medicinal applications, encompassing the therapeutic applications of chronic illnesses, and various malignant disorders. The potential antimutagenic effect of leaf extract of *Ziziphus spina-christi* was investigated in cultured human lymphocytes through assays (8-OHdG assays and sister chromatid exchange). This extract demonstrated significant antimutagenic activity in vitro when tested on cultured human lymphocytes. Moreover, the intake of leaf extract of the plant notably decreased the carcinogenic effects skin cancer. The leaf extract seems to shield cells from various forms of DNA damage through a range of single or multiple mechanisms. One of these mechanisms includes the powerful antioxidant capability of *Ziziphus spina-christi* leaf extract, demonstrated to alleviate over 90% of oxidative stress induced in cells. Among the antioxidants present in this extract are terpenoids, glycosides, cyclopeptide alkaloids, flavonoids, phenols, and alkaloids. The leaf extract can inhibit cancer development by inducing cell death in cancer cells by activating Bax-independent apoptotic pathway. *Ziziphus spina-christi* leaf extract offers advantages in preventing cancer by decreasing the mutagenic effects of cancer-inducing agents (Khabour et al., 2023).

Nettle, belongs to Urticaceae family, is utilized in the treatment of numerous ailments. Presently, the predominant utilization of nettle root in medical conditions is associated with prostate gland disorders. Due to its widespread effectiveness in treating prostate cancer, nettle extracts have been widely utilized in Europe to address benign prostatic hyperplasia, given their demonstrated anti-prostate activity. The key bioactive compounds found in nettle root, responsible for its therapeutic effects, comprise flavonoids, lignans, lectins, fatty acids, sterols,and polysaccharides. The aqueous extract derived from nettle leaves notably suppresses adenosine deaminase activity in prostate gland. Furthermore, hydrophilic compounds (steroids) found in the root extract of nettle hinder sodium-potassium pump activity in the membrane of prostate cells, thereby reducing the growth and the metabolism of prostate cells.Na+/K+ pump (Mirzaei et al., 2019).

Another extract from Iranian date palm fruit is employed in the management of benign prostatic hyperplasia and is utilized for treating an enlarged prostate. Studies indicate that concentrated sawdust extract inhibits 5-alpha reductase activity, which plays a role in the conversion of testosterone to dihydrotestosterone (Mirzaei et al., 2019; Song et al., 2020). Sawdust is rich in antioxidants like methyl gallate and epicatechin, which help in preventing cellular damage, decrease inflammatory activity, and provide protection against chronic diseases, including in mice with enlarged prostate glands (Mirzaei et al., 2019).

Carica papaya Linn., belonging to the Caricaceae family. It is widely cultivated in India and has been utilized globally for its medicinal attributes. The anticancer potential of leaf extract of papaya has been assessed in different cancer cell types through in vitro studies. PLE demonstrated encouraging anticancer properties by inhibiting prostate cancer cells proliferation, with minimal effects on normal cells, potentially achieved through apoptosis and cell cycle arrest. The antitumor impact of PLE is linked to the activation of both the caspase-3/7 pathway and p53-dependent mitochondrial pathway as shown in Fig. 1. PLE halts prostate cancer cells in the S phase prior to triggering apoptosis, indicating a mechanism behind the antitumor activity of the PLE fracion. PLE demonstrated to diminish key characteristics of metastasis, such as adhesion, migration, and invasion, by reducing the extracellular matrix (ECM) that serves as chemoattractants for the adhesion and migration of PC-3 cells (Singh et al., 2020).

Vaccinium corymbosum, also known as blueberry, belongs to Ericaceae family. Different phytochemicals are present in Blueberries including anthocyanins, that demonstrate promising antioxidant and anticancer and antioxidant properties. Researchers have identified mechanisms underlying the anticancer activity of blueberries, including oxidative stress, the generation of free radical, oxidative stress leading to apoptosis, DNA disruption, suppression of cell proliferation, and increase in the inflammatory response. A study investigated the chemopreventive effectiveness of blueberries and their influence on angiogenesis and invasion. The analysis focused on their ability to target signaling pathways such as NF-κB, PI3K/Akt, MAPK, and transforming growth factor β in an animal carcinogenic model of hamster buccal pouch (HBP) carcinogenesis model. Blueberry and its primary component, malvidin, were observed to suppress STAT-3 phosphorylation in an oral cancer cell line.This inhibition led to mitochondrial-mediated apoptotic pathway and cell cycle arrest in the G1 and S phase (Prakash et al., 2021).

Combating Drug Resistance: The Role of Natural Sensitizers

Cancer drugs have revolutionized treatment but face challenges such as resistance development, often leading to treatment failure. Examples include resistance to trastuzumab in HER2-positive breast cancer and imatinib in CML and GISTs due to mutations. Drug toxicity, like cisplatin's nephrotoxicity and sunitinib's side effects, also impacts patient quality of life. Heterogeneity among cancer cells and high drug costs create treatment disparities. Overcoming these limitations is essential for improving cancer care and patient outcomes (Santos et al., 2020).

Chemosensitization by phytochemicals involves utilizing naturally occurring compounds found in plants to augment the efficacy of chemotherapy drugs in cancer treatment. These natural compounds, referred as phytochemicals or phytonutrients, are plentiful in fruits, vegetables, herbs, and other plant-derived foods (Choudhari et al., 2019). Various phytochemicals, including curcumin, resveratrol, quercetin, silybin, and epigallocatechin gallate (EGCG), have been investigated for their ability to sensitize cancer cells to chemotherapy through different mechanisms. Curcumin, derived from turmeric, enhances chemotherapy effectiveness by modulating multiple signaling pathways crucial for cancer cell growth, proliferation, and drug resistance, including NF-κB (Aras et al., 2014). Resveratrol, found in red grapes, berries, and peanuts, sensitizes cancer cells to chemotherapy by inhibiting drug efflux pumps, fostering apoptosis, and suppressing cell survival pathways. Quercetin, present in onions, apples, and tea, exhibits antioxidant, anti-inflammatory, and pro-apoptotic properties, which can enhance chemotherapy efficacy. Combining resveratrol with either quercetin or curcumin influences ovarian cancer therapy with doxorubicin, reducing cardiotoxicity and acting as a chemosensitizer (Ko et al., 2017). Silybin, derived from Silybum marianum, overcomes drug resistance in colorectal cancer by inhibiting the expression of GLUT1. EGCG, abundant in green tea, sensitizes cancer cells to chemotherapy by modulating signaling pathways involved in cell proliferation, apoptosis, and drug resistance, demonstrating synergistic effects when combined with cisplatin in ovarian cancer cell lines (Gavrilas et al., 2022).

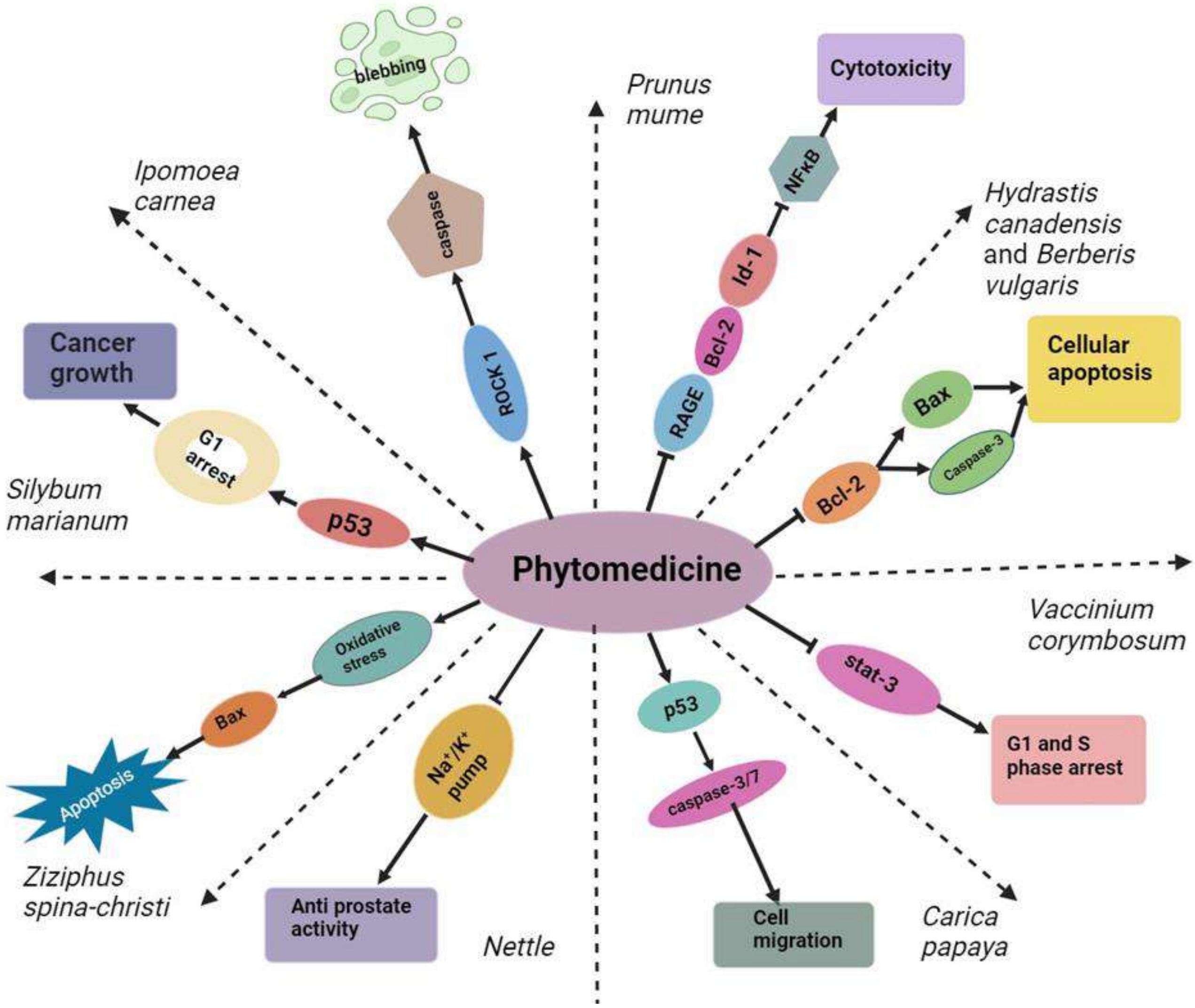

Fig. 1: A schematic diagram depicting how diverse herbal plants target distinct types of cancer and aid in various types of cancer prevention.

Various plant secondary metabolites have demonstrated the ability to augment the efficacy of anti-cancer agents when utilized concurrently in experimental studies. For instance, apigenin, a flavonoid compound, has shown synergistic effects with TRAIL (Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand) in HeLa cervical cancer cells. Furthermore, it exhibits promising results in human acute lymphoblastic leukemia cell lines, as well as in human prostate cancer cell lines (DU145) and human colon cancer cell lines (DLD-1) (Sevastre et al., 2022). Berberine, another natural compound, enhances the effectiveness of cisplatin in ovarian cancer cell lines (VCAR3). Furthermore, curcumin exhibits synergistic effects in human and rat glioblastoma cell lines when combined with cisplatin, etoposide, camptothecin, and doxorubicin. In human ovarian carcinoma cell lines, it also improves the efficacy of oxaliplatin or cisplatin (Liu et al., 2019). Genistein, found in soybeans and soy products, has been investigated for its potential to boost chemotherapy efficacy by inhibiting angiogenesis, promoting apoptosis, and modulating estrogen receptor signaling. Furthermore, in murine xenograft models featuring BxPC-3 cells and in human pancreatic cancer cell lines (BxPC-3), genistein enhances the efficacy of cisplatin(Banerjee et al., 2008). These phytochemicals possess the potential to integrate plant-derived compounds with conventional anti-cancer medications, thereby enhancing treatment outcomes by potentially boosting the effectiveness of chemotherapy drugs across various malignancies. However, further research is needed to elucidate their mechanisms of action and therapeutic applications (Talib et al., 2022).

Phytochemicals in Preclinical Trials

Preclinical studies are essential for assessing the safety, efficacy, and mechanism of action of potential drug candidates before advancing to human clinical trials. They provide valuable insights that guide decision-making throughout the drug development process, ultimately contributing to the development of safe and effective therapies for patients. Several phytochemical compounds have demonstrated potential in combating various types of cancer (Sohel et al., 2023). Allicin, derived from *Allium sativum*, has shown promising effects against cholangiocarcinoma by inhibiting cell growth in vitro and suppressing CCA cell proliferation in vivo through intraperitoneal injections (Chen et al., 2018). Glycyrrhizin, extracted from *Glycyrrhiza glabra*, exhibits potential against lung adenocarcinoma by intervening in cell growth via the TxA2-associated pathway (Deng et al., 2017). Epigallocatechin-3-gallate (EGCG), sourced from *Camellia sinensis*, demonstrates promise in combating breast cancer by promoting programmed cell death and inhibiting cell division (Zan et al., 2019). Quercetin, from *Quercus leucotrichophora*, exhibits efficacy in addressing cervical cancer by inducing various beneficial effects such as cell cycle arrest and apoptosis (Kedhari Sundaram et al., 2019). Meanwhile, other natural compounds like artemisinin, jatrorrhizine, berberine, palmatine, resveratrol, carvacrol, trans-caryophyllene, oridonin, carvacrol, and trans-caryophyllene show potential in targeting various types of cancers, highlighting the vast potential of natural compounds in cancer therapy (Manjamalai and Berlin Grace, 2012; Bao et al., 2014; Tan et al., 2014; Lang et al., 2019; Rodríguez-Enríquez et al., 2019). Ginseng, derived from Panax ginseng of the Araliaceae family, has shown potential in addressing breast cancer. In studieSs conducted on MCF-7 cells, ginseng exhibited beneficial effects at concentrations ranging from 100 to 400 µM. It was found to promote programmed cell death, reduce tumor size, and elevate levels of ROS. These findings suggest that ginseng could be a viable therapeutic option for breast cancer management (Kim et al., 2020). Additionally, *Allium wallichii* has exhibited effectiveness against various cancer types, including prostate, breast, and cervical cancers. It contains a diverse array of chemicals, such as steroids, terpenoids, flavonoids, reducing sugars, and glycosides. In studies involving PC3, MCF-7, and HeLa cells, *Allium wallichii* demonstrated lethality to cancer cells at concentrations of 69.69 µg/ml, 55.29 µg/ml, and 46.51 µg/ml, respectively. These results underscore the potential of *Allium wallichii* as a valuable natural resource in combating different types of cancer (Table 1) (Bhandari et al., 2017). Cannabisin-G and Berberine from *Berberis vulgaris* exhibited promising effects against breast adenocarcinoma, delaying tumor growth, reducing tumor size, and inhibiting the expression of heparinase (Pierpaoli et al., 2015). Kaempferol from *Spinacia oleracea* inhibited the metastatic potential of breast cancer and displayed potent antiproliferative properties (Lee et al., 2017). Genistein from *Genista tinctoria* stimulated Ras and Raf-1 protein expression and induced G2/M cell cycle arrest in breast cancer MDA-MB-231 cells (Li et al., 2008). Thymol from *Thymus vulgaris* and Thymoquinone from *Nigella sativa* showed potential against osteosarcoma and mammary gland cancer, respectively, by modulating the PI3K/AKT pathway and exhibiting anti-proliferative and anti-metastatic characteristics (Table 1) (Chang et al., 2011; Iskender et al., 2016).

Luteolin, found in *Capsicum annuum* of the Solanaceae family, has demonstrated efficacy in combating colorectal cancer. In male rat models, the application of luteolin at a dose of 0.2 mg/kg led to the elimination of colorectal cancer-related polyps. This indicates the potential of luteolin as a treatment option for colorectal cancer (Osman et al., 2015). Similarly, gingerol extracted from *Zingiber officinale* of the Zingiberaceae family has shown promise in cervical cancer treatment. In studies conducted on HeLa, CaSki, and SiHa cells, as well as nude mice xenografted with HeLa cells, gingerol displayed efficacy at concentrations ranging from 25 to 200 µM and dosages of 2-5 mg/kg. Its mechanism of action involves initiating DNA damage, elevating levels of p21, activating p53, and arresting the cell cycle at the G2/M phase. Additionally, gingerol modulates the levels of apoptotic markers associated with p53, such as PARP and cleaved caspase 3 (Table 1) (Rastogi et al., 2015). These discoveries underscore the potential of gingerol as a valuable treatment option for cervical cancer.

Phytochemicals in Clinical Trials

Clinical trials have been completed or are currently underway to evaluate the potential therapeutic benefits of natural compounds in different types of cancer (Lin et al., 2020). One such compound is curcumin, which has completed a Phase 1 trial for colorectal cancer. The trial aimed to evaluate the chemo-preventive properties of curcumin in preventing the development of colorectal neoplasia. A Phase 1 trial, conducted for prostate cancer, examined the combined use of epigallocatechin gallate (EGCG) and quercetin to improve the absorption of green tea polyphenols in men preparing for prostatectomy (Table 2). Furthermore, a Phase 2 trial for squamous cell carcinoma is currently active, focusing on the chemo-preventive potential of quercetin in patients with Fanconi anemia. Resveratrol, a compound known for its role in regulating Wnt signaling, completed a Phase 1 trial for colon cancer. Genistein, investigated in a Phase 1/2 pilot study for metastatic colorectal cancer, aimed to enhance chemotherapy response rates by suppressing Wnt signaling. Additionally, luteolin's therapeutic effect on squamous cell carcinoma is being explored in an early Phase 1 trial. A Phase 2 trial for breast cancer investigated the biomarker effects of American ginseng root extract (Table 2). Allicin, evaluated in a Phase 1 trial for lymphomas, aimed to establish the maximum tolerated dose (MTD) and recommended dosage (RD). Lastly, ginger root extract's impact on colorectal cancer was examined in a Phase 2 trial, focusing on its effects on eicosanoids in colon mucosa (ClinicalTrials.gov). Together, these trials enhance our comprehension of the possible advantages of natural compounds in both preventing and treating cancer.

Table 1: Various photochemical in preclinical trials

Phytochemical	Botanical name	Family	Cancer Type	Cell Line/ animal model	Active Concentrations/ dose	observations	Refences
Allicin	*Allium sativum*	Amaryllidaceae	Cholangio-carcinoma	HuCCT-1, QBC939 (in vitro) nude mice bearing CCA xenografts (in vivo)	0-40 µM 10 mg/kg and 20 mg/kg	Inhibited CCA cell growth, triggered cell death, reduced levels of STAT3 and Bcl-2, and increased Bax expression.	(Chen et al., 2018)
Glycyrrhizin	*Glycyrrhiza glabra*	Fabaceae	Lung Adenocarcinoma	A549 cells in nude mice	15-45 mg/kg/d	Cell growth was regulated by inhibiting the TxA2-associated pathway.	(Deng et al., 2017)
epigallocatechin-3-gallate (EGCG)	*Camellia sinensis*	Theaceae	Breast Cancer	MCF-7 cells xenograft model in female SCID	100 mg/kg by oral	Promotes planned cell death and suppresses cell division.	(Zan et al., 2019)
Quercetin	*Quercus leucotrichophora*	Fagacea	Cervical Cancer	HeLa	100 Mm	Quercetin diminishes cell viability, diminishes colony formation, induces G2-M cell cycle arrest, provokes DNA damage, and fosters apoptosis.	(Kedhari Sundaram et al., 2019)
Ginseng	*Panax ginseng*	Araliaceae	Breast Cancer	MCF-7	100–400 µM	Promotes programmed cell death, diminishes tumor size, and elevates levels of ROS.	(Kim et al., 2020)
Steroids, terpenoids, flavonoids, reducing sugar and glycosides	*Allium wallichii*	Amaryllidaceae	Prostate cancer, breast cancer, cervical cancer	PC3 MCF-7 HeLa	69.69 µg/ml 55.29 µg/ml 46.51 µg/ml	Lethal to cancerous cells.	(Bhandari et al., 2017)
Luteolin	*Capsicum annuum*	Solanaceae	Colorectal cancer	Male rats	0.2 mg/kg	The polyps were eradicated.	(Osman et al., 2015)
Gingerol	*Zingiber officinale*	Zingiberaceae	cervical cancer	HeLa, CaSki, and SiHa, Nude mice xenografted with HeLa cells	25-200 µM 2-5 mg/kg	Initiating DNA damage, elevating p21 levels, activating p53, and halting the cell cycle at the G2/M phase. Additionally, modulating the levels of apoptotic markers associated with p53, such as PARP and cleaved caspase 3.	(Rastogi et al., 2015)
Cannabisin-G, Berberine	*Berberis vulgaris*	Berberidaceae	breast adenocarcinoma	FVB mice	2.5-20 mg/kg	delays the growth of tumors while reducing their number and size. reduces the expression of heparanase in tumors, which causes the vascular networks inside the tumors to become underdeveloped.	(Pierpaoli et al., 2015)
Kaempferol	*Spinacia oleracea*	Amaranthaceae	breast cancer	MCF-7	25 Mm	inhibit the metastatic potential of breast cancer and has potent antiproliferative properties.	(Lee et al., 2017)

Genistein	*Genista tinctoria*	Fabaceae	Breast	MDA-MB-231	0-20 Mm	Ras and Raf-1 protein expression was stimulated by genistein, which also caused phosphorylated ERK1/2 to be slowly and steadily activated. One possible explanation for genistein-induced G2/M cell cycle arrest is the Ras/MAPK/AP-1 signal pathway.	(Li et al., 2008)
Thymol	*Thymus vulgaris*	Lamiaceae	Osteosarcoma	MG63	200-1,000 µmol/l	Elevated levels of ROS and triggered programmed cell death.	(Chang et al., 2011)
Thymoquinone	*Nigella sativa*	Ranunculaceae	Mammary gland cancer	MDA-MB-231	1- 50 µM	Inhibiting the PI3K/AKT pathway. Exhibits both anti-proliferative and anti-metastatic characteristics.	(Iskender et al., 2016)
Artemisinin	*Artemisia annua*	Asteraceae	Breast Pancreas Prostate Lung	MDA-MB-231 MIA-PaCa-2 PC-3 A549	18.2±4.7 31.4±5.0 56.4±4.6 8.4±0.2	Cytotoxicity, antitumour, antiapoptotic	(Lang et al., 2019)
Jatrorrhizine Berberine Palmatine	*Coptidisrhizoma*	Ranunculaceae	Hepatocellular carcinoma	HepG2 MHCC97-L	2.52 µg/mL 20.7 µg/mL 6.6 µg/mL	Inactivation of EEF2, downregulation of VEGF, suppression of angiogenesis	(Tan et al., 2014)
Resveratrol	*Vitis vinifera*	Vitaceae	Cervical cancer	HeLa	188 ± 19 µM	↑ content of LAMP1, Atg7, LC3B, PINK1 and PARK2 proteins; ROS overload; ↓ glycolysis; ↓ oxidative phosphorylation protein contents and fluxes	(Rodríguez-Enríquez et al., 2019)
Carvocrol, trans-caryophyllene	*Wedelia chinensis*	Asteraceae	lung cancer	C57BL/6 mice	10-100 µg	Target lung cancer by scavenging free radicals	(Manjamalai and Berlin Grace, 2012)
Oridonin	*Rabdosiarubescens*	Labiaceae	Gallbladder cancer	Athymic nude mice	5, 10, or 15 mg/kg	Inhibition of NF-κB, an increase Bax/Bcl-2 ratio, induces apoptosis and cell cycle arrest.	(Bao et al., 2014)

Table 2: Various phytochemical in clinical trials (ClinicalTrials.gov) (https://clinicaltrials.gov/)

Natural compound	Identifier/ Status	Phase	Cancer Type	Title	Experiment model	No. of study population	Dose	Hypothesis
Curcumin	NCT01333917/ COMPLETED	Phase 1	Colorectal cancer	Curcumin Chemoprevention of Colorectal Neoplasia	40 Years to 80 Years (Adult, OlderAdult)	40	4 grams per day	Curcumin inhibits various targets associated with the onset, advancement, and advancement of tumors, making it a hopeful chemopreventive substance.
Epigallocatechin gallate (EGCG) And Quercetin	NCT01912820/ COMPLETED	Phase 1	Prostate Cancer	A Phase I Randomized, Double-Blind, Placebo-Controlled Two-Arm Study of Quercetin and Green Tea to Enhance the Bioavailability of Green Tea Polyphenols in Men Scheduled for Prostatectomy	40 Years to 75 Years (Adult, OlderAdult)	32	quercetin PO BID	Green tea's anticancer effects are anticipated to be enhanced by quercetin.
Quercetin	NCT03476330/ ACTIVE, NOT RECRUITING	Phase 2	Squamous Cell Carcinoma	Quercetin Chemoprevention for Squamous Cell Carcinoma in Patients with Fanconi Anemia	2 Years and older (Child, Adult, OlderAdult)	48	4000mg/day	Quercetin is anticipated to hinder or postpone the onset of SCC.
Resveratrol	NCT00256334/	Phase 1	Colon Cancer	Resveratrol for Patients with Colon Cancer	18 Years and older (Adult,	11	20-125 mg/da	Resveratrol regulates Wnt signaling, which is

	COMPLETED				OlderAdult)		y	activated in colon cancer.
Genistein	NCT01985763/ COMPLETED	Phase 1 Phase 2	Metastatic Colorectal Cancer	Genistein Combined with FOLFOX or FOLFOX-Avastin for Treatment of Metastatic Colorectal Cancer: Phase I/II Pilot Study	18 Years and older (Adult, OlderAdult)	13	60mg/ day	Genistein suppresses Wnt signaling, potentially decreasing resistance to chemotherapy and enhancing response rates.
Luteolin	NCT03288298/ UNKNOWN STATUS	Early Phase 1	Squamous Cell Carcinoma	Therapeutic Effect of Luteolin Natural Extract Versus Its Nanoparticles on Tongue Squamous Cell Carcinoma Cell Line: In Vitro Study	(Child, Adult, OlderAdult)	4	___	Luteolin and nano-luteolin demonstrate a capacity to hinder tongue squamous cell carcinoma cells by prompting apoptosis.
Ginseng	NCT00631852/ COMPLETED	Phase 2	Breast Cancer	A Phase II Biomarker Trial of Gelatin Encapsulated Extract of American Ginseng Root (L EAG) in Breast Cancer	18 Years and older (Adult, OlderAdult)	16	250 mg	Different biomarkers of tumors and inflammatory mediators will be analyzed in breast cancer tumors.

Conclusion

In contemporary oncology, there is a strong emphasis on developing safe and effective methods for cancer treatment. Plant-derived bioactive compounds are increasingly recognized as potential cytotoxic agents, mitigating the side effects commonly associated with synthetic drugs. Combining chemotherapy drugs with herbal medicines enhances treatment efficacy through various mechanisms, including apoptosis induction, inhibition of cell proliferation, cell cycle arrest, and modulation of gene expression and protein signaling pathways across diverse cancer cell lines. While cancer treatment currently relies on a limited array of plant-based products and their active constituents, notable progress has been made in managing and controlling cancer progression. However, there remain numerous unexplored opportunities and knowledge gaps. Thus, the chapter underscores the significance of medicinal plants in maintaining human health and provides a catalogue of phytochemicals derived from these plants that show potential for cancer treatment.

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Chapter 20

Calotropis procera as an Alternative to Buparvaquone in Treatment of Theileriosis

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ABSTRACT

Theileriosis is a tick-borne disease and is transmitted by the members of *Ixodidae* and *Theileria annulata* and *Theileria parva* are the major species causing infections. It destroys a host's RBCs and WBCs leading to a reduction in the normal levels of PCV and Hb and so it is an obligate intracellular blood parasite. It is an economic disease due to its global prevalence. There are several methods for its control. Application of acaricides, medicines, and vaccinations are the most common methods. Buparvaquone being an antiprotozoal drug is being used in the treatment of this disease and is only a drug of choice against theileriosis. However, there is now evidence of developing resistance against this drug by the parasites. So, natural products have now become a hope and *Calotropis procera* has become a source of light for the prevention and treatment of theileriosis. After the application of *Calotropis procera,* the host's RBCs, WBCs, PCV, and Hb show a good response and are increased toward their normal values. It has better efficacy as compared to the buparvaquone. It is applied orally at a dose rate of 0.3mg/kg for the treatment of theileriosis. However, there is a need for further research to find its exact mechanism of action.

KEYWORDS		
Ixodidae, Theileriosis, *Calotropis procera,* Treatment, Buparvaquone	Received: 02-May-2024 Revised: 16-Jul-2024 Accepted: 04-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Theileria parva (*T. parva*) and *Theileria annulata* (*T. annulata*) are the causative agents of theileriosis in the cattle (Bishop et al., 2020; Kernif et al., 2024). They are important members of the order *Piroplasmodia* and are obligate intracellular hemoprotozoan parasites (Clift et al., 2020). The *T. annulata* causes tropical theileriosis (Verma et al., 2023), also known as mediterranean theileriosis (Dolatkhah et al., 2023). The other species of *Theileria* that affects cattle and causes east coast fever is known as *T. parva* (Surve et al., 2023). If we discuss the theileriosis in sheep and goats, then we come to know that *Theileria ovis* and *Theileria lestoquardi* (Norouzi et al., 2023). Although not a dog-specific infection, theileriosis has been detected in dogs in some parts of the world. Numerous species of *Theileria,* including *T. annae*, *T. sable*, *T. buffeli*, *T. orientalis*, *T. ovis*, *T. annulata*, *T. luwenshuni*, and *T. equi* has been reported in dogs (Tascı et al. 2024). Equines are infected by *Theileria equi* (Jaimes-Dueñez et al., 2023). *Ixodidae* members of ticks (Kahl and Gray, 2023) including *Rhipicephalus*, *Dermacentor, Hyalomma* (Shiri et al., 2024), and *Haemaphysalis* (Lakew et al., 2023) are the main vectors that transmit this disease worldwide. The sporozoites are present in the blood of infected ticks and during their feeding, a tick transmits these sporozoites into the animal's bloodstream, and as a result, the host will become infected with theileriosis. These sporozoites then infect the animal's lymphocytes producing macroschizonts and these macroschizonts undergo the process of merogony and as a result, merozoites are produced which then infect the RBCs. This is somewhat a kind of cancerous process because here the untrolled merogony can occur. These merozoites are then again transferred to a tick during its feeding from a host (Liu et al., 2022; Elati et al., 2024). These merozoites then develop in the gut of a tick (Rehman et al., 2023). The clinical signs associated with theileriosis include tick infestation, fever, pale mucous membranes, enlargement of lymph nodes, anorexia, in-appetence, emaciation, respiratory distress, nasal discharge, lacrimation, and a sharp decrease in the milk production (Jaiswal, 2023; Kumar et al., 2023; Onizawa and Jenkins, 2024), anemia and hypoxia. In severe cases, diarrhea and dysentery are also observed (Khan et al., 2021). At a later stage of this disease, some animals also show neurological signs (Gul et al., 2015). It worsens the economy of animals (Atif et al., 2023). This disease affects the economic planning of dairy farmers (Tirivanhu et al., 2023). The development of effective vaccines against theileriosis is still under investigation (Agina et al., 2020). Hence, the application of the available medications remains a single choice. However, there is the usage of some natural products now in the prevention and treatment of theileriosis. *Calotropis procera* is one of them. This chapter describes it in detail.

Overview of Available Medication against Theileriosis

Buparvaquone which is a class of antiprotozoal drugs, is commonly used in the treatment of theileriosis over a long period (Yousef et al., 2020a). It is applied intramuscularly to the animals and is administrated according to an optimum dose rate of 2.5mg/kg (Muhittin and Canbar, 2023). Oxytetracycline at a minimum dose rate of 10 mg/kg (Patowary et al., 2024) to a maximum dose rate of 20mg/kg is also used in combination with buparvaquone (Singh et al., 2024) and as a result, synergistic effects are obvious (Atif et al., 2023). Moreover, iron supplements also remain candidate for administration (Yousef et al., 2020b). The buparvaquone causes a disturbance in membrane potential because it inhibits the physiological process of the electron transport chain and ultimately it leads to death of the parasite (Nehra et al., 2024). There is a competitive inhibition of energy metabolism and mitochondrial respiration (Mhadhbi et al., 2015). The therapeutic failure of buparvaquone against theileriosis has been reported during the past few years (Hacılarlıoglu et al., 2023; Agarwal et al., 2023a; Agarwal et al., 2023b). There is presence of a resistance gene known as cytochrome B gene in *Theileria* isolated from the animals (Chatanga et al., 2019; Jawad and Al-Fatlawi, 2023; Fadel et al., 2023; Steketee et al., 2023; Abed and Abd, 2023). The buparvaquone, being an expensive drug is not available to each farmer (Surve et al., 2023). As buparvaquone remains the only drug of choice for the treatment of theileriosis, developing resistance will lead to unmeasurable consequences, as theileriosis causes economic losses worldwide, being an important disease of cattle. Hence, the scientists are now giving focus to the use of alternative methods. The application of ethnoveterinary medicines has promising results. Recently, *C. procera* has been discussed as an option for the prevention and treatment of theileriosis.

Introduction to *C. procera*

An evergreen shrub known as the *C. procera* is mainly found in arid and semi-arid regions of the world. Being a multipurpose plant, it is a common material for the synthesis of nanoparticles and thus has a valuable role in the medicine (Kaur et al., 2021). Asia and Africa are its growing regions (Gul et al., 2015). Aak is its common name in the subcontinental region (Wadhwani et al., 2021). The alkaloids, steroids, glycosides, proteins, and enzymes are its important phytochemicals. Talking about its properties then we come to know that it has anti-inflammatory, wound healing, anti-oxidant, and thus anti-aging properties (Amini et al., 2021). It has also anti-cancerous and anti-diabetic effects (Dogara, 2023). It is also famous for having antimicrobial properties (Abidin et al., 2021; Ahmad Nejhad et al., 2023). Its ethanolic extracts of root bark show the highest antimicrobial activity (Asoso et al., 2023). This antimicrobial property is also evident against different parasitic species (Okeke et al., 2023). This also includes a range of protozoal species (Amini et al., 2021).

***Calotropis procera* Against Theileriosis**

The *C. procera* acts as a valuable option while treating theileriosis (Farah et al., 2014; Abdela and Bekele, 2016). It has great effectiveness when compared to buparvaquone (Chhabra et al., 2014). It is applied orally in the animals and 0.3mg/kg is the dose rate at which it is administrated. After the application of *C. procera,* animals become highly resistant to tick infestation (Durrani et al., 2009). If we compare its efficacy with buparvaquone, then we come to know that it is better than buparvaquone (Chhabra et al., 2014). It has even good results when it is applied in sub-clinical infections (Siddiqui et al., 2017). An emulsified herb is its effective preparation against theileriosis (Al-Snafi, 2016). Also, its flower extracts have good efficacy against theileriosis (Titus et al., 2023).

Effect of *C. procera* on Blood of Affected Animals

Theileriosis causes a significant decrease in the concentration of RBCs, WBCs, PCV, and Hb of a host (Abdullah and Hadi, 2023). Hb level decreases up to 3mg/dl, and PCV decreases up to 9% (Khan et al., 2021). The level of RBCs within a host increases after treatment with *C. procera.* Similarly, the concentration of PCV and Hb also increased in infected animals after treatment with *C. procera*. Moreover, WBCs also show a marked increase after treatment with *C. procera*. All of these parameters increase with the passage of days after post-treatment of *C. procera* (Babar et al., 2018). Durrani et al. (2009) summarized the effects of *C. procera* and buparvaquone on the blood parameters of a host after the parasite has caused significant effects on the host's blood cells (Tables 1, 2 and 3).

From the comparison of the above tables, this can be suggested that there is a significant difference between the hematological effects of buparvaquone and *C. procera*. Although both of them have positive effects on RBCs, WBCs, PCV, and Hb. The *C. procera* causes an early increase in the concentration of these parameters as compared to the buparvaquone (Durrani et al., 2009).

Table 1: Hematological values after infection with theileriosis

Variable	Unit	Normal value	0 day post-infection	7 days post-infection	14 days post-infection
WBCs	10^3/ul	8.41 ± 0.28	8.30 ± 0.30	5.57 ± 0.41	5.21 ± 0.45
RBCs	10^6/ul	9.31 ± 0.02	7.4 ± 0.20	6.20 ± 0.23	5.9 ± 0.26
PCV	%	37.29 ± 1.7	28.08 ± 3.2	26.08 ± 3.5	20.08 ± 3.8
Hb	g/dl	12.51 ± 0.17	8.37 ± 0.24	8.39 ± 0.26	8.43 ± 0.28

Table 2: Hematological values after treatment with buparvaquone

Variable	Unit	Normal value	0 day post-treatment	7 days-post treatment	14 days-post treatment
WBCs	10^3/ul	8.41 ± 0.28	5.21 ± 0.45	5.68 ± 0.42	6.20 ± 0.49
RBCs	10^6/ul	9.31 ± 0.02	5.9 ± 0.26	6.20 ± 0.23	6.21 ± 0.23
PCV	%	37.29 ± 1.7	20.08 ± 3.8	23.08 ± 3.6	24.01 ± 3.8
Hb	g/dl	12.51 ± 0.17	8.43 ± 0.28	8.92 ± 0.30	8.93 ± 0.30

Table 3: Hematological values after treatment with *C. procera*

Variable	Unit	Normal value	0 day post-treatment	7 days-post treatment	14 days-post treatment
WBCs	10^3/ul	8.41 ± 0.28	5.21 ± 0.45	5.69 ± 0.42	6.25 ± 0.50
RBCs	10^6/ul	9.31 ± 0.02	5.9 ± 0.26	6.25 ± 0.26	6.66 ± 0.27
PCV	%	37.29 ± 1.7	20.08 ± 3.8	24.01 ± 3.7	24.05 ± 3.9
Hb	g/dl	12.51 ± 0.17	8.43 ± 0.28	8.99 ± 0.31	9.03 ± 0.38

Future Perspectives

The world is continuously becoming susceptible to antimicrobial resistance including all antibacterial, antifungal, and antiparasitic resistances. The drugs that have had excellent results in the past are now becoming ineffective. The same is the case with buparvaquone, an antiprotozoal drug effective against theileriosis. *Theileria* is becoming resistant to buparvaquone day by day as it is the only drug of choice against theileriosis and is being used irrationally. Oxytetracycline is used as a supportive drug but again there is development of antimicrobial resistance against oxytetracycline. Recently, researchers have been able to develop a new product from the extracts of a natural shrub known as *C. procera*. However, there is a lack of proper knowledge of its mechanism of action against theileriosis. So, the researchers have to work more on this shrub for its practical implementation in the field. Also, there is a need to focus on the development of new antiprotozoal drugs, otherwise, the problem of antimicrobial resistance will affect one health. There is a need to educate the local farmers and community to inhibit the irrational use of antimicrobial drugs. Moreover, the development of inexpensive vaccines is a need of hour.

Conclusion

Theileria annulata and *T. parva* are the main causative agents for bovine theileriosis. Ticks of the *Ixodidae family* are responsible for the transmission of these parasites. The ticks feed on an animal and it gets infected with *Theileria*. The most common clinical signs are fever, tick infestation, a drop in milk production, emaciation, enlargement of lymph nodes, pale mucous membranes, and splenomegaly. Only a few drugs are available for the treatment of theileriosis. The most commonly used drugs are buparvaquone and oxytetracycline. The buparvaquone is used at a dose rate of 2.5mg/kg and oxytetracycline is used at a dose rate of 10-20mg/kg. The buparvaquone can alone be used against theileriosis but when it is combined with oxytetracycline, promising results are observed. On the blood analysis, the levels of RBCs, WBCs, PCV, and Hb within a host are markedly decreased, leading to a condition known as anemia. *Theileria* is now becoming resistant to buparvaquone. The reason behind this is that there is a mutation in the cytochrome B gene which is becoming a resistant gene. As theileriosis causes emaciation in the affected animals, it has effects on a country's economy, and the development of antiprotozoal resistance will create a mess all over the world. So, researchers have come up with the idea of using natural products. For theileriosis, *C. procera*, a natural shrub present in the arid and semi-arid regions, is giving promising results against theileriosis. It commonly grows in Asian and African countries. It causes an increase in the level of RBCs, WBCs, PCV, and Hb more rapidly than the buparvaquone. It is administered orally at a dose rate of 0.3mg/kg. Also, it can be used to prevent theileriosis and can be administrated in subclinical infections. However, the exact mechanism of action of *C. procera* is still unknown. So, there is a need to detect its exact mechanism of action so that it can be implemented practically. Moreover, farmers should be educated to prevent the irrational use of buparvaquone. Furthermore, vaccines should be developed to minimize economic losses. Also, there should be regulated use of buparvaquone until the development of new medicines and vaccines.

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Chapter 21

Use of *Withania coagulans* for Gut Health in Human and Animals

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ABSTRACT

Traditional medical systems have claimed that a plethora of plants can cure a wide range of diseases and conditions. Among these, *Withania coagulans* is one herb that has been utilized with considerable medicinal significance to treat a variety of diseases and disorders. There is great potential for improving both human and animal gut health through the use of *Withania coagulans*. Pharmacological research has confirmed the plant's potential for medical application in a variety of areas, including immunomodulatory, anti-inflammatory, anti-diabetic, anti-oxidant, anti-microbial, and anti-cancer properties—all of which are crucial for preserving gut health. In conclusion, *W. coagulans* is useful for researching natural products, as evidenced by all of these advantages. Certainly, more separation, chemical modification, and synthesis will improve the pharmaceutical application of the active chemicals. Clinical trials are necessary to fully leverage the active compounds' beneficial effects in the area of gut health and can be used for a variety of ailments.

KEYWORDS		
Inflammatory, Withania coagulans, pharmacological, anti-oxidant, anti-diabetic	Received: 12-Jun-2024 Revised: 18-Jul-2024 Accepted: 17-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

The creation of novel medications depends heavily on medicinal plants. Plants are valuable sources of medicinal compounds; currently, at least one plant-derived component is included in 25% of US pharmaceutical prescriptions. Numerous plants have been claimed to treat a wide range of illnesses and ailments in traditional medical systems. One of the major medicinal herbs, *Withania coagulans*, also referred to as "Indian cheese maker" or "vegetable rennet," is a member of the Solanaceae family (Mathur et al., 2011). Language-specific names for the plant include Tukhme-Kaknaje-hindi in Persian and Akri or Puni-ke-bij in Hindi. In Sindhi, "Punir band" or "Punir-ja-fota" is called "Khamjira," in Punjabi, Spicebajja, and Afghanhamjira. W. Columbidans Located in the eastern Mediterranean region and spreading to South Asia, dunal is a tiny, gray-white shrub that grows to a height of 60-120 cm. Berry ripening occurs in January-May, whereas the shrub flowers from November to April. From the seed comes the natural renewal. The size of the leaves is 1.5 cm in width and 2.5 to 7.5 cm in length. The whitish flower measures 7 to 12 mm in diameter (Gupta, 2012).

In order to identify the adaptive mechanisms that underpin Withania coagulans' ecological success in the heterogeneous environments of Punjab, Pakistan, fifteen populations with distinct adaptations were gathered from a variety of ecological regions, including (i) roadside, (ii) hilly regions, (iii) arid regions, and (iv) wasteland. The root endodermis width, stem and leaf cortex thickness, total soluble proteins, photosynthetic pigments, and its cell area were all high in the roadside populations. Populations thriving in mountainous terrain had superior growth characteristics, including rapid expansion and biomass output. Furthermore, there was an increase in the total quantity of chlorophyll (chl a/b), chemical osmolytes (the glycine betaine supplementation and proline), and expanded epidermal, cortical, vascular bundle, metaxylem, and phloem regions in the roots. Enhancement in growth was observed in the areas of pith, vascular bundle, epidermal thickness, and cortical thickness in the stem area. On the other hand, the population of barren land displayed a large rise in the amount of carotenoid content, as well as in the vascular bundle area, metaxylem area, and xylem vessels as well as phloem area. Higher root dry weight, greater shoot ionic content, larger root size, thick cortical, and larger vascular bundle area in the wasteland population were all greater than in the other populations. Comparable measurements were made of the pith area, cortical thickness, and cell area in stems, while the phloem region, extensive vascular bundles, and high stomatal were found in leaves. Then, in response to a range of environmental factors that would enhance the distribution and survival of species (Iqbal et al., 2023).

With dioecious and a polygamous blooms, a persistent leathery calyx enclosing the fruits (berries), and ear-shaped, fruity-smelling seeds, the plant has a shrubby habit. Fruit pedicels with hollow pith, branched and unbranched trichomes, a huge collenchymatous cortex, intra-xylary phloem, and a spongy parenchyma; the pericarp contains exocarp, mesocarp, and endocarp; the seeds have a significantly expanded endosperm and a highly lignified sclerenchyma cell. Rich in organic acids, tannins, phenolic compounds, carbohydrates, steroids, free amino acids, and esterase, the plant (Pramanick and Srivastava, 2015).

Taxonomy

Kingdom: plantae
Division: magnoliophyta
Class: magnolipsida
Order: solanales
Family: solanaceae
Genus: withania
Species: w. Coagulans

Composition of *Withania coagulans*

W. coagulans is also rich in phytochemicals, including nicotine, flavonoids, tannins, and β-sterols; moreover, it includes choline, cuscohygrine, dl-isopelletierine, withanine, withananine, pseudo withanine, somniferine, somniferinine, tropine, pseudo tropine, and novel alkaloids, anaferine and anhygrine (Johri et al., 2005). Together with these, the plant also has a high concentration of iron, hantreacotane, acylsteryl glucosides, ducitol, starch, and a range of amino acids, such as glutamic acid, proline, alanine, tyrosine, glycine, aspartic acid, cystine, and tryptophan. (Gupta and Rana, 2007) According to several research, different *W. coagulans* components and their active ingredients have a wide range of pharmacological and therapeutic qualities, making them suitable for use as novel medicinal therapies for a variety of illnesses (Khan et al., 2021).

Economic Importance

Because *W. coagulans* has the ability to coagulate milk, it is also known as paneer, "The cheese maker," or "vegetable rennet" in Punjab, Pakistan. The berry pulp and husk, which contain an enzyme with milk coagulating activity, are responsible for the fruit's ability to coagulate milk. In Punjab, coagulating enzyme for clotted milk is obtained from the berries of *W. coagulans*, which are referred to as "paneer" (Hemalatha et al., 2008). Additionally, it contains antifungal and antibacterial qualities and is used to treat degenerative disorders, rheumatism, ulcers, and bronchitis (Tripathi et al., 2019).

Medicinal uses for Various Plant Parts

W. coagulans has been traditionally employed for its therapeutic characteristics in relation to its many parts, including its foliage, roots, seeds, and fruit. The following list includes a few therapeutic applications for each component.

Leaves

Due to their analgesic and anti-inflammatory qualities, *W. coagulans* leaves have been utilized in traditional medicine. They are frequently applied topically to lessen discomfort, lower inflammation, and accelerate the healing of wounds. Additionally, the leaves can be applied topically or as a mixture to treat joint and skin disorders (Pramanick and Srivastava, 2015).

Fruit

Historically, the digestive and laxative qualities of *W. coagulans*' fruit have been utilized. Constipation is said to be relieved, regular bowel motions are encouraged, and digestion is supported. As previously noted, the fruit can also be used to make cheese as an organic coagulant or rennet alternative (Sampathkumar et al., 2019).

Roots

Traditional medical systems such as Ayurveda place great importance on the roots of *W. coagulans*. They are renowned for having adaptogenic qualities, which support general wellbeing and assist the body in adjusting to stress. The immune system, vigor, and mental clarity are all supported by the root extracts. The possible anti-diabetic, anti-inflammatory, and anti-cancer properties of the *W. coagulans* extracts of root are another reason for its application (Azhar et al., 2020)

Seeds

Seeds of *W. coagulans* are utilized for their therapeutic qualities, especially in the treatment of diabetes. Compounds in the seeds have the ability to reduce blood sugar and may even assist control blood glucose levels. In conventional medicine, they are utilized to promote appropriate blood sugar regulation and as a natural treatment for diabetes (Daiya and Kasera, 2019).

Withania coagulans Function in Both Animal and Human Gut Health

Since ancient times, people have used herbal plants as a remedy for a variety of health issues. With its many benefits and least amount of adverse effects ever documented, Ayurvedic medicine is used extensively. Rich in medicinal properties, *Withania coagulans* (Family: Solanaceae) has been used to treat wasting illnesses, diabetes mellitus, hepatic ailments, both acute and chronic, aberrant cell growth, and neurological and physical difficulties (Hemalatha et al., 2006). About the phytochemistry, biological activity, and pharmacognostic qualities of *W. coagulans,* this review offers important new information.

It contains the active ingredient withanolides, it has been shown to have anti-inflammatory in nature, cardio-protective, anti-fungal, hepato-protective, antibacterial, diuretic, anti-oxidative, hypoglycemic, and anti-mutagenic qualities. For toothache relief, inhaling the plant's smoke is recommended, as is chewing on the twigs to clean teeth. Several phytochemicals that are accountable for the diverse pharmacological effects of Withania coagulans have been identified by isolation (Gupta and Keshari, 2013).

Pharmacological Properties

Milk coagulation is accomplished using the plant's berries. Ayurvedic, Unani, and traditional Indian medical systems have long placed a strong emphasis on it. Many studies have demonstrated the intriguing biological activity of the withanolides that were isolated from W. coagulans. A number of sedative, emetic, alterative, and diuretic properties have been linked to the plant's sweet fruits (Kuroyanagi et al., 2012).

They help with persistent liver issues. They have served as a blood cleanser in several locales. Along with other intestinal illnesses, they are additionally employed for dyspepsia and flatulent colic. Asthma, biliousness, and stranguary are treated with these. (Jain et al., 2012).

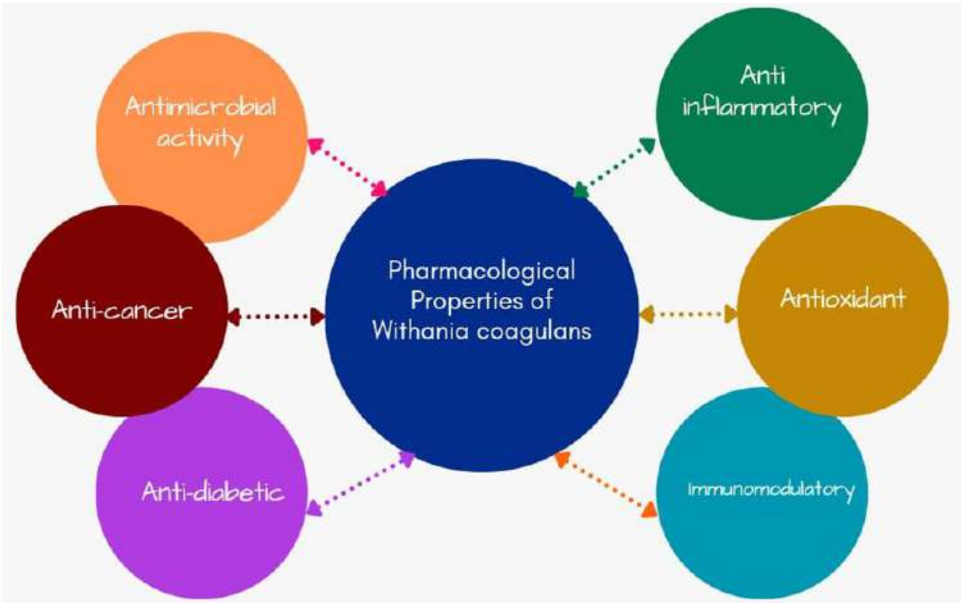

Fig. 1: Pharmacological Properties of Withania coagulans

Antioxidant

W. coagulans can help neutralize dangerous free radicals and lessen oxidative stress since it has antioxidant action. The plant has antioxidant potential due to the presence of flavonoids, withanolides, and other chemicals (Dhanani et al., 2017).

W. coagulans shows signs of having anti-tumor capabilities. According to research, certain of its bioactive components, like withanolides, may be cytotoxic to cancer cells, prevent tumor growth, and cause some cancer types to undergo apoptosis, or programmed cell death. But more research is required to completely comprehend its workings and possible uses in the treatment of cancer (Gupta, 2012).

Anti-inflammatory

The anti-inflammatory qualities of *W. coagulans* may aid in the body's reduction of inflammation. The presence of bioactive substances such as flavonoids, withanolides, and other phytochemicals is responsible for these benefits (Maurya, 2010).

Anti-diabetic

The possible anti-diabetic effects of *W. coagulans* have been investigated. Research points to withania as having a role in blood sugar management, improving insulin sensitivity, and reducing the risk of problems related to diabetes. Specifically, *W. coagulans* seeds have demonstrated encouraging results in the treatment of diabetes (Jaiswal et al., 2009). Fruits of W.

coagulans have been shown to have hypoglycemic and anti-diabetic properties; this may be because the extract contains substantial amounts of Mg (13) and Ca (14) (Lopez-Ridaura et al., 2004). Since intensity and concentration are proportionate, according to the Boltzmann distribution law. Compared to the other inorganic minerals, the concentrations of Mg and Ca were found to be much greater. As previously noted, the management of diabetes is significantly impacted by the larger concentration of magnesium and the lower concentration of potassium (Fox et al., 2001). As a result of its ability to correct hyperglycemia, preserve antioxidant status, and lower proinflammatory markers in the kidneys, withania coagulans may slow the onset and progression of renal damage in people with diabetes. The current study's results suggest that it may be useful to postpone the development of diabetic kidney problems. Further research is need to determine the therapeutic efficacy in humans, though (Ojha et al., 2014).

Immunomodulatory

The ability to control or modulate the immune system is one of *W. coagulans*' immunomodulatory abilities. Immunomodulatory actions, immunological response support, and immune function enhancement are possible benefits. Various bioactive chemicals found in the plant are responsible for these qualities. For broilers to perform better, have better immunity, and produce better meat under oxidative stress, intake of *Withania coagulans* might be suggested as a powerful substitute for synthetic chemicals (Ali Tavakkoli et al., 2021).

Adaptogenic

As an adaptogen—a class of naturally occurring compounds that support general wellbeing and assist the body in adjusting to stress—*W. coagulans* is one of these chemicals. It might lessen stress, increase resilience, and assist the body's capacity to handle both mental and physical difficulties. Heat-stressed broiler performance was satisfactorily boosted by *Withania coagulans* (Alba et al., 2015).

Antimicrobial Activity

The ethanolic extract of the entire plant and its leaves has been shown to contain withanolides that exhibit antifungal and antibacterial activities. Between 6 and 100 µg/ml, withaferin shown strong antibacterial action against Gram-positive pathogens, but it had no effect on non-filamentous fungus or Gram-negative bacteria (Nur-e-Alam et al., 2003).

The volatile oil isolated from *W. coagulans* fruits shown anthelmintic and antibacterial activities against both *V. cholerae* and *Staphylococcus aureus*. Using the human pathogenic bacteria *Aspergillus niger, Drechslera rostrata, Allescheria boydii, Curvularia lunata, Stachybotrys atra, Nigrospora oryzae, yeast Microsporum canis*, and 17β-*Hydroxy withanolide* K (3) showed antifungal activity (Sudhanshu et al., 2012).

Alzheimer's Disease

According to Khodaei et al., (2012), Alzheimer's disease is pathologically characterised by the presence of both external amyloid beta protein deposits and intracellular neurofibrillary tangles made of hyperphosphorylated tau (τ) protein. Withanolide A has demonstrated the greatest promise of all the withanolides in treating Alzheimer's disease through the Aβ pathway. BACE-1 is the rate-limiting enzyme in this pathway, and withanolide A was shown to dramatically reduce the expression of this enzyme. The putative spasmolytic and a calcium channel inhibiting properties of W. coagulans have prompted research. Moreover, the raw strain of W. coagulans has been shown to exhibit the calcium channel blocking action, as demonstrated by its capacity to impede contractions caused by potassium chloride (KCl).

Isolated from rabbits, the substance 7α -epoxy-1-oxo-(5α)-witha-2, 24-dienolide, 5,20 alpha (R)-dihydroxy-6α demonstrates spasmolytic and Ca2+ antagonistic effects that are useful against contractions that are caused by K+ as well as those that occur spontaneously. Furthermore, this withanolide exhibits possible cholinesterase repression and calcium antagonistic capacity, all the while preserving a safe characteristic for human neutrophil function. According to Khodaei et al., (2012), these results point to the possibility of more research into the application of this substance in treating of Alzheimer's disease and its associated consequences (Ali et al., 2015).

Probiotic Effects

By producing prebiotic compounds, including as enzymes that aid in the breakdown of indigestible carbohydrates, W. coagulans' probiotic qualities improve intestinal digestion. It is noteworthy that certain enzymes derived from W. coagulans have use beyond digestion; they are useful instruments in biotechnology and aid in the development of more sustainable and productive production methods. Moreover, W. coagulans is a great option for the homofermentative thermophilic fermentation of food and lignocellulosic wastes into L-(+)-lactic acid. We give a summary of W. coagulans' dual nature in this review, which includes its use in bio based material creation and functional meals (Ram et al., 2023).

Neurological Disorders

Sleep disruption, depression, epilepsy, catalepsy, and anxiety are among the CNS disorders that can be relieved by the withanolides and glycowithanolides found in the isolated bioactive chemical W. coagulans. When this compound's whole fruit extract is used, CNS sedative effects have been seen in rats, dogs, and rabbits. The plant parts in question have the capacity to influence a wide range of neurotransmitters. Specifically, the fruit's whole alkaloids, aqueous extract, and alcoholic extract have all been shown to be able to cause depression of the central nervous system in albino rats, which is indicated by reduced investigating behaviour, hypothermia, and calmness throughout. Also demonstrated to have CNS depressive effect is the molecule 3β-hydroxy-2,3-dihydrowithanolide F (Tripathi et al., 2019).

Antimutagenic Effects

It is still unclear what the fundamental mechanism is that underlies W. coagulans' anti-mutagenic activity. The antimutagenic properties of W. coagulans extracts of fruits were examined using rat bone marrow cells that had been exposed to cyclophosphamide-induced micronucleus production. The outcomes demonstrated that, in comparison to the cyclophosphamide group25, a single intraperitoneal injection of W. coagulans extract of fruit at doses of 500, 1000, and 1500 mg per kilogram of body weight before 24 hours greatly inhibited the production of micronuclei in a dose-dependent manner in mouse bone marrow cells (Mathur and Agrawal, 2011).

Warnings Regarding Paneer Dodi Precautions

Breastfeeding and Pregnancy

Not enough information is available to determine whether paneer dodi may be used safely either way. So, before using it while pregnant or nursing, please speak with your doctor.

Children and Elders

Insufficient information exists on its safety in these age groups. Consequently, before consuming paneer dodi, speak with your physician.

Cultivation and Challenges in Conservation

Due to W. coagulans' many medical advantages, overuse has resulted (Gupta et al., 2022). The varied genetic makeup of the species is decreased because W. coagulans is unable to grow and must be collected from the wild (Rathore et al., 2016). Two primary obstacles to withania's commercial cultivation are its variable alkaloid production and volume across plant to plant and its long gestation period (four to 5 years) between cultivation and harvesting. The inability of the W. coagulans flower to reproduce due to their unisexual nature poses a serious obstacle to this strategy.

The growing demand in the pharmaceutical industry leads to an overuse of natural populations The natural regeneration rate of the plant species is not able to keep up with the rate of exploitation, which makes it vulnerable and endangered in its native habitat The plant species are vulnerable to extinction due to factors such as habitat destruction, overexploitation, adverse environmental conditions, and reproductive failure Thus, it is not viable to acquire wild plant material to meet market demand; instead, alternative approaches must be devised. Withania has attracted a great deal of interest from academics (Rathore et al., 2016).

Future Prospects

Future study on *W. coagulans* has promising indications from the range of activity identified for its extracts, fractions, and withanolides. In today's pharmaceutical industry, withanolides may find a significant role. It is certain that the active compounds' pharmacological usefulness will be increased by large-scale isolation, chemical changes, and synthesis. There are currently no known pharmacophores for the different pharmacologically active withanolides. A range of illnesses require the use of the active substances in clinical trials. *W. coagulans* is important for natural product research, as demonstrated by all these advantages.

Conclusion

In conclusion, both traditional and modern medicine have been developed solely on the basis of medicinal plants. One such plant that has been used to cure a wide range of illnesses and ailments is *Withania coagulans,* which has great medicinal significance. The utilization of *Withania coagulans* holds significant promise for promoting gut health in humans and animals. The plant's potential for medicinal use has been validated by a number of pharmacological investigations such as anti-inflammatory, anti-diabetic, anti-oxidant, immunomodulatory, anti-microbial and anti-cancer which are essential for maintaining a healthy gastrointestinal tract. The pharmacological use of the active compounds will undoubtedly be enhanced by further separation, chemical modifications, and synthesis. Clinical trials are necessary to employ the active compounds for a variety of ailments. All of these benefits show why *W. coagulans* is valuable for studying natural products.

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Chapter 22

Myths and Realities Adhered to pH for Control of Poultry Gut Microbes

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ABSTRACT

The health of the gastrointestinal tract (GIT) affects the productivity of animals. Because poultry products are rich in protein and nutrients at a lower cost than other meat sources, the poultry industry contributes significantly to closing the nutritional gap in many countries. Bacterial infections are treated with antibiotics. However, bacteria developed resistance to antibiotics due to selective pressure. Antibiotics can be reduced in chicken farms by borrowing some strategies. Infection resistance is a natural characteristic of healthy poultry birds. Despite this, environmental factors and other relevant factors have been undervalued in research on the nutritional health and growth of poultry. Animal production depends on the host-microbiome relationship to achieve good performance and growth rates. Metagenomic techniques have replaced conventional methods for poultry microbiome studies, which were low throughput and associated with insufficient genomic information and high sequencing costs. In this book chapter we focus on the myths about pH and gut microbiome control, the realities of pH and gut microbiome management, the potential benefits of essential oils for gut health and performance, strategies for managing gut microbiome, and methods of managing gut microflora through in-ovo feeding.

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INTRODUCTION

Manipulating gut microbiota can improve the digestion and absorption of nutrients in poultry. Beneficial bacteria in the gut can ferment indigestible components of feed, releasing additional nutrients for absorption. Increased growth performance and feed efficiency in poultry occur from this improved nutrient utilization and ultimately increase overall production. Poultry's gut microbiota is essential for the growth and function of the immune system. Necrotic enteritis and coccidiosis are two conditions that can be prevented by some helpful microbes that can selectively suppress or inhibit the growth of pathogenic bacteria in the gut (Stanley et al., 2014). By promoting a balanced gut microbiota composition, poultry can exhibit improved resistance to infectious diseases, leading to better health outcomes and reduced mortality rates. Modulation of gut microbiota composition can enhance the immune function of poultry. Beneficial bacteria interact with the immune system, promoting the development of immune cells and enhancing their responsiveness to pathogens (Awad et al., 2017). Enhancing disease resistance and lowering the need for antibiotic interventions are two benefits of this increased immune function that improve the general health and welfare of poultry flocks. Improving the composition of the gut microbiota can minimize the excretion of toxic compounds like phosphorus and ammonia in chicken excrement (Stanley et al., 2014). Research has demonstrated that some probiotics and prebiotics can lower the adverse effects of stress in poultry (Klasing, 2007). By promoting healthy gut microbiota, poultry producers can reduce the impact of stressors such as transportation, handling, and environmental changes. Manipulating gut microbiota can influence the composition of muscle and fat deposition in poultry, ultimately improving carcass quality. By optimizing gut microbiota composition, poultry producers can achieve desirable carcass characteristics, meeting consumer preferences and enhancing marketability (Adewole and Akinyemi, 2021). The pH level of the gut plays a crucial role in maintaining gut health and microbial balance. The GIT has different regions with varying pH levels, which create specific environments suitable for different microbial populations (Mowat and Agace, 2014). In the poultry gut, the acidic environment of the proventriculus and gizzard helps in the breakdown of feed and facilitates the activity of digestive enzymes (Shang et al., 2018). pH affects the growth and survival of gut microbes, favoring certain species while inhibiting others (Guillén et al., 2021). Changes in gut pH can disrupt the microbial balance, leading to dysbiosis which is associated with various health issues in poultry, including enteric diseases and reduced performance (Stanley et al., 2014). pH influences the solubility and availability of nutrients for absorption in the gut. Optimal pH levels are necessary for efficient nutrient utilization by the host and the gut microbiota. Maintaining an appropriate pH balance in the gut contributes to overall gut health, immune function, and performance in poultry (Mcdonald et al., 2010).

Myths about pH and Gut Microbiome Control in Poultry

Many myths are surrounding pH and gut microbiome control in poultry farming some are few:

Lowering pH is Always Beneficial for Gut Health

The pH of the gut environment plays an essential role in preventing pathogen growth, although low pH levels can also harm the beneficial bacteria in the gut. The microbial ecosystem may be disrupted when pH is lowered to extremes (Sadeq et al., 2015).

Acidifiers are Always Safe and Effective

In poultry feed, acidifiers are sometimes used to lower pH levels in the gut, but their effectiveness and safety depend on dosage, formulation, and the flock's specific needs. Acidifiers can adversely affect bird health and performance if misused or overused.

pH is the Sole Determinant of Gut Health

pH is an important factor, but it is not just one aspect of gut health. The balance of the gut microbiome, along with factors like diet, stress levels, and environmental conditions, also significantly impact poultry health and productivity (Apajalahti et al., 2004)

Antibiotics are the Most Effective Means of Controlling Gut Microbiota Composition in Poultry

Antibiotics have been historically used in poultry farming to promote growth and prevent disease, but they are not the most effective means of controlling gut microbiota composition. Effective methods for controlling gut microbiota composition in poultry include the use of probiotics, prebiotics, synbiotics, and nutritional management (Dibner and Richards, 2005).

pH Levels in Poultry Feed Directly Correlate with the Growth Rate of Birds

pH of the feed can affect the microbial populations in the bird's digestive system, which in turn can impact nutrient absorption and utilization. However, the growth rate is influenced by many other factors including genetics, nutrition, environment, health status, and management practices (Pan and Yu, 2013).

Realities of pH and Gut Microbiome Management in Poultry

pH and gut microbiome in poultry are crucial for maintaining optimal health and performance. Here are some key realities and considerations:

Importance of Gut Microbiome

The gut microbiome plays an important role in poultry health, affecting nutrient absorption and immune function. A diverse and balanced microbiome is essential for efficient digestion and disease resistance (Pan and Yu, 2013).

pH Regulation

pH levels in the GIT influence microbial composition and function. The acidic environment of the crop and proventriculus helps in initial digestion and pathogen control. Most pathogens grow at a pH level of 7 or higher, and beneficial microorganisms live in an acidic environment (5.8-6.2) and compete with the pathogens (Ford, 1974). However, maintaining proper pH balance throughout the gut is essential for microbial diversity and nutrient absorption.

Feed Composition

The composition of poultry feed significantly impacts gut pH and microbiome. High-fiber diets can promote a healthy microbial community by providing substrates for beneficial bacteria. However, diets high in easily digestible carbohydrates can lead to dysbiosis and pH fluctuations (Stanley et al., 2014).

Probiotics and Prebiotics

Probiotics are live microorganisms that have health benefits when consumed in suitable amounts. They can help to control gut pH and promote the growth of beneficial bacteria. Prebiotics, on the other hand, are non-digestible compounds that stimulate the growth or activity of beneficial microbes. Consuming both probiotics and prebiotics can help maintain gut health in poultry (Roto et al., 2015).

Water Quality

Water pH and quality also influence gut health in poultry. Poor water quality, with high levels of contaminants or pathogens, can disturb the gut microbiome and increase exposure to diseases.

Antibiotic Alternatives

Increasing concerns about antibiotic resistance, that is why growing interest in alternative strategies for managing gut health in poultry. This includes the use of organic acids, essential oils, and herbal extracts which can help control gut pH and microbial composition (Mountzouris et al., 2015).

Impact of Fermentable and Non-fermentable Carbohydrates on gut pH and Microbial Composition

A fermentable diet in broiler chickens focuses on using feed components that can undergo microbial fermentation in the gut, particularly in the cecum and large intestine. This approach is based on enhancing gut health, improving nutrient utilization, and promoting better overall growth performance and health in broilers. Fermentable diets typically contain ingredients rich in non-starch polysaccharides (NSPs). When fermentable fibers are included in the diet, they pass through the upper GIT undigested until they reach the cecum. Here, beneficial microbes ferment these fibers, producing short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate (Tejeda and Kim, 2021). Inulin a fermentable diet reduces the pH in the lower GIT of broilers, Inulin improves the concentration of metabolic activity of butyrate-producing bacteria (Clostridium) in the caecum (Rehman et al., 2008).

A non-fermentable diet in broilers typically focuses on ingredients that are highly digestible in the small intestine, and proventriculus of birds under the action of enzymes and do not provide substrates for microbial fermentation in the hindgut. Limiting fermentation can decrease the incidence of dysbacteriosis and other gut health issues related to excessive or imbalanced microbial activity in the cecum. Total bacteria count, Lactobacillus species, and SCFAs level decreased with an increase in non-fermentable intake. Low levels of non-fiber carbohydrate diet decrease digestibility, total gut weight, and gastrointestinal secretions. High levels of dietary non-fiber carbohydrates decrease the digestion and absorption of macronutrients (Jiang et al., 2017).

How Dietary Fiber Sources can Influence Gut Microbiota Composition in Poultry

Dietary fiber is an essential part of the broiler diet but at low to moderate levels. Low to moderate levels of Dietary fiber trigger GIT development and enzymatic production in poultry at this level they also affect the growth performance of birds. High dietary fiber usually characterizes low energy density which reduces feed intake, Feed conversion ratio, and body weight gain in broilers. A high-fiber diet increases *Escherichia coli* and *Campylobacter jejuni* count in the gut which causes inflammation (Jha and Mishra, 2021). When added to chicken diets, oligosaccharide fiber has prebiotic effects by improving gut microbiota, altering gut immunity, promoting intestinal mucosal health, and raising the gut's production of SCFAs (Singh and Kim, 2021). The alfalfa dietary fiber enhances the growth of many intestinal bacteria which changes gut microflora and so alters functions such as carbohydrate metabolism and genetic information processing some intestinal colonies such as *Anaerofilum* and *Dielma* are also produced which start fermentation and produce fatty acids (Qiu et al., 2022).

Potential Benefits of Essential oils for Gut Health and Performance

Chamomile essential oil contains chamazulene and bisabol these components are antimicrobial they reduce inflammation in the gut and enhance their absorption. In broiler chickens, chamomile may help promote digestive health by stimulating the secretion of digestive enzymes and enhancing nutrient absorption (Al-Mashhadani et al., 2013). The use of cinnamon oil in feed results in increased gizzard percentage (Saied et al., 2022). The essential oil of cloves contains eugenol which has the ability to promote Lactobacillus growth and multiplication. Lactobacillus is useful in enhancing the growth performance of broilers and has the potential to alter the villi of the small intestine. Treatments with clove essential oil demonstrated decreased goblet cell population, greater villus height, and a lower ratio of villus height to crypt depth (Gole et al., 2020). The inclusion of Fennel EO to the corn-based diet resulted in greater villus width and villus surface area while it reduced lamina propria thickness Fennel essential oil also reduced ileal *E. coli* and *Lactobacillus* populations (Ghiasvand et al., 2021). Savory essential oil affects the morphology of a broiler intestine it increases the villus height and crypt depth, which increase absorption of nutrients. When 150mg/kg of savory oil is used it enhances FCR and daily weight gain in broilers (Mousapour et al., 2020).

Strategies for Managing Gut Microbiome in Poultry

Feed formulation is a method used to match birds' daily nutrient requirements for proper growth and production

(Moss et al., 2021). Feed formulation plays an important role in digestion, nutrient absorption, and gut microbiome (Adedokun and Olojede, 2019). Improper feed formulation and use of low-quality protein can lead to poor digestion, increased digest viscosity, lower nutrient digestibility, and prolonged transit time in the intestines causing higher levels of undigested protein in the ceca. This can trigger proteolytic fermentation which can negatively affect performance and health, and promote the growth of Clostridium perfringens, which can alter the gut microbiome (Riddell and Kong, 1992). Alternative approaches can be adopted to uphold gut health and microbiome integrity, which are essential for ensuring the profitability and sustainability of the poultry industry amidst limitations on antimicrobial usage. Raising poultry without AGPs can experience a higher risk of intestinal problems which can be challenging and will require different managing strategies for optimizing gut health. In order to maintain gut health and microbiome different types of feed additives are used such as Probiotics and prebiotics (Kiarie, 2016). After hatching, a chick's gut starts without any microbes but quickly gets colonized by environmental microbes, going through various stages of development. The microbial makeup of each bird can be influenced by factors like diet, housing, and genetics, giving each bird its unique microbiome. Probiotics, prebiotics, or symbiotics are used to manage healthy microbial composition of the gut (Fathima et al., 2022).

Probiotics

In sufficient amounts, live microorganisms help balance the gastrointestinal microbiota of birds, thus promoting their health (Alagawany et al., 2018). When the gut is stocked with beneficial bacteria, nutrients are absorbed faster, growth rates are faster, feed efficiency is better, and the immune response is stronger against potentially pathogenic microorganisms (Vilagravel et al., 2010). For best results, poultry should receive probiotics at an early stage (Edens, 2003). Supplementing feed or water with probiotics immediately after hatching is the most common and suitable way to administer probiotics in poultry production (Vilagravel et al., 2010). There are different types of probiotics, including single strains and combinations of different microorganisms (Park et al., 2016). It is primarily Lactic acid bacteria, Bifidobacteria, and Saccharomyces which are abundantly used in poultry (Figueroa-González et al., 2011).

The best results can be achieved in poultry through the use of probiotics as early as possible (Edens, 2003). Supplementation of probiotics in feed or water immediately after hatching is the most common and appropriate method for administering probiotics to poultry (Vilagravel et al., 2010). In multiple studies, probiotics have been shown to be more effective when added to drinking water (Blajman et al., 2014). Torshizi et al., (2010) conclude that water dilutes acidity, enzymes, and other digestive secretions, thereby reducing their adverse effects on probiotics. pH levels and bile salts play an important role in the survival and colonization of probiotic species. Probiotics should be derived from the host and be resistant to gastric acid and bile salts in addition to adhering to the intestinal mucosa. Lactobacillus species are commonly used in probiotic products (Alagawany et al., 2018).

In-ovo Feeding

Injecting probiotics into the incubating egg is a method used for the early colonization of beneficial bacteria (De Oliveira et al., 2014). Administering probiotics to chicken embryos helps establish a healthy start of gut microbiome (Roto et al., 2016). Probiotic inoculation in-ovo can be conducted through two methods:

I. **In-Ovo stimulation** (applied on day 12 of egg incubation):

During in-ovo stimulation, prebiotic species are deposited onto the air cell of the egg on day 12. This encourages the development of innate gut microflora, which the chicks ingest when they begin to pip (Sławin´ska et al., 2014).

II. **In-ovo feeding** (administered on days 17–18 of egg incubation):

In in-ovo feeding, probiotic species are injected into the amnion or embryo (Bednarczyk et al., 2016).

Prebiotics

A variety of fermented ingredients are able to change the composition and function of the digestive microbiota (Gibson et al., 2010). Carbohydrate compounds are considered prebiotics (Davani-Davari et al., 2019). Valcheva and Dieleman (2016) found that prebiotics influence the gut microbiome differently depending on their chemical structures (short-chain versus long-chain), dosage, and duration of ingestion. A prebiotic prevents pathogenic bacteria from colonizing the intestinal epithelium through either direct adsorption or competitive exclusion and encourages beneficial microorganisms to grow (Spring et al., 2000).

Symbiotic

Prebiotics and probiotics are both found in this product. Prebiotic compounds stimulate probiotic growth by providing a specific substrate for fermentation in symbiotic relationships (Schrezenmeir and De Vrese, 2001).

Organic acids

Carbonyl acids are chemically composed of R-COOH groups. A wide variety of SCFAs, including formic, acetic, propionic, butyric, and carboxylic acids, are commonly used in poultry production (Dibner and Buttin, 2002). Lactobacilli and bifidobacteria grow in diets acidified by digestive enzymes, while harmful bacteria such as E. coli. The competition for nutrients results in a decrease in toxins (Partanen and Mroz, 1999).

Conclusion

By managing gut microbiota, we can optimize nutrient utilization, enhance immunity, and improve the overall performance and welfare of poultry. However, it's crucial to dispel myths surrounding pH control and recognize the complexities involved in maintaining gut health. Gut microbiome management involves a difficult approach, considering factors like feed composition, water quality, and the use of additives such as probiotics, prebiotics, and organic acids. These strategies not only influence gut microbiota composition but also impact poultry performance and carcass quality. Furthermore, the choice between fermentable and non-fermentable diets can significantly affect gut health and microbial balance. Balancing dietary fiber sources and incorporating essential oils can further modulate gut microbiota composition and promote digestive health. Effective management of gut microbiota begins early, with strategies like in-ovo feeding providing a foundation for healthy gut development in chicks. By integrating these approaches into poultry production systems, we can achieve better immunity, high-performing flocks while minimizing the need for antibiotic interventions.

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Chapter 23

Biological Control of Toxocariasis in Canines and Felines

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ABSTRACT

Toxocariasis is a highly zoonotic disease of cats and dogs. *T. cati* is responsible for the transmission of infection in cats while *T. canis* causes infection in dogs. *Toxocara* belongs to the phylum Nematoda, and they are known as the roundworms of the intestine. In young cats and dogs, the disease is of an acute nature with severe signs and symptoms. Fatality rate is quite higher in young kittens and pups as compared to the adult ones. Scientists are focusing on the cheaper and effective treatment of toxocariasis in cats and dogs. As an alternative treatment strategy, botanicals are the best option because of their multiple medicinal effects and immune boosting activities. In this chapter, we will discuss the multiple biological control strategies for toxocariasis.

KEYWORDS		
Toxocara, Toxocariasis, *T. canis*, *T. cati*, Biological control	Received: 05-Jun-2024 Revised: 21-Jul-2024 Accepted: 05-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Toxocariasis is a zoonotic disease that affects dogs and cats, while humans get infected rarely (Waindok et al., 2021). The word 'Toxocara' has been derived from 2 Greek words 'Toxon' meaning 'bow' and 'caro' meaning 'flesh' (Al-Ghabban, 2023). Etiological agents for toxocariasis in dogs and cats are *Toxocara canis* and *Toxocara cati* respectively (Rostami et al., 2020; Zheng et al., 2020). *T. canis* and *T. cati* belong to the phylum Nematoda, they are also known as roundworms of the intestine (Magistrado, 2020; Wangchuk et al., 2020; Camacho-Giles et al., 2024).

T. canis completes its life cycle stages in definitive hosts (dogs and other canids) and paratenic hosts (humans and other mammals) (Waindok et al., 2021; Mendoza Roldan and Otranto, 2023). *T. canis* infects both young puppies and adult dogs, infection in adult dogs is less severe as compared to the young puppies and most of the time infection is asymptomatic or mild diarrhea (Saichenko et al., 2021; Schwartz et al., 2022). Signs and symptoms in young pups are very severe, including vomiting, diarrhea, enlargement of the liver, retarded growth rate and some other complications may also occur (El-Saber Batiha et al., 2020; Morelli et al., 2021). If *T. canis* remains untreated in young pups, it may cause fatality, so treatment and prevention in the young ones is very essential (De Bonis et al., 2021; Schwartz et al., 2022; Uchańska et al., 2022).

T. cati completes its life cycle in definitive hosts (cats) and paratenic hosts (mammals and birds) (Mendoza Roldan and Otranto, 2023; Aleem et al., 2024). *T. cati* is also known as a feline roundworm, it infects both domestic and wild felids (Holland, 2023). In adult cats, most of the time infection is asymptomatic as the adult stage of the parasite is present in the gut of the host (Morelli et al., 2021; Ursache et al., 2021). However, the infection in young kittens is very severe and can be fatal (Mendoza Roldan and Otranto, 2023).

Multiple treatments are under use for the control of toxocariasis in canines and felines (Dantas-Torres et al., 2020), but the major problem with using these treatments is increasing resistance (Chinemerem Nwobodo et al., 2022). The parasite has somehow developed resistance to these treatments, and we need to focus on the development of new drugs that are potent against *Toxocara* and have a high safety index in the organism (Liu et al., 2020; Paliy et al., 2021; Asghari et al., 2022). In this chapter, we will discuss the life cycle, signs and symptoms, and the biological strategies for the control of *Toxocara* spp. in canines and felines.

Life Cycle

T. canis infects all the wild and domestic canids, but more severe infection occurs in puppies as compared to the adult dogs (Morelli et al., 2021; Khatoon, 2024). *T. cati* also infects a wide range of domestic and wild felids. However, the infection in kittens is more potent as compared to the adult cats (Dantas-Torres et al., 2020; Bonilla-Aldana et al., 2024). The life cycle of *Toxocara* spp. can be direct (include one host) or indirect (include multiple hosts) (Nijsse et al., 2020; Holland, 2023). Life cycle starts with the shedding of eggs in the excreta of the definitive host (*T. cati*: felids; *T. canis*: canids) (Velusamy et al., 2023; Aleem et al., 2024; Udainiya et al., 2024). Eggs take over 1-4 weeks to embryonate and become infective, containing L3 (third larval stage) (Jaramillo-Hernández et al., 2020; Whitcup, 2021; Schwartz et al., 2022). These infective eggs, when ingested by the definitive host, hatch there and the larvae penetrate into the wall of the gut (Morsy, 2020; Wu and Bowman, 2020). The larvae migrate through the bronchial tree, esophagus and lungs in cats (*T. cat*i) and younger dogs (*T. canis*), where they get swallowed into the gastrointestinal tract through cough (Jaiswal et al., 2023; Morsy, 2020; Ziegler and Macpherson, 2019). While in adult dogs' patent (produces eggs) infection may also occur but most of the time the larvae got arrested in the tissues (Singla and Juyal, 2005; Schnieder et al., 2011). During the late gestation period in female dogs, these arrested larvae are reactivated and infect the puppies by the means of transplacental and trans-mammary routes, and adult worms become established in the small intestine (Wiebe and Howard, 2009; Adeppa and Gnani Charitha, 2024).

Toxocara spp. can also complete their life cycle by the indirect transmission through the ingestion of paratenic hosts (Overgaauw and Nederland, 1997; Holland, 2023). Paratenic hosts ingest the infective eggs, after ingestion they get hatch there and penetrate into the gut wall (Christaki, 2020; Chávez-Ruvalcaba et al., 2021). After the penetration in the gut wall, they travel to different body tissue and encyst there (Carrero et al., 2020; Hailu et al., 2020). Life cycle is completed when the larvae get consumed by the definitive host within the tissues of the paratenic hosts, and the larvae convert into the adult worm in the small intestine (Morley, 2022; Tielens and Van den Bergh, 2022).

Signs and Symptoms of Toxocariasis

Signs and symptoms of toxocara vary widely, severe sign and symptoms are seen in young kittens and young puppies (Schwartz et al., 2022). Infection in adult dogs and cats often goes asymptomatic and no clinical sign appears (Carlin and Tyungu, 2020). Adult animals recover from this infection on their own, but in the case of young animals if the infection goes untreated, it may become fatal for the animal (Garber and Glauser, 2023). Some signs and symptoms of toxocariasis include:

- Cough
- Fever
- Enlargement of abdomen
- Abdominal pain
- Wheezing
- Skin rashes
- Muscle and joint problems
- Eye problems (eye pain, redness, and loss of vision)
- Liver enlargement
- Decreased growth rate
- Loss of appetite
- Lungs problem (pneumonia)
- Digestive disorders (Meliou et al., 2020; Docu Axelerad et al., 2021; Thu et al., 2022)

Biological Control

Toxocariasis is a severe fatal disease in kittens and puppies caused by *T. cati* and *T. canis* respectively (Am and El-Menyawe, 2015; Chen et al., 2018). For the treatment and prevention of toxocariasis, multiple drugs are in use, but they have very low efficacy and resistance to commercially available drugs is increasing day by day (Van Den Broucke et al., 2015; Biswas et al., 2022). So, we are in dire need to focus on the new drugs development (Gribkoff and Kaczmarek, 2017; Tiberi et al., 2018). Botanicals and natural products have been proven effective against *T. canis* and *T. cati* (Sheikh et al., 2023; Štrbac et al., 2023). Some of the biological agents which can be used against *Toxocara* spp. are given as follows:

Essential oils

Multiple researchers have focused on essential oils for the treatment and control of the *Toxocara* parasite (Reis et al., 2010; Shehata et al., 2022; Mengarda et al., 2023). The Brazilian Red Propolis has captured the attraction of the researchers for its magnificent antiparasitic activity (Simone, 2010; King, 2017). The Brazilian Red Propolis extracted has been used against *Trichomonas viginalis* and very potent results were seen in controlling the trichomoniasis (Sena-Lopes et al., 2018;

Asfaram et al., 2021). Essential oils (EO) have been extracted from the Brazilian Red Propolis to check its antiparasitic activity against *T. cati* (Sinott et al., 2019; Rivera-Yanez et al., 2021). EO demonstrated potent activity against *T. cati* and this can lead us to formulate new anthelminthic drugs for the treatment and control of toxocariasis (Aboelhadid and Abdel-Aziz, 2021; Magnaval et al., 2022). However, the mechanism of action of EO from the Brazilian Red Propolis is scant in the literature (Fernandes et al., 2014).

Plant Extracts

Plants and plant extracts are well known for their anthelminthic activity. This property of botanicals attracts researchers to work on plant extracts to find new potent drugs for the treatment and control of various parasitic diseases (Oliveira et al., 2017; Spiegler et al., 2017). Aquous and ethanolic extract from *Alseis yucatanensis* and *Macrocepis diademata* demonstrated very effective results in the inhibition of the larval stage of *T. canis*. Linolenic acid extracted from *Cucurbita maxima* arrested the larval stage of the parasite to get converted into an adult parasite. These plant extracts have the ability to interact with the energy mechanism of the parasite, resulting in the death at the larval stage. Another mechanism of the action of plant extracts is that they bind with the free protein available in the gastrointestinal tract of the host, which ultimately kills the parasite (Tagboto and Townson, 2001).

Botanical Compounds

In history, people used different parts of the plants to treat multiple problems. Now-a-days scientists have focused on a single compound of the different parts of the plants (Khan and Ahmad, 2019). There are many plant compounds which can be used for the treatment of *T. canis* and *T. cati*. The secondary metabolites that can be used for the effective treatment of *Toxocara* spp. include flavonoids, tannins, saponins, alkaloids, and glycosides (Hrckova et al., 2013). The isolated compounds from different parts of the plants include quercetin, pyrethrin, certain piperamides and curcuminoids palasonin, ascaridole, asarone, thymohydroquinone, and kaurenes (Parugrug et al., 2022). Botanical compounds can be used to treat the Toxocara infection in canines and felines. These compounds can be used to make more effective commercial drugs. However, the safety index of these compounds must be tested.

Conclusion

Toxocariasis is a highly zoonotic disease of cats and dogs. *T. cati* is responsible for the transmission of infection in cats while *T. canis* causes infection in dogs. *Toxocara* belongs to the phylum Nematoda, and they are known as the roundworms of the intestine. Signs and symptoms of toxocariasis vary widely, severe sign and symptoms are seen in young kittens and young puppies. Infection in adult dogs and cats often goes asymptomatic and no clinical sign appear. Adult animals recover from this infection on their own but in the case of young animals if the infection goes untreated it may become fatal for the animal. In this chapter, we have concluded that multiple biological compounds are effective against *T. canis* and *T. cati.*

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Chapter 24

Hibiscus sabdariffa Sour Tea against Hypertension

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ABSTRACT

Hibiscus sabdariffa L. (HS), a traditional edible beverage and safe medication used to treat high blood pressure has great potential to be used as a dietary supplement to lower blood pressure. The impact of HS on lowering blood pressure has also just received scientific validation, particularly in diabetic patients and new mothers. Current findings evaluated the most recent mechanisms discovered to explain *Hibiscus sabdariffa* extracts' ability to lower blood pressure. These encompassed the diminution in calcium (Ca^{2+}) influx into blood vessels' smooth muscle cells, cholinergic and histaminergic processes, diuretic impact, endothelium-derived nitric oxide-cGMP-relaxant route, diminished diffusion separation among capillaries and myocytes, and new vessel formation. The hypotensive action is likely primarily attributed to phenolic compounds, anthocyanins (such as cyanidin-3-sambubiosides and delphinidin-3-sambubiosides), and anthocyanins intermediate.

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Hibiscus sabdariffa, Traditional medicine, Phenolic compounds, Blood Pressure,	Revised: 21-Jul-2024 Accepted: 05-Aug-2024	

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INTRODUCTION

Globally, hypertension is the predominant cause of circulatory and heart diseases and early mortality. Over the last forty years, the global mean vascular blood flow (BP) has either been consistent or slightly dropped due to the extensive use of hypotensive drugs. Besides, hypertension has become more quotidian, mostly in low and middle-income nations (LMICs). In 2011, it was recorded that 1.40 billion individuals globally (30.1%) were agonized from hypertension. Adults with hypertension were more likely to have it in low and middle-income countries (LMICs) (30.5%) than in high-income nations (350 million individuals). Various regional heterogeneity in the widespread of hypertension is manifested by differences in the extent of risk factors for the state, such as bad food choices, low potassium consumption, high sodium intakes, being overweight, alcoholism, and a lethargic lifestyle (Mills et al., 2020).

Despite the increasing prevalence of the circumstance, there remains a dearth of comprehensive analyses of the monetary effects of hypertension, or the levels of blood pressure management, therapies, and general knowledge of the problem are inadequate, particularly in low- and middle-income countries. More research is needed to accurately assess the prevalence and financial impact of hypertension globally. The effectiveness of implementing methods for the prevention and treatment of hypertension, particularly for low-income individuals, requires further research. Multimodal techniques must be employed for the prevention and management of hypertension to overcome barriers at the individual, supplier, system, and community levels. Hypertension.

Hibiscus sabdariffa

Hibiscus sabdariffa is one of the members of the Malvaceae family and is a recognized medicinal plant with global repute (Mohagheghi et al., 2011). There are more than 300 species of hibiscus, which are utilised as attractive plants and are found in tropical and subtropical climates worldwide. Nearly every warm country in the world, including the Kingdom of Saudi Arabia, Egypt, Mexico, Sudan, Indian states, Philippines, and Vietnam, has the plant. The primary purpose of roselle cultivation is for human consumption, and China, Egypt, Mexico, Sudan, and Thailand are the top producers of roselle blooms. For their fibers, several hibiscus types are planted (Singh et al., 2017). *Hibiscus sabdariffa* is named “red sorrel” or “roselle”. In a warmer, more humid area, Roselle may adapt to an array of soil types, however, the permeable ground is ideal (Chewonarin et al., 1999).

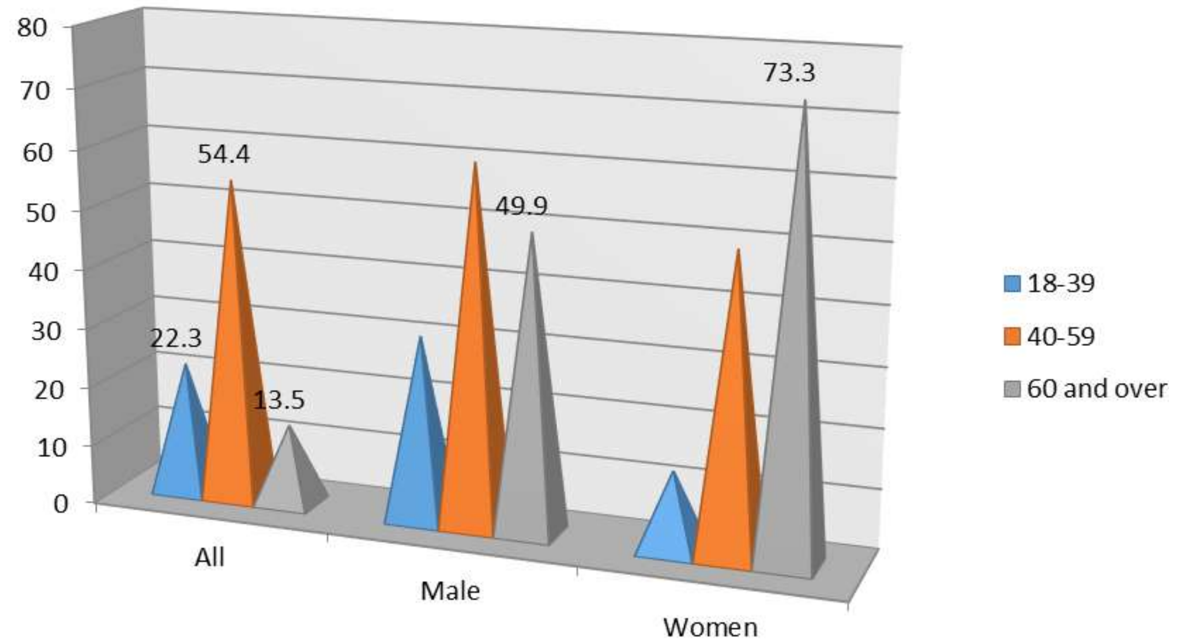

Fig. 1: Percent prevalence of hypertension among different age and gender groups

Table 1: Taxonomical classification of *Hibiscus sabdariffa*

Kingdom	*Plantae*
Subkingdom	*Tracheobionata*
Super division	*Magnoliophyta*
Division	*Spermatophyta*
Class	*Magnoliopsida*
Subclass	*Dilleniidae*
Order	*Malvales*
Superorder	*Lilianae*
Family	*Malvaceae*
Genus	*Hibiscus*
Species	*Hibiscus sabdariffa*

Origin of *Hibiscus sabdariffa*

Murdock marshaled impressive evidence that sometime around 4000 BC, the black people of western Sudan (the Nuclear Mande) domesticated *H. cannabinus* and *H. sabdariffa*. Murdock placed this region alongside those listed by Vavilov and considered it to be one of the world's principal centers of plant domestication (Murdock, 1959; Wilson et al., 1964). Some people believe that roselle evolved in India and the Kingdom of Saudi Arabia, but others believe it originated in West Africa and spread across various regions of the planet, including the United States and Asia (Mat Isa et al., 1985).

Botanical Description

The species is an upright perennial herb belonging to the genus Malvaceae. It has a virtually hairless crimson tubular stem. Plain leaves have a petiole, 3-4 angled or divided blades with sharp or obtusely serrated lobes. Blooms are isolated, axial, and virtually sessile, with a circumference of 5-7cm. The calyx is firm, bright red and meaty, cup-shaped, profoundly parted, and conspicuously lobe-nerved; sepals are five, yellow, and double longer as the calyx. The epicalyx-segments eight to twelve are unique, elliptical to straightforward, and adjacent at the tip of the calyx. The stigma is capitate, the style is single, 5-split near the top, and the stamens are many. The filaments join to form a staminal column. Less than the calyx in length, the fruit is ovoid, pointed, and possesses packed, rigid, and pointy hairs. Its length ranges from 1-2cm (Tarboush et al., 1997).

Table 1: Salient plant features and therapeutic effects of various *Hibiscus* varieties.

Common Name	Botanical name	Floral Characters	Therapeutic Features	Ref.
Roselle	*Hibiscus sabdariffa*	The stalks are utilized to produce bast fiber. The blooms possess a diameter of eight to ten centimeters are white to light yellowish, and have a thick, noticeable calyx at the lowest point of each lobe.	The hypotensive, antidyslipidemic, antihyperglycemic, body fat mass reduction, reno-protective, anti anemic, antioxidant, anti-inflammatory, and anti-xerostomic properties of *Hibiscus sabdariffa* are the most frequently mentioned health advantages of the plant.	(Ali et al., 2005) (Gonzalez et al., 2022)
Taiwan cotton rose	*Hibiscus taiwanensis*	The leaves are broad ovate to circular simple leaves with long petioles. It can withstand droughts and is resilient to both pollutants and arid soil.	In traditional medicine, *H. taiwanensis* stalk and roots were traditionally employed as anti-inflammatory, pain reliever, antifungal, antipyretic medication, and anthelmintic medicines.	(Wu et al., 2005) (Lim, 2014)
Dixie rosemallow	*Hibiscus mutabilis*	The flowers of the 'Rubra' cultivar are crimson. Flowers that bloom alone typically have a cup-like shape. Typically, the blooming season extends from midsummer to fall.	Leaves and flowers are attributed to have are employed for treating infections of the skin and bumps because of their refreshing and emollient properties.	(Dasuki, 2001)
Large leaf rosemallow	*Hibiscus macrophyllus*	With its huge leaves and golden blossoms, the giant leaf rosemallow is an Asian variety of tropical wood tree belonging to the *Malvoideae* subfamily.	The herbs' crude extracts are useful for a wide range of medical purposes, including liver-protective, renal protective, hypersensitivity, anti-diabetic, anti-inflammatory, anti-obesity, anti-proliferative, and anti-ulcerative effects.	(Basri et al., 2021) (Singh et al., 2021)
Kenaf	*Hibiscus cannabinus*	The fibres in kenaf can be identified in the bast (bark) and core (wood), with a mixture of long bast fibre (57%) and short core fibre. There are deep lobed leaves towards the base of the stalks.	According to reports, kenaf possesses qualities linked to anodynes, aperitif, sexual stimulants medications for inflammation, and antioxidants for both leaves and seeds.	(Mariod et al., 2017) (Ryu et al., 2017)
China rose	*Hibiscus rosa-sinensis*	Chinese hibiscus flowers are showy and conspicuous trumpet-shaped flowers	Numerous disorders can be treated using the antioxidant, antibacterial, hypoglycemic, antiulcer, liver-protective, antifertility, antigenotoxic, and anti-inflammatory properties found in the various components of *Hibiscus rosa sinensis* species.	(Anil et al., 2012) (Khristi et al., 2016)
Everblooming confederate rose	*Hibiscus paramutabilis*	Everblooming Confederate rose has big round-shaped leaves white, pink or rose pink flowers blooming from spring to early winter	Flower infusion is utilised as a stimulant and for treating lung and chest issues. Recommended for wounds, particularly scalds and burns that take a long time to recover, as well as menorrhagia, urinary retention, and chronic coughs. Leaves and flowers are applied to wounds and illnesses on the skin.	(Bates, 1965) (Deepo et al., 2022)
Rose of sharon	*Hibiscus syriacus*	The most common type is a deciduous shrub with leaves that are roughly trilobate. The young wood's axils contain solitary blooms that range in hue from white, pastel pink, or red to blue and purple. Typically, the center of the sepals has a huge crimson splash.	The plant's components successfully reduced the amount of lipopolysaccharide, ultraviolet B radiation, and surface cell inflammation brought on by itching wounds.	(Kim et al., 1991) (Yang et al., 2020)

Sea hibiscus	*Hibiscus tiliaceus*	A coastal plant found in the tropics and subtropics is sea *hibiscus*. This species is a fast-growing tree that can reach a height of 20 meters and is often found near mangroves. The leaves resemble hearts. Cylindrical flowers featuring a stigma and a heart the hue of maroon. They begin the day yellow, become reddish-orange in the late afternoon, then fade mauve the following morning.	*H. tiliaceus* leaf and trunk were historically employed for treating tuberculosis and cough, while its roots have been administered as an emetic and antifebrile. In several Asian and African nations, *H. tiliaceus* flowers are used as contraceptives and to alleviate infections of the ears. Leaves are employed as a laxative in Indo-Chinese culture.	(Chan et al., 2016)

Agroecology

Although roselle may withstand humid, hot tropical and subtropical climates, damage from frost can still occur. There are nine to ten zones of hardiness for it. Roselle blooms best in broad daylight in the garden, though it may be cultivated in a protected environment and can withstand some shade (Qi et al., 2005).

Varieties

The genus *Hibiscus* is comprised of 275 annual and perennial herbaceous species, alongside numerous woody shrubs and tiny trees (Braglia et al., 2010). Some of the renowned varieties with distinguished plant characters are enlisted in Table 1.

***Hibiscus sabdariffa* Sour tea's Impacts on Hypertension**

Numerous studies have investigated the phytoconstituents, pharmaceutical, and toxicological characteristics of *H. sabdariffa* (Khosravi et al., 2009). Around the world, *H. sabdariffa* calyces are utilized to brew hot and cold beverages. Among the numerous chemical components of sour tea L-ascorbic acid, anthocyanin, anisaldehyde, b-sitosterol, b-carotene, cyanidin-3 rutinoside, citric acid, delphinidin, gossypetin, galactose, alkaloids, hibiscetin, pectin, mucopolysaccharide, wax, querecitin, stearic acid, polysaccharides, and protocatechuic acids are included. For curing a variety of conditions, like fever, liver ailments, and elevated blood pressure folk medicine make use of calyx extracts (Onyenekwe et al., 1999).

Numerous investigations using both human and animal models have demonstrated that a liquid extract or infusion of sour tea affects blood pressure, blood sugar and lipid levels, and the progression of atherosclerotic lesions. Lin et al., (2007) stated that tea infusion ameliorates cholesterol by 8.35–14.45% after 4 weeks of continuous ingestion. Chen et al., 2003 demonstrated that sour tea infusions reduce triglycerides, cholesterol, low-density lipoproteins cholesterols (LDLc) and LDLc/HDLc in hyperlipidemic rats. Faraji et al., 1999 manifested that tea infusion reduces BP in hypertensive individuals. Even though the exact method for lowering blood pressure is still unknown, some studies have shown that it directly affects the blood vessel muscles the rennin-angiotensin system, Ca channels, the sympathetic nervous system, and the histamine and cholinergic systems. The primary mechanisms proposed for their hypotensive actions are the diuretic and antioxidant properties.

There is a long history of using acidulated tea to treat hypertension, especially in Iran, where this practice is well ingrained in culture (Manu et al., 2021). Considering the use of other diuretic ingredients, such as garlic, in the treatment of hypertension and the first administration of furosemide as the only drug, if not the primary therapeutic alternative (Ali et al., 1991).

According to available research, angiotensin-converting enzymes inhibitor prevent the enzyme from acting on angiotensin I, which prevents the production of angiotensin II and the expulsion of aldosterone from the adrenal glands, both of which could ultimately contribute to a reduction in blood vessel resistance. The inhibition of the angiotensin converting enzyme inhibits the release of bradykinin, a vasodilator hormone. Simultaneously, prostaglandins that function as vasodilators rises. The end outcome of these three processes is a reduced blood pressure with no change in cardiac output or rhythm (Ajay et al., 2007).

The present study demonstrated that the methanolic extract of *Hibiscus sabdariffa L*. calyces produced a vasodilator effect via endothelium-dependent and independent vasodilator pathways in isolated aortas from spontaneously hypertensive rats. The endothelium-dependent vasodilator component is caused by stimulation of the endothelium-derived nitric oxide/cGMP-relaxant pathway, whereas the endothelium-independent component may be caused by reduction of $Ca2+$ influx. The current research provides more support for the traditional usage of *Hibiscus sabdariffa L.* as an antihypertensive medication and explains how the plant lowers blood pressure in vivo (Arellano et al., 2004). The Hibiscus calyces' aqueous infusion contains a high concentration of anthocyanins and proanthocyanidins, which may be the bioactive substances lowering blood pressure. Previous studies demonstrating the antihypertensive effects of anthocyanins via the inhibition of the angiotensin II converting enzyme and the ensuing vasodilatation effect lend weight to this notion. In addition to having a diuretic effect and increasing the urine's salt concentration while maintaining normal potassium levels (Wahabi et al., 2010).

Communities with low socioeconomic status find it desirable that regularly eaten nutritional items, like teas, can effectively and safely cure common diseases like hypertension. If these conventionally used products are shown to be beneficial, they will have some advantages over pharmaceutical preparations, such as being more easily accessible, less expensive, and increasing treatment compliance. *Hibiscus sabdariffa* calyces are used in many nations' traditional medicine not just for brewing tasty beverages but also for curing a wide range of illnesses. Many scientists have been inspired by this to investigate the biological effects of the plant and its chemically active constituents in humans and other living organisms (Hirunpanich et al., 2006).

Polyphenol-rich extract of 100 mg/kg roselle supplemented daily for 8 weeks was shown to improve coronary flow and raise left ventricular developed pressure in a diabetic cardiomyopathy model. This suggests that roselle increases cardiac relaxation rate and contractility and has a potent effect as a cardioprotective agent (Mohammed Yusof et al., 2018). In a different study, it was shown that roselle polyphenol-rich extract, which was rich in phenolic acids and flavonoids could improve coronary blood flow, lower heart rate, and bring systolic function back to normal. These beneficial effects were brought about by pharmacological agonists for the L-type Ca^{2+} channel, ryanodine receptor, B-adrenergic receptor, and sarcoendoplasmic reticulum calcium transport ATPase (SERCA) blocker, all of which were eliminated by roselle polyphenol extract in isolated rat hearts (Lim et al., 2017).

Due to its inability to produce relaxing substances like nitric oxide, damage to the endothelium is one of the typical mechanisms leading to decreased vasorelaxation. According to a previous study, roselle aqueous extract supplementation at a dose of 100 mg/kg for 28 days caused vasodilatory effects by activating potassium channels, which causes vascular smooth muscle cells to become hyperpolarized. This effectively lowers systolic blood pressure in nicotine-induced vascular endothelial dysfunction. The supplementation also contained hibiscus acid, protocatechuic acid, delphinidin-3-sambubioside, kaempferol-3-O-sambubioside, and cyanidin-3-sambubioside (Si et al., 2017). In an ex vivo study, roselle calyx methanolic extract at concentrations of 10 ng/mL to 1 mg/mL was able to induce a vasodilator effect in isolated aortas through the inhibition of Ca2+ influx and activation of the nitric oxide/cGMP-relaxant pathway, which accounts for the roselle's blood pressure-lowering effect (Ajay et al., 2007). A four-week course of treatment with roselle and olive in hydroalcoholic powder at doses of 125, 250, and 500 mg/kg also improved heart protein expression and the eNOS gene, reversed the suppression of serum nitric oxide caused by L-NAME, and decreased an aortic media width in a hypertensive rat model (Ahad et al., 2020).

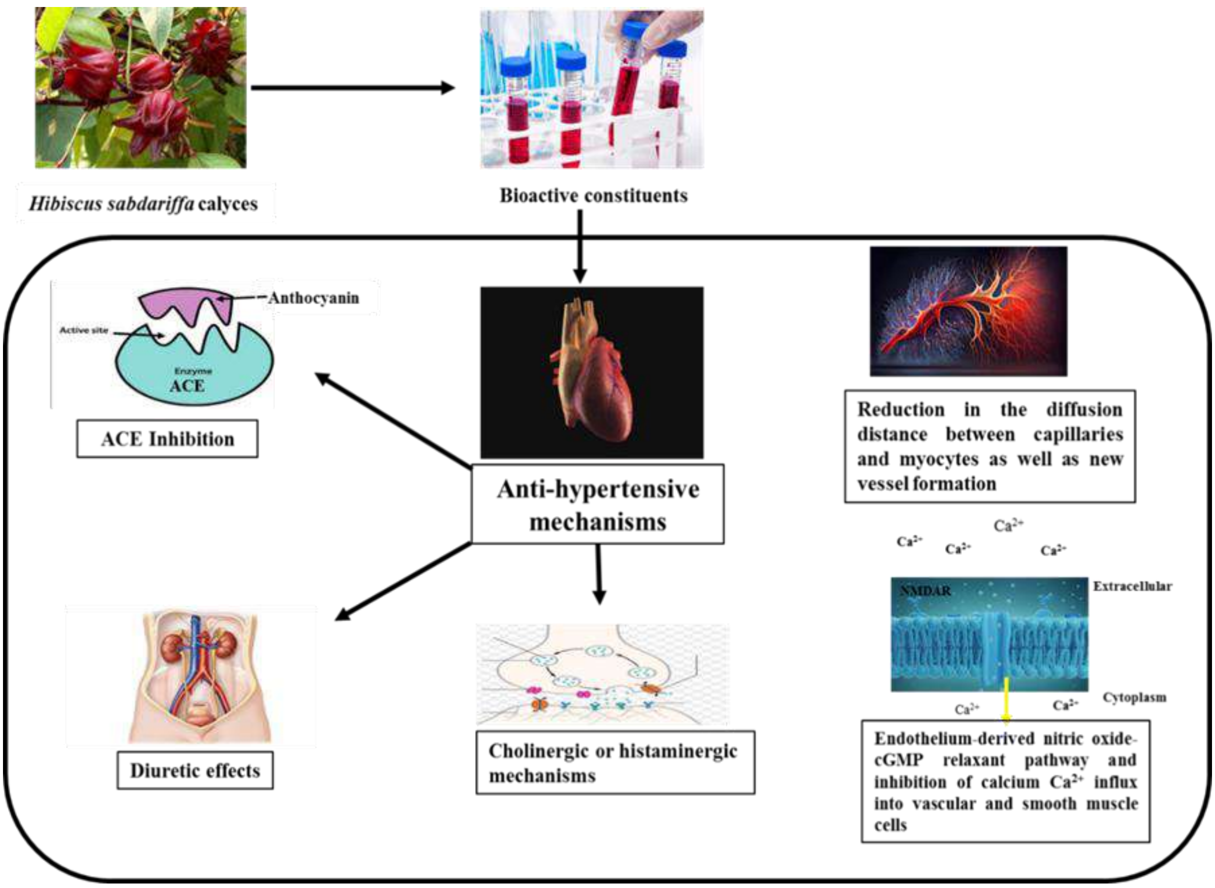

Fig. 3: Mechanistic actions of *Hibiscus sabdariffa* against hypertension.

Conclusion

Infusion of *Hibiscus sabdariffa* leaves, or calyces, as a traditional beverage, demonstrates its effectiveness in lowering blood pressure with an uncommon level of toxicity. While *Hibiscus sabdariffa* shows promise in treating hypertension, further research on the following areas is needed to optimize its utilization as an anti-hypertensive medication. additionally, in the culinary sector. Scary research demonstrated other processes that are also significantly related to the inhibition of ACE, which was corroborated by the majority of reported mechanisms of *Hibiscus sabdariffas'* anti-hypertension effect. Research on the interactions between various processes is still lacking. To develop suggestions for use which possess the ability to have a broad positive impact on public health, more excellent studies on humans and animals that are guided by real therapeutic practices are required. Notwithstanding anthocyanins, pure chemical experiments conducted in vivo or in vitro are the best ways to identify the compounds that also contribute to the anti-hypertensive effect. It's also important to investigate how these bioactive components interact with one another.

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Chapter 25

Perspectives on the Deworming Effect of *Cannabis sativa* in Companion and Production Animals

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ABSTRACT

Parasitic diseases are considered the most prevalent and important health problems in companion and production animals, causing zoonotic problems, a high mortality rate, feed efficiency rate and costs incurred for their treatment and control. Therefore, the use of different deworming drugs in the veterinary field is common. In previous works, it has been indicated that an effective anthelmintic drug should have a good range of action to achieve a high cure rate with a minimum dose, in addition to not presenting toxicity to the host and being economical. However, the treatment of parasitic diseases is complex because of current drug resistance. Currently, different studies have been carried out using alternative treatments, such as the use of plants that have medicinal properties. In this way, medicine based on herbal medicines could become a precursor in the conversion of local knowledge into global knowledge, using medicinal plants with a factor of sustainable development in people and animals from various parts of the world. Some plants have healing properties. They naturally synthesize and accumulate some molecules such as alkaloids, volatile oils, vitamins, and minerals in some regions of the leaves, fruits, seeds, and rhizomes. This situation can be useful for improving clinical treatments. The medicinal properties of plants have been applied in treatments for parasitic infections in humans and various animal species. A range of plants have been reported in the literature for their anthelmintic importance. Several studies present results aimed at showing that certain plant species have nutritional value, but also show results related to the reduction of parasitosis in some animals. Therefore, this chapter discusses some perspectives of the medicinal effect and dewormer of *Cannabis sativa* in animals, as an alternative for resistance to dewormers in animals.

KEYWORDS
Cannabinoids, Deworming, Medicinal, CBD, THC

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INTRODUCTION

Cannabis belongs to the (*Cannabaceae* family), this family brings together different species, these plants occur annually, they can be female or male with distinctive leaves with fingers that show serrations and unisexual flowers. *C. sativa* is the only specie identified of (*Cannabis sativa* L, 2019), on the other hand, the definition of hemp is usually used for *C. sativa* cultivars that are grown with other fines such as industrial or pharmacological fines, but the Marijuana is related to crops whose purpose is the pharmacological preparation associated with medicinal or recreational uses (Johnson, 2019). Cannabis is composed of >500 substances, made up of 120 terpenes and sesquiterpenes and >110 (phyto) cannabinoids, within these are shown; The classic cannabinoids are Cannabidiol (CBD, CBN) and tetrahydrocannabinoid (THC). that have been given importance in their pharmacological use (Russo, 2011), for example, Synthetic or plant-based THC (△9-THC) and other cannabinoids are used for the treatment of some clinical signs such as nausea, spasticity, neuropathic pain, epilepsy, glaucoma, multiple sclerosis, and eating disorders associated with cancer treatments (Allan et al., 2008; Alexander, 2016).

Some studies indicate the deworming effect that this plant may have, however, its effect in its entirety has not been fully explored. The high prevalence reports of groups of helminth parasites that present resistance to anthelmintics, the residual drug products in animal products and the high cost of anthelmintics available on the market have made studies focus their attention on research on medicinal plants. As an alternative to the unwanted effects of anthelmintics. Therefore, the objective of this chapter is to analyze some perspectives on the medicinal and deworming effect of *Cannabis sativa* in animals, as a response to the problem of resistance to dewormers in animals.

Chemical Composition of *Cannabis sativa*

This finding led to the review of endogenous coordinators that activated them, called endocannabinoids. Currently, the definition of cannabinoids includes phytocannabinoids, endocannabinoids and synthetic analogues. An example of the different components of each group is presented in Fig. 1.

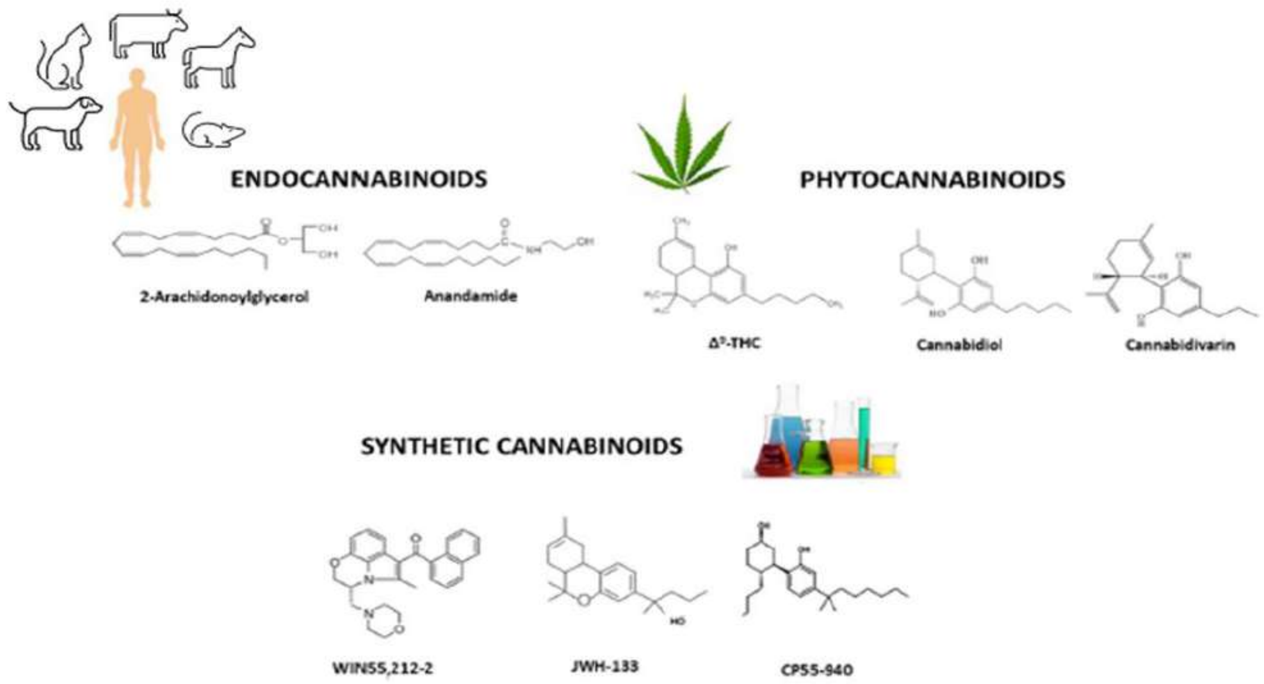

Fig. 1: Representation of the compounds of the main molecules present in THC, tetrahydrocannabinol, endo, phytocannabinoids and synthetic cannabinoids.

General use of Cannabinoids in Animals

Cannabidiols (CBD) have increased in popularity because of legalization in some of US States and other countries and are now recommended by human and veterinary doctors. Despite this, there are still concerns about the legislation, toxicity and benefits of CBD in veterinary patients because clinical experiments are scarce. When an online questionnaire was conducted in the United States, the results reported that almost 60% of pet owners included CBD in their treatments for dogs, and 12% in their cats, as a management for osteoarthritis, seizures, cancer or anxiety. (Kogan et al., 2016). Of the total sample, 64% found benefits for pain threshold management. 50% of owners reported that it helped their pets rest better, 49% that it reduced anxiety, and 30% that it reduced seizures in their pets. Therefore, it can be concluded that pet owners choose cannabis products for their pets because they are natural and generally perceive them as a maintenance therapy for pain management (Wallace et al., 2020). Some studies for the general use of cannabinoids in animals have confirmed the evidence of their functioning and effectiveness; in general, these compounds have been used in dogs, cats, horses, mice, non-human primates, and bovines. Below are the most common applications in veterinary medicine:

Pain Management

Various studies indicate that this plant has a system with physiological functions, including an analgesic action (Walker et al., 2002). This conclusion is based on preclinical trials that documented the presence of receptors for these substances, as well as the enzymes necessary for the synthesis and degradation of endocannabinoids in peripheral and central structures related to pain control. These studies also demonstrated the antinociceptive and antihyperalgesic effects of endocannabinoids in various models of transient (physiological), inflammatory and neuropathic pain (Iversen et al., 2002).

Epilepsy

Currently, there has emerged an appreciable approach towards phytocannabinoids developed for the treatment of some neurological disorders, such as the specific case of epilepsy (Leo et al., 2016). The recent conclusions available to date allow us to propose the hypothesis that the endocannabinoid system (ECS) is of importance for the regulation of the activities of the nervous system in areas directly or indirectly damaged in patients with this disease. These experiments are supported by several investigations with a description of electrophysiological, biochemical and pharmacological brain anatomy (Capasso, 2017).

Behavioral Disorders

Several studies have highlighted the effectiveness of CBD as a therapy for some behavioral disorders in dogs (Morris et al., 2020; Corsetti et al., 2021). Additionally, it is important to consider veterinary data documenting the potential application of CBD as an effective complementary treatment for anxiety. A notable example is a study with a nine-year-old pug dog who had a history of anxiety and aggression (reactivity when seeing other dogs) since the age of two. After administering three doses of CBD (5mg twice daily with food) as part of an alternative therapy, reactivity decreased by up to 50%. Subsequently, the patient continued to show significant improvement with continued use of the cannabinoid (Krause, 2019).

Skin Diseases

CB1 and CB2 receptors are expressed in canine keratinocytes, showing greater immunoreactivity in dogs with allergy problems compared to healthy dogs (Chiocchetti et al., 2022). Furthermore, these canine skin cells express TRPV1 receptors (Barbero et al., 2018). Published studies have provided information on how cannabinoids can be used to control pruritus, using ALIAmides such as Adelmidrol®, a compound that may be beneficial for this condition. Cannabinoid receptor agonists, such as PEA, have been shown to attenuate inflammation in the skin of mice in a model of allergic contact dermatitis (Petrosino et al., 2018) and reduce skin lesions and pruritus in atopic dogs (Noli et al., 2015). In addition, great interest has been paid to the use of this plant because of its potential deworming effect on animals.

Perspectives on the Deworming Effect of *Cannabis sativa* in Animals

Promoting the benefits of medicinal cannabis in veterinary practice is important since it is a plant with scientific support regarding its use in problems such as resistance to deworming drugs worldwide. However, the usefulness of the medicinal plant for veterinary use is not common in many countries due to legal regulation; But CBD can be feasible and has become a widely used compound in the veterinary clinic; Everyday, there is more data available on the beneficial effects of cannabinoids in animals, because these substances intended mainly for administration in humans are tested for the first time in animal models (Landa et al., 2016). Therefore, in this section, the major results will be described regarding the deworming effect of *Cannabis Sativa* in the work carried out on humans and animals. At the end of the 1990s and during the period 2000-2010, the sequencing of complete human, animal and parasite genomes was carried out, which made it possible to identify new drugs to counteract pathogens. In addition to vertebrates, the order *Chordata*, such as the *Ascidian Ciona* intestinalis and the *Lancelet Bramchiostoma floridae*, have been reported to have binding mechanisms for these substances (Elphick, 2007). In addition, results are emerging on the effect of extracts on protozoa, helminths and even ectoparasites such as fleas and ticks (Anday and Mercier, 2005).

Deworming Effect on Protozoa

In laboratory tests using the ciliate model of *Tetrahymena pyriformis*, it was observed that △9-THC at concentrations of 3.2 to 24μM inhibited development, shape/size, and mitosis in cultures with synchronized division by blocking RNA synthesis and DNA (McClean and Zimmerman, 1976).

The plant and its derivatives also inhibited the development and formation of cysts of the parasite *Naegleria fowleri*, the cause of primary amoebic meningoencephalitis (Pringle et al., 1979). It is important to note that laboratory experiments focused on these pathogens have not been effective in designs where the central nervous system is affected. On the other hand, research in a murine model supplemented with a dose of THC (40 mg/kg i.p.) and then parasitized intranasally with *A. Culbertsoni*, had a greater number of positives than the untreated ones (Marciano-Cabral et al., 2001). Additionally, evidence has been presented showing the use of this plant as a treatment against malaria. In mice with brain infection by murine malaria, a dose of CBD (30mg/kg for 7 days) and the antimalarial artesunate (day 5 p.i.) were used; shortages and anxiety problems before or after deworming led to an increase in the survival of animals (Campos et al., 2015). In another study, mice freely fed leaves and seeds of the plant showed a slight effect on parasites, but a significant reduction in clinical signs, suggesting that the plant could induce a state of tolerance to malaria with asymptomatic carriage. In people or animals that consume it daily (Akinola et al., 2018). Research results have identified hemozoin as a product of hemoglobin digestion by *P. falciparum*, as a target for THC and CBD, compounds that have potential antimalarial activity (De Sousa et al., 2021).

Toxoplasmosis is a disease that has as its etiology a complex, *Toxoplasma gondii,* most cases are asymptomatic, but if the disease becomes chronic, it can lead the parasite to the Central Nervous System, having neuropsychiatric signs and behavioral disorders, complicating it with epilepsy and schizophrenia. (Milne et al., 2020). In the laboratory, tests were carried out on mice infected with acute or chronic toxoplasmosis; THC caused a decrease in seizures, while synthetic substances such as JZL184 (MAGL inhibitor), ACEA (CB1 agonist) and AM630 (CB2 antagonist) eliminated effects that can induce seizures and the agonist AM251 (CB1 antagonist) and HU308 (CB2 antagonist) had greater effects. These data indicate a benefit to eliminate neurological alterations caused by the parasitic load in the nervous system (Ghanbari et al., 2020).

The most important protozoan diseases are caused by the genus *Trypanosoma* and *Leishmania*. Chagas disease is caused by *T. cruzi*. This pathology is a public health problem that can cause diseases related to the heart, in addition to megacolon and megaesophagus, it also causes serious problems of the nervous system (Pérez-Molina and Molina, 2018). The cannabinoid (+) WIN55,212 has been used, presenting good results, with high levels of reduction in the parasitosis of cardiac myoblasts; However, in vivo experiments with infected mice showed increased heart rate, inflammation, and increased parasitosis without any beneficial effect on heartworms. These data indicate that cannabinoids could have a negative effect on cardiac repair, suggesting their therapeutic usefulness in chronic infections of this type (Croxford et al., 2005). In experimental *African trypanosomiasis*, therapeutic experiments in rats revealed effective therapeutic results of *C. sativa* in an aqueous presentation used as an extract (Nok et al., 1994).

Giardia intestinalis (*G. intestinalis*) is an important parasite that causes diarrhea in humans and animals worldwide. This type of organism releases extracellular vesicles (EV) that influence its pathophysiology. New characteristics of *G. intestinalis* EV production have been described, where its ability to release two different populations of EVs is observed: large extracellular vesicles (LEV) and small extracellular vesicles (SEV). Proteomic analysis showed differences in proteins relevant to infection and host-pathogen interactions between the two EV subsets, including cytoskeletal and antioxidant stress response proteins in LEV. Recent experiments evaluate the effect of two inhibitors of EV release in mammalian cells, identified as peptidylarginine deiminase (PAD) and cannabidiol (CBD), on *Giardia* EV release. The results indicated that both inhibitors could effectively reduce EV release, and the PAD inhibitor specifically affected LEV release and reduced parasite adhesion to host cells in vitro. These findings suggest that LEV and SEV play different roles in the host-pathogen interaction and that treatment with VE inhibitors, such as this plant, could be a new therapeutic approach for chronic giardiasis (Gavinho et al., 2020).

Anthelmintic Effect on Helminths

Nematodes, cestodes and trematodes, are parasites with distinctively defined shapes. In several regions, farmers have used *cannabis* as an anthelmintic (Roulette et al., 2016). Extracts from this plant have demonstrated nematicidal activity against plant pathogens, such as Meloidogyne incognita (Mukhtar et al., 2013). In addition, studies have been carried out in animals infected with the intestinal nematode *Nippostrongylus brasiliensis,* whose life cycle is like that of hookworms harmful to humans. The data indicate that inhibition of the CB1 receptor with the synthetic molecule AM6545 promoted an increase in parasite load and egg production, as well as a decrease in the Th2 cytokine IL-5. Interestingly, transcriptomic analyzes integrated with mass spectrometry and qPCR in the advancing stages of *N. brasiliensis* revealed that this and other worms can produce their own endocannabinoids (eCBD), peaking in their infectious larval form. These findings suggest that parasite-produced endocannabinoids, a previously undescribed group of CBDs, play a role in the host immune response, which could facilitate parasite expulsion (Batugedara et al., 2018).

Antiparasitic Effect on Ticks

Ticks, parasitic arachnids of the order *Ixodida*, feed on the blood of host mammals and birds, which represents a concern for both the livestock industry and the health of pets and their owners. Although tick-borne diseases are a significant concern, there is a paucity of information on how certain molecules derived from these parasites may interact with cannabinoid receptors (Schön, 2022). It has been suggested that *Cannabis sativa* extracts from the leaves and roots may have a relevant suppressive effect on egg hatching and total larval mortality, with an effective dose of 40mg/mL against *Riphicephalus (Boophilus) Microplus*, an important tick. in public health. Application of a 45% extract to larvae-infected cattle has been reported to reduce tick burden 96 hours after application. It has been suggested that acetylcholinesterase (AChE) from *R. microplus* could be a likely target. Bioinformatic predictions indicate that CBD could be a potent inhibitor of this enzyme, which positions it as a promising compound for future research in the control of ectoparasites (Nasreen et al., 2020).

Conclusions

Compounds of plant origin offer a wide range of benefits for human and animal health, making them promising alternatives for the treatment of parasitic diseases. These compounds include macrocyclic lactones, terpenes and polyphenols. The plant, known as hemp, marijuana or ganja, is distinguished from most plant species by its various industrial products and phyto-medicinal compounds, highlighting phyto-cannabinoids such as THC and CBD. CBD is a phyto-cannabinoid present in hemp, and more than 140 phyto-cannabinoids have been identified with medicinal properties for the treatment of various diseases. Although the use of cannabinoids in parasitic infections is promising due to their in vitro activities, more research in animal models and vectors is needed to fully understand their efficacy and safety. For example, THC has been observed to aggravate certain parasitic brain infections, such as *Acanthamoeba* spp., rather than improving the outcome. Furthermore, studies in murine models of malaria suggest that regular cannabis users could become asymptomatic carriers of the disease, which represents a public health problem. It is important to consider that synthetic cannabinoids could be harmful in chronic Chagas disease, compromising cardiac homeostasis and contributing to heart failure, the main cause of death due to *Trypanosoma cruzi*. Furthermore, the sandfly vectors of *Leishmania* spp. could spread parasites tolerant or resistant to phyto-cannabinoids if they have constant access to *Cannabis sativa* plants for food. Recent studies also suggest that several nematodes produce their own endocannabinoids, which could help soil-transmitted helminths evade and suppress host immune responses. Therefore, these concerns should be addressed in future research. Although the use of known phyto-cannabinoids and synthetic cannabinoids in parasitic diseases requires further exploration, it represents an interesting area of research that shows potential in veterinary applications due to their antiparasitic properties.

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Chapter 26

Ameliorative Effect of Dietary Turmeric Supplementation in Fish

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ABSTRACT

Antibiotics pose enormous negative consequences including bacterial resistance and their accumulation in muscles, so they are excluded from aquaculture and livestock sector feeds. Therefore, a variety of alternative antimicrobial agents are being employed to provide the productivity and health advantages that have historically been connected to antibiotics. Phytogenic product-based extracts from proven antibacterial herbs and spices are among the most often used substitutes. Turmeric and its derivatives exhibit promising antioxidant, anti-inflammatory, and antibacterial properties in the field of applied animal research. Curcumin, the primary biologically active compound found in turmeric, is being employed in fish nutrition and other organisms due to its beneficial effects, such as its ability to stimulate the immune system, act as an antioxidant, fight against microorganisms, and reduce inflammation. Turmeric in all forms is reported to benefit farmed organisms including poultry as well as fish by enhancing growth parameters and reproduction indicators, boosting immunological response, enhancement to make them resistant against disease, along with facilitating comprehension of digestive, metabolic, immune, and excretory processes hen supplemented in diet. Curcumin, despite its beneficial effects, has limitations including a lack of solubility in water (hydrophobicity), while nanoparticle-based curcumin has been extensively documented for its capacity to enhance the bioavailability and solubility of lipophilic curcumin.

KEYWORDS
Antibacterial, Curcumin, Fish feed supplementation, Nano encapsulated curcumin, Turmeric

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INTRODUCTION

Phytogenic substances have gained significant popularity as substitutes for antibiotics used in the feed of monogastric species such as poultry and fish. This is due to the negative consequences of indiscriminate antibiotic use in organism's diet, including development of antibiotic-resistant bacteria besides buildup of antibiotics accumulation in edible muscles. Currently, the European Union (EU) has implemented a prohibition on the utilization of synthetic growth enhancers in organism's diets. Meanwhile, the Food and Drug Administration (FDA) intends toward impose limitations on usage of antibiotic growth promoters (AGP) in organism's diets. Presently, researchers are placing emphasis on the utilization of organic and non-antibiotic growth promoters (NGPs) to enhance animal disease resistance and promote growth. This is achieved by incorporating different feed additives to improve the functions of the gastrointestinal tract (GIT) and enhance overall health and growth (Sharif et al., 2021).

Turmeric *(Curcuma longa)* and its Bioactive Compound Curcumin

Turmeric, a perennial herb with tuberous rhizomes, belongs to Zingiberaceae family. It is known as "golden spice" which is frequently employed as powdered curry throughout Southeast Asian food (Fig. 1). Turmeric possesses therapeutic properties that are beneficial for the health of humans as well as animals (Prasad et al., 2014). The dry turmeric rhizome is composed of three to six percent terpenes including terpenoids, six to eight percent protein, six to ten percent fat, sixty to seventy percent carbohydrate, and three to six percent fiber (Johannah et al., 2018). Curcumin, commonly referred to diferuloylmethane, being a chemical with water repellent properties and polyphenol characteristics that is derived from *C. longa*. Turmeric has long been recognized as a highly effective natural antioxidant in Indian ayurvedic therapies and traditional Chinese medications (Zheng et al., 2018). Turmeric as well as its byproducts have antibacterial, antioxidative, anti-inflammation, orexigenic, immunomodulation, in addition to gastroprotective properties in the health of animals (Johannah et al., 2018).

Sources and Biosynthesis of Curcumin

Curcumin, the primary biologically active compound found in turmeric, is being employed in fish nutrition and other organisms due to its beneficial effects, such as its ability to stimulate the immune system, act as an antioxidant, fight against microorganisms, and reduce inflammation. *C. domestica* and *C. longa* are extensively cultivated in China, India, as well as Indonesia (Galli et al., 2018). The process of curcumin production in *C. longa* is depicted in Fig. 2.

Curcumin, despite its beneficial effects, has limitations including a lack of solubility in water (hydrophobicity), a volatile chemical composition, rapid metabolic processes, and inadequate concentration absorbed in organism's body. Absorption rate of curcumin is dependent upon the organisms as well as gender (Hewlings and Kalman, 2017).

Fig. 1: *C. longa* and its derivatives (Alagawany et al., 2021).

Curcumin Nanoparticle

Nanoparticle-based curcumin has been extensively documented for its capacity to enhance the bioavailability and solubility of lipophilic curcumin. Earlier research has indicated that the dissolution and absorbing rate of nanocurcumin surpasses that of regular curcumin. In addition, curcumin nanoparticles exhibit higher bioavailability and are more easily deposited in Sprague-Dawley rat tissues compared to regular curcumin (Song et al., 2011).
In recent times, numerous research investigations have been carried out to investigate the use of curcumin nanoparticles as a standalone treatment, as well as in blend with additional substances, for the diets of monogastric organisms including fish. The majority of research focus on the augmentation of growth, promotion of reproductive and metabolic functions, as well as the modulation of the immune system and antioxidant properties of curcumin as well as its nanoparticles (Reda et al., 2020).

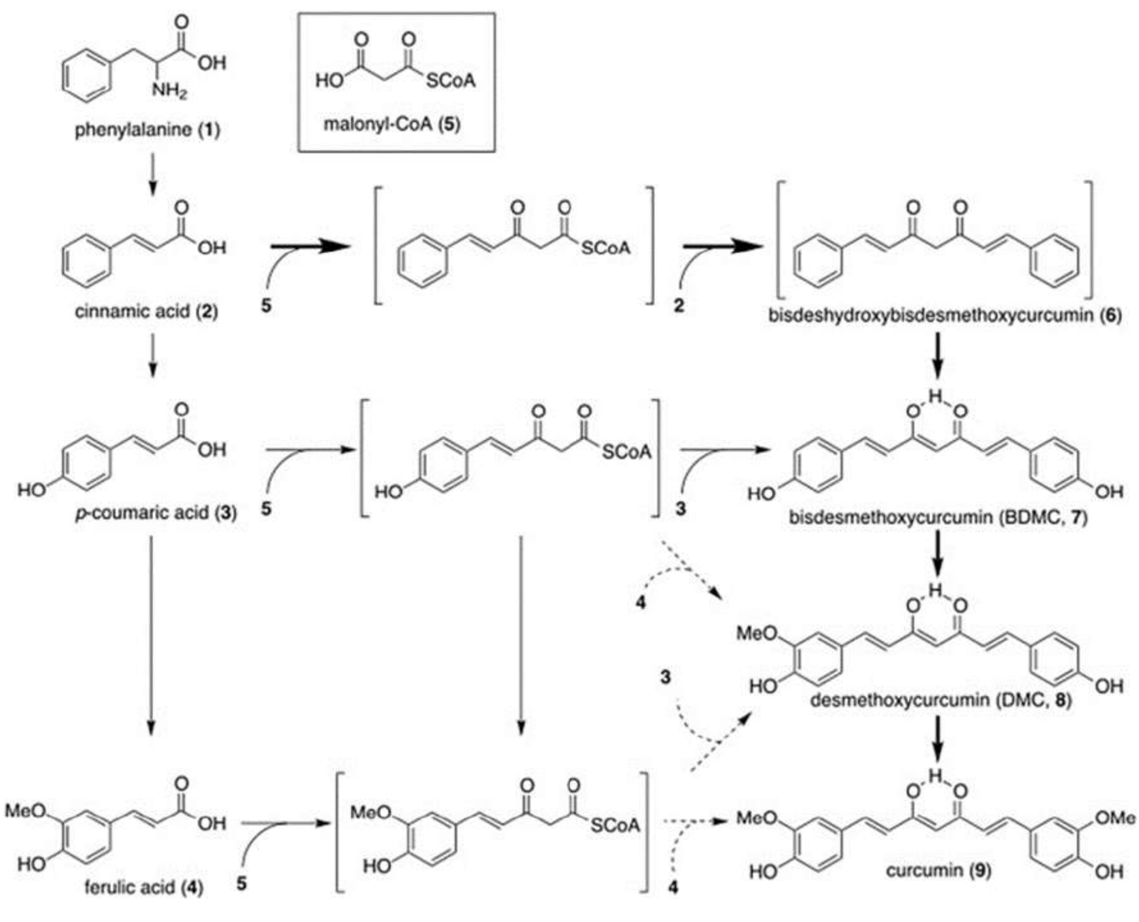

Fig. 2: Biosynthetic pathway of curcumin in turmeric herb (Kita et al., 2008).

Ameliorative Effects and Nutritional Importance of Curcumin on Fish

Various researches has reported the impacts of many types of curcumin in field of aqua feeding. The fish industry is seeing rapid growth globally and plays a crucial role in addressing the increasing demand for animal protein, particularly in developing nations (Perry et al., 2013). When compared with farmed animals including chicken, fish are superior source for micronutrition (such as vitamins along with minerals), amino acids in addition to essential fatty acids (Guerreiro et al., 2018). Nevertheless, as a result of the swift expansion of aquaculture in both horizontal and vertical dimensions, coupled with land scarcity issues, the majority of fish rearing is conducted in intensive as well as demanding farmed circumstances. These factors contribute to the occurrence of outbreaks of infectious diseases (Van Doan et al., 2018). Therefore, fish producers frequently rely on antibiotics as well as pesticides for improvement of health as well as production of fish. Nevertheless, the unapproved and extensive use of antibiotics in aquaculture can potentially give rise to antibiotic-resistant bacteria, leading to environmental risks, alterations in bacterial populations, and the buildup of antibiotic remnants in fish tissues. Consequently, this situation raises concerns regarding public health. In order to address the issues caused by the excessive application of antibiotics for fish ecosystems, scientists have suggested the utilization of phytogenic such as curcumin as substitute for antibiotics in the aquaculture sector (Gangwar et al., 2013).

Growing and Feeding Efficiency

The addition of turmeric at a dosage of 20 gram per kilogram for 8 weeks duration considerably improved rainbow trout growing indices. Furthermore, the fish to which feed was supplemented by curcumin exhibited greater feed conversion ratios (FCR) compared to organisms on a regular feed (Yonar et al., 2019). Furthermore, Mahmoud et al. (2017) showed that supplementing the diet of tilapia fish with curcumin at doses of 50 or 100 milligram per kilogram can enhance growing factors for example weight gain (WG), specific growth rate (SGR), as well as daily weight gain (DWG). It also improves feeding efficiencies by reducing the feed conversion ratio (FCR) and enhances the protein efficiency ratio. Furthermore, several studies have reported that incorporating curcumin into the diet of Nile tilapia at concentrations of 5, 10, and 20 gram per kilogram can improve growing indicators as well as feed proficiency (El-Barbary, 2018). Jiang et al. (2016) found that *Carassius carassius*, when supplemented with diet containing 5 milligram per kilogram of curcumin, experienced improved growth indices (increased weight gain, feed efficiency, and hepatopancreas weight). Additionally, the fish showed increased activity of digestion enzymes (trypsin in addition to lipase), along with enhanced anti-oxidative activity as well as increased expression of messenger RNA genes related to the gastrointestinal tract.

Blood Indices

Blood and circulatory criteria is widely employed to evaluate physiological state, trauma levels, well-being, and illness status of fish. In addition, hematobiochemical variables can indicate the health status of fish by identifying abnormalities caused by the usage of immunostimulants. Yonar et al. (2019) showed that adding curcumin to the diets of rainbow trout significantly improved their hematological characteristics. In addition, the study demonstrated a significant increase in both total protein and IgM levels in fish that were given curcumin. This suggests that the administration of curcumin may lead to the stimulation of humoral immunity. Previous research has demonstrated that adding curcumin to the diet of Nile tilapia fish at doses of 5, 10, and 20 gram per kilogram improves various aspects of their health, including hematological parameters, total serum protein, hepatic thermal shock protein, glycogen production, and bactericidal activity (El-Barbary, 2018). Supplementing the food of common carp (*Cyprinus carpio*) with curcumin at a dosage of 100 mg/kg significantly enhances the hematological parameters (Yonar, 2018).

Immunity

Immune factors are significant markers that can be utilized to evaluate the nutritive, physiological, also functional condition regarding fish, besides their ability to respond to the outside conditions. Inclusion of turmeric (20 gram per kilogram) in daily feed of rainbow trout significantly enhanced immunological reactions by promoting the activity of antioxidant enzymes and suppressing peroxidation of lipids (MDA) (Yonar et al., 2019). Furthermore, researchers have also discovered a substantial increase in immunological values following the addition of curcumin, in comparison to the control group. In their study, Mahmoud et al. (2017) demonstrated that adding curcumin to the diet of Nile tilapia fish at doses of 50 or 100 milligram per kilogram can enhance the antioxidative state by increasing catalase and GSH levels and decreasing MDA levels. Additionally, curcumin supplementation was found to boost the immunological response by increasing lysozyme activity and elevating the levels of total immunoglobulins, including IgG and IgM. According to Yonar (2018), common carp which were given a meal containing curcumin at a dosage of 100 milligram per kilogram experienced a significant reduction in the levels of MDA (malondialdehyde) in their kidneys and livers, as compared to the control group.

Disease Resistance

In their study, Baldissera et al. (2018) found that silver catfish exhibited complete resistance to *Streptococcus agalactiae* when they were given a diet containing 150 mg/kg of curcumin. When rainbow trout were fed a diet containing 2% curcumin, they had a much higher survival rate (76.67%) compared to the control group (36.67%) after being infected with *Aeromonas salmonicida*. The authors suggested that curcumin treatment may be necessary to increase the synthesis of cellular along with humoral immune factors, which could potentially reduce mortality and protect fish from *A. salmonicida* subsp infection (Yonar et al., 2019). Prior research has shown that incorporating curcumin into the diet enhances the ability of fish species like *Labeo rohita* (Behera et al., 2011) as well as Nile Tilapia (Mahmoud et al., 2017) to fight *A. hydrophila* infection. Manju et al. (2009, 2013) demonstrated the fact that nutritional curcumin (five, ten gram per kilogram) in addition to its synthetic analogue salicyl curcumin (five gram per kilogram) have protective effects contrary to lipid oxidation as well as DNA damage. Additionally, they found that both compounds can improve the survival frequency and resistance to disease in *A. testudineus*. Currently, there is a lack of research on the use of turmeric nanoparticles in fish nutrition. Existing studies primarily focus on administering very high doses of curcumin to fish, which have shown positive effects. To achieve cost-effectiveness, it is necessary to adjust curcumin content in fish diet as a substitute for antibiotics. Hence, it is crucial to identify the most effective the nano formulations of turmeric for fish diet to achieve disinfected healthy fish species and enhance the productivity of aquaculture species. Curcumin exhibits pleiotropic benefits against illnesses by interacting with several molecular targets, consequently activating pathways of cell signaling such as death and inflammatory (Alagawany et al., 2021). Fig. 3 illustrates the advantageous function of curcumin in various fish species.

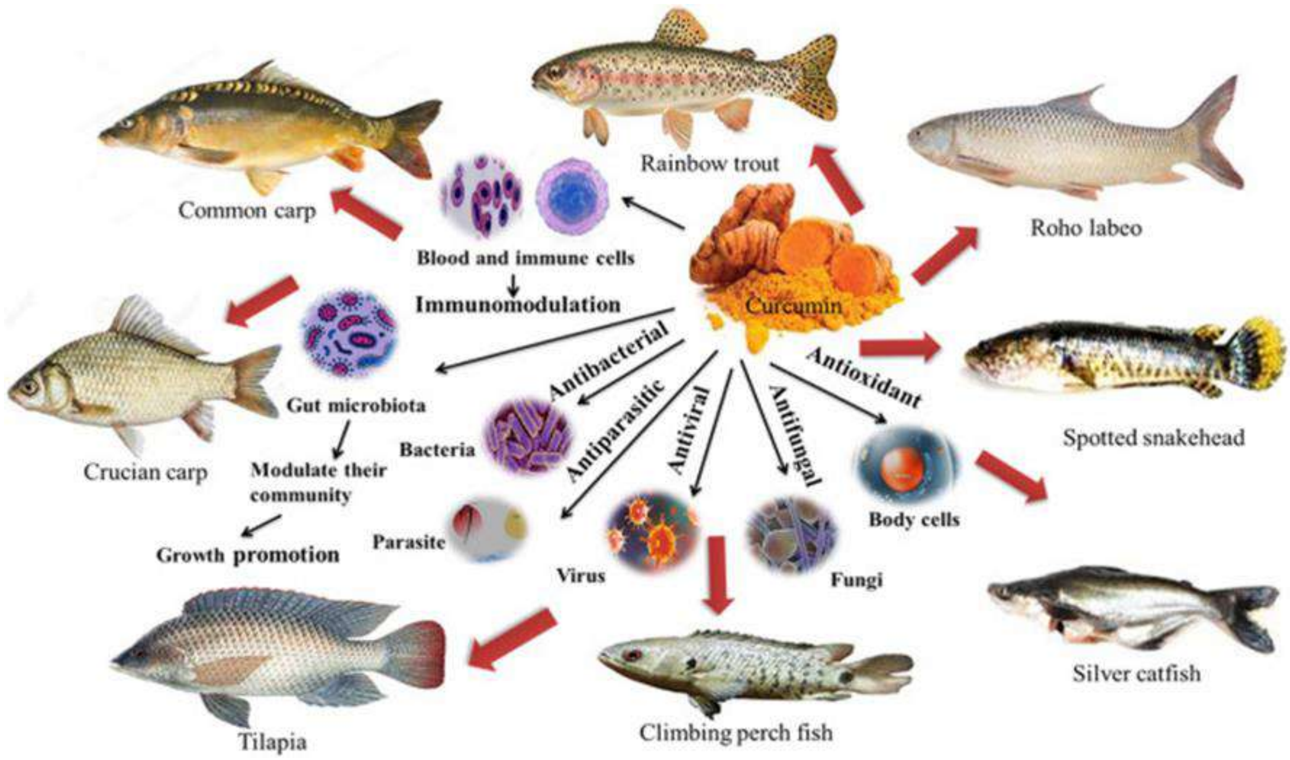

Fig. 3: Health aspects of curcumin in different fish species (Alagawany et al., 2021)

Aquatic Toxicants

El-Barbary (2016) proposed that turmeric and garlic may have a synergistic impact in enhancing the viability of *Oreochromis niloticus* during their exposure to aflatoxicosis. Alongside wastewater generated by various industrial processes, significant quantities of hexavalent chrome (Cr6+) discharged into water bodies can result in severe ecological repercussions for aquatic animals (Shaw et al., 2019). According to Awasthi et al. (2019), the presence of Cr6+ can lead to significant harm to the speckled snakehead (*Channa punctatus*). This harm mostly manifests as genetic damage, increased apoptotic parameters, and heightened oxidative stress. On the other hand, they discovered that curcumin was able to lessen these effects. This was demonstrated by a notable decrease in the number of reactive oxygen species, frequencies of apoptotic cells, and induction of micronuclei. Additionally, curcumin caused a reduction in the messenger RNA (messenger RNA) intensities for the cat, bax, p53, as well as apaf-1 genes. In addition, curcumin boosts the activities of SOD, CAT, and GSH, and stimulates the production of the Bcl-2 gene. Incorporating curcumin into the diet has the potential to enhance liver function and improve the overall health of several fish species. In a latest investigation, Mohamed et al. (2020) found that the treatment of curcumin at a dosage of 200 mg/kg diet could have positive effects on growth indices and protect the renal, hepatic, including bronchial tissues from damage caused by chromium exposure. In contrast, numerous scientists have postulated that these pesticides have the potential to modify the functioning of anti-oxidative enzymes as well as disrupt cell redox reactions (Rodríguez-Fuentes et al., 2015). An instance of this is malathion (MA), a pesticide that has been found to have detrimental effects on the growth and health of C. carpio fish. It has been observed to raise oxidative stress biomarkers (MDA) and hinder immunological reactions, even when used in low dosages (Yonar et al., 2017). Additionally, it was discovered that the application of turmeric (100 mg/kg) for a duration of 14 days in fish was able to mitigate the negative impacts of MA by significantly increasing the activities of CAT, GSH-Px, and SOD in the plasma, while simultaneously reducing the levels of MDA. Chlorpyrifos (CPF), which is an additional organophosphate insecticide, is extensively employed in the field of agriculture. The toxic effects of CPF pose a concern to both people as well as aquatic animals by triggering antioxidant response (Dawood et al., 2020).

Dietary curcumin substantially increases plasma immunoglobulin levels and lysozyme activity in Nile tilapia species and rainbow trout that are exposed to challenges, according to recent research (Mahmoud et al., 2017). The detrimental consequences of pesticide toxicity on fish were alleviated through the incorporation of curcumin into their nutrition, which enhanced immunological responses such as phagocytic cell activity. Therefore, it can be deduced that curcumin is comprised of substantial bioactive constituents that demonstrate immunomodulatory properties in response to the deleterious impacts of pesticides on fish. previous studies have indicated that incorporating curcumin into fish diets may have the potential to effectively safeguard fish biodiversity and stimulate the aquaculture industry, even when confronted with various aquatic pollutants originating from industrial effluents (Yonar et al., 2019).

Other Beneficial Effects of Turmeric on Fish Health

El-Houseiny et al. (2019) detected that supplementation with turmeric along with black pepper powder in the diet of *Clarias gariepinus* may reverse the detrimental effects of cadmium-induced testicular toxicity, hepatorenal injury, and growth retardation. Cadmium has become a significant problem in freshwater ecosystems because of its increasing concentrations and severe toxicity (Zhu et al., 2018). In the experiment El-Houseiny et al. (2019) categorized a total of 180 robust fish (*C. gariepinus)* into six categories, with three identical pairs in each group. The initial, subsequent, and third groups were administered a standard diet devoid of any supplementary substances, a standard feed complemented with TP (0.5 percent), besides a standard feed complemented with TP (0.5 percent) and BPP (0.1 percent), correspondingly. The fourth group was exclusively subjected to a Cd concentration in the water of 0.8 mg/L. Cd exposure was imposed on the fifth and sixth groups, which were fed diets fortified with TP or TP"+ BPP. The growth performance indicators, somatic indices, complete chemical composition, and Cd residues were evaluated. The levels of adenosine triphosphate (ATP), reproductive hormones, oxidative stress, and lipid peroxidation were estimated, as were liver and kidney function markers. Indicators of hepatosomatic and gonadosomatic processes, in addition to growth, crude lipid, protein, and ash content, were all negatively impacted by Cd, according to their findings. Furthermore, an analysis revealed that the concentrations of alanine transaminase and also potassium, in addition to malondialdehyde were all substantially elevated. However, the levels of lysozyme activity, immunoglobulin M, testosterone, estradiol, catalase, superoxide dismutase, and ATP content all decreased significantly. However, by adding TP and TP+BPP to the dietary regimen of fish impacted by Cd toxicity, the majority of the observed disturbances were effectively mitigated. The combination of TPand BPP supplementation led to the most substantial degree of recovery. By incorporating a combination of TP and BPP into its nutrition, *C. gariepinus* is able to enhance its growth and reduce the deleterious impacts of Cd on its reproductive system, kidneys, and liver. In their research, Hoseini et al. (2022) investigated the potential of incorporating turmeric into the diet of common carp, *C. carpio,* to alleviate transportation stress. The study was conducted to observe the effects of four different turmeric-containing diets (0% (CTL), 0.5% (0.5 T), 1% (1 T), and 2% (2 T)) on common carp (mean weight: 45.2 g) over a period of two weeks. Following that, the fish were transferred into plastic bags containing 2.5 L of water and 5 L of purified oxygen. The bags were then driven for a duration of 3 hours in a van. Both blood and water samples were collected both before and after the transit. Water quality indicators declined due to transportation activities, as evidenced by reductions in oxygen concentrations and pH levels. Conversely, alkalinity, total ammonia, and unionized ammonia levels increased. Following transit, the fish from the treatment containing 1 T exhibited the most elevated concentrations of dissolved oxygen in the water; this disparity was found to be statistically significant. Significant decreases in total immunoglobulin (Ig) and plasma total antioxidant activity (TAC) were observed because of transportation-induced stress. The transportation-induced stress on the fish led to elevated concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and lysozyme in their plasma. Decreases in plasma cortisol, glucose, ALT, AST, ammonia, SOD (exclusively in 1 T), CAT, and MDA indicate that the transportation stress was mitigated in the 0.5 T and 1 T interventions. Furthermore, elevated concentrations of plasma total Ig and TAC were observed in the fish (Hoseini et al., 2022).

Dietary turmeric, nano encapsulated curcumin, and curcumin have distinct anti-stress properties against salt-induced stress in Pacific white shrimp *Penaeus vannamei*, according to a recent study. The research investigation comprised ten interventions, one of which served as a control group. For nine weeks various doses of dietary turmeric, nanoencapsulated curcumin, and curcumin was administered. In comparison with control group, in both stressed and non-stressed crustaceans, the addition of all three turmeric forms increased the total protein, total haemocyte count, and differential haemocyte count. However, the crustaceans that were provided with nanoencapsulated curcumin at a concentration of 0.150 exhibited the greatest increase and highest survival rate notably. The control group demonstrated the most minimal and most maximal levels of antioxidant enzyme activity, including CAT, SOD, and GSH-Px, respectively. Various types of dietary curcumin enhanced the antioxidant capacity and resilience of *P. vannamei* to sudden changes in salt levels. Nanomicellar transporters in shrimp nutrition enhance immune function and antioxidant responses in challenging circumstances by facilitating the effective transport of feeding immune stimulating agents (Moghadam et al., 2022).

Conclusions

Turmeric and its derivatives exhibit promising antioxidant, anti-inflammatory, and antibacterial properties in the field of applied animal research. It is both harmless and non-hazardous, other than being inexpensive. Additionally, it possesses exceptional actions, which makes it further alluring to researchers in comparison to former plant-based chemicals. There is still a wide range of possibilities for future investigations in the field of nanotechnological instruments for advancing curcumin investigation in biological and veterinary science. Additionally, although curcumin nanoparticles effectively reduce the required quantity of it, the utilization of nanoscale product may result in detrimental consequences and may impose constraints on its capacity to target delivery systems precisely. Therefore, it is critical to conduct research on the toxicokinetic of nanocurcumin to enable effective delivery of curcumin to the intended organs and reduce its toxicity. These improvements will benefit farmed organisms including poultry as well as fish by enhancing growth parameters and reproduction indicators, boosting immunological response, enhancement to make them resistant against disease, along with facilitating comprehension of digestive, metabolic, immune, and excretory processes. Furthermore, these inquiries may contribute to the identification of alternative antibiotics that are viable for use in agricultural sites.

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Chapter 27

Propolis, a Useful Adjuvant against Neurological Disorders

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ABSTRACT

Bees gather propolis, a natural, safe viscous substance, to retain the hive's homeostasis and protect it physiologically and biochemically. Propolis is highly recognized for its medicinal properties, it retains numerous biological effectuality including free radical scavenging, anti-cancerous, antimicrobial, and antioxidant properties. Furthermore, the depression-reductant action of propolis was illustrated in several biological studies. Propolis mitigates the tiers of corticotropin and corticosterone in stressed and depressed models. It shows potential therapeutic effects against neurodegenerative and neurologic disease models, like epilepsy, Parkinson's, and Alzheimer's disease. Propolis suppressed neuronal detriments and altered the histopathology linked with Parkinson's disease and epilepsy in animal models. It has been shown that propolis can lessen amyloid fibrillation and the effects of amyloid buildup. Propolis constantly diminishes express of inflammatory markers, conserves antioxidants, and ameliorates the cognitive scores of models under study. Propolis inhibits nerve cell apoptosis by diminishing the expression of genes linked in apoptotic signaling channels. Interestingly, propolis has been demonstrated to be useful in reducing pain, oxidative stress, and neuroinflammatory symptom severity. The animals' melancholy behavior and intellectual disability were reduced as a result of the modulation of endocrines and biochemical indicators.

KEYWORDS		
Propolis; Anti-depressant; Corticosterone; Histopathology; Amyloid fibrillation; Neuroinflammation.	Received: 15-Jun-2024 Revised: 18-Jul-2024 Accepted: 20-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Propolis is a combination of the Greek "Pro" (at the entranceway) and polis (city) and correlates an essence in the shield of the hive. Propolis is an intuitive pure, toxic resinous substance assembled by bees to sustain hive galvanization stability and to endow biochemical and physical shield to the hives (Zulhendri et al., 2021). It is a resinous material, composed of various floral parts along with the secretion of saliva and beeswax, which manifests a multimillion-dollar market stock. Propolis is tough and dainty at low temperatures. However, after heating (25–45°C), it transforms refined, resilient, elastic and stickyious. The melting points scaled between 60 to 100°C. The frequently used solvents for propolis include acetone, chloroform, methanol, ethyl alcohol, H_2O, and dichloromethane. Propolis is a complicated amalgam of ingredients, and that's why the recruited solvents for extraction must be well suited for the polarity of the chemical constituents one is interested in (Silveria et al., 2021). It's a balsamic and sticky material with complicated varied chemistry and is taken as a matrix with mounted biotechnological potency. Numerous biological attributes of propolis extracts are illustrated in scientific research, such as hepatoprotective, oxidant scavengers, antiviral, immunomodulant, anti-inflammatory, and antiparasitic. Such a wider range of characters hints at its effectiveness and applicability in the development of medicinal items for harnessing in human health (Santos et al., 2012).

History and Research on Propolis

Bee glue, or propolis, has been known for ages. Propolis had therapeutic benefits, which the ancient Greeks, Romans as well Egyptians utilized extensively in their treatment. Propolis extract was not a particularly well-liked subject throughout the Middle Ages, and its application in conventional medicine vanished. Nonetheless, conventional local medicine continues to use the understanding of propolis' therapeutic benefits. Along with the ad fonts philosophy of the Restoration, Propolis also became popular again in Europe. Scientists have managed to demonstrate that propolis is just as active and significant as our ancestors believed it to be. After World War II, studies on the chemical structure of propolis were carried out. These studies began at the turning point of the 20th century. Improvements in chromatographic analysis permitted isolation and removal of many elements from propolis. Thus far, a minimum of 180 distinct chemicals have been found (Kuropatnicki et al., 2013).

Fig. 1: Bee propolis a hive protectant

Peter, 2019 (What is propolis, its uses and how to collect it?) https://thebeestore.com.au/blogs/bee-blog/what-is-propolis-its-uses-and-how-to-collect-it

Origin

Propolis was included within the 17th-century in England pharmaceutical manuals as an approved medication. Between the 17th as well as twentieth centuries, propolis gained immense popularity in Europe because of its antimicrobial properties. Stradivari utilized bee glue as a violin finish in Italy. Due to its therapeutic qualities, propolis became extremely popular in late 19th century. During World War II, it was used in various Soviet hospitals to treat TB because of the reported decrease in lung issues and improvement in appetite (Wagh, 2013). Brazil produced over 41,721kg of propolis in 2012, which is equivalent to about $5,401,643. Some of the important bioactive compounds from propolis varieties of different geographic regions has being illustrated in table below as cited by Wagh, 2013.

Table 1: Main Bioactive compounds in propolis gathered from different geographic locations

Provenance	Plant specie	Phytoconstituents	References
Subtropical Asia, Vinland, and Europe	Species of Populous, *P. nigra L.*	Polyphenols	Wagh, 2013
Russia	*Betula verrucosa*	Polyphenols	Wagh, 2013.
Brazil	Species of *Baccharis, B. dracunculifolia.*	Diterpenes, prenylated p-coumarins	Wagh, 2013.
Venezuela	Species of *Clusia.*	Polyprenylated benzophenones	Wagh, 2013.
Pacific region	Unknown	Terpenoids	Wagh, 2013.
Canary Island	Unknown	Furofuran lignans	Wagh, 2013.
Kenya	Unknown	Polyphenols	Wagh, 2013.
Cyprus and Greece	Unknown	Flavonols and terpenes	Wagh, 2013.

Chemical Composition of Propolis

The major proportion of propolis is occupied by resin, a sticky material. Resin is a solid or extremely viscous material that can be synthetic or plant-based and is usually convertible into polymers as explained in the fields of materials science and polymer chemistry. In reaction to damage, plants release resins for their defensive properties. The plant is shielded from diseases and insects by the resin. Wax, essential oils, pollens, and other organic compounds make the remaining half of propolis (Simone et al., 2009).

Propolis' Types

Propolis comes in a variety of forms, which are determined by its chemical makeup, botanical background, as well as geographical location. Poplar, European, Brazilian, and Pacific propolis are among the most widely used. Propolis of the poplar variety is found in non-tropical areas of Asia, North America, along Europe. Poplars (Populus spp.) of many species are used to make it, with P. nigra being the most popular kind. Flavones, flavanones, cinnamic, and esters make up the majority of the chemical makeup of poplar propolis (Bankova et al., 2005), whereas mono- and sesquiterpenes predominate in the essential oil's chemical composition (Ristivojević et al., 2015). Subtypes of propolis from poplar i.e. bluish and amber hued, are illustrious, which varies in chemistry, due to intensive progression of chromatographic techniques and their implementation in the chemical properties of propolis (Morlock et al., 2014; Ristivojević et al., 2015). Additionally, several scientists have identified a greenish kind of poplar propolis (Chasset et al., 2016). Kaempferol, caffeic acid, as well as luteolin are metabolites found in blue propolis, whereas quercetin, pinocembrin, tectochrysin, as well as pinobanksin are polyphenols found in orange propolis. Compounds including coumarics, chrysins, galangins, and pinobanksins-3-acetates also appear across both kinds of poplar propolis' chemical makeup. The mentioned substances are indicators of green poplar propolis: apigenin, galangin, apigenins-methyl-ethers, and galangins-methyl-ethers (Chasset et al., 2016). Orange propolis is the most common kind in Europe. But in addition to the region's geographical setting, a number of other elements affect propolis's chemical-based composition: sunshine, humidity, development of phytochemicals, as well as the mineral content of the surrounding soil.

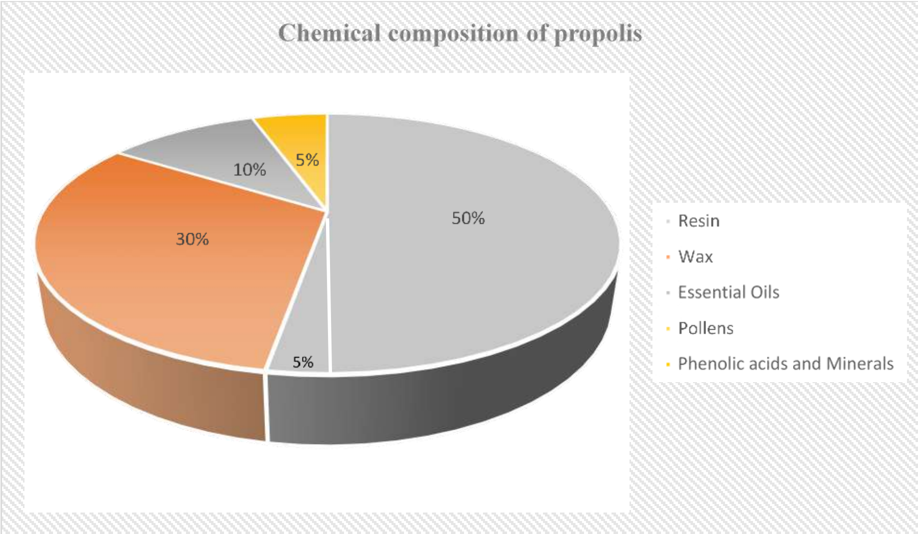

Fig 2: Chemical proportion of propolis

The plant used to make red propolis, or Clusia propolis, is Clusia (Clusia spp.), which is native to Venezuela along with Cuba. Red propolis has a high concentration of propyl gallates, catechins, epicatechins, methyl eugenols, trans-anetholes, trans-methyl isoeugenol, triterpene alcohol, isolations, and xanthohumol among other chemicals. It also contains formononetins, biochanins A, and pinocembrins. In addition to it demonstrated antibacterial and antifungal qualities, red propolis also possesses analgesic, anti-inflammatory, and liver-protective qualities. Food can be kept fresher longer by using this supposed nutraceutical (Lopez et al., 2015).

Another kind of propolis that has been described is Brazilian green propolis, also known as alecrim propolis, which is derived from Baccharis dracunculifolia. It is distinguished by having an especially high concentration of prenylated phenylpropanoids, such as artepillin C, as well as sesquiterpenes, such as farnesol, diterpenes (a derivative of isocupressic acid), propolis-benzofurans A and B, and agathicates. Moreover, this propolis was shown to include ferulic acid, kaempferols, kaempferides, cinnamics, 72 K. Pobiega, M. Gniewoszs, and K. Kraśniewska caffeic acids (Weinstein et al., 2005, Fernandes-Silva et al., 2013). Birch propolis is a well-known product in Russia. Propolis from birch (Betula verrucosa) is utilized in this preparation. Apart from poplar propolis, flavones as well as polyphenols are the primary constituents of birch propolis (Bankova, 2005). Mediterranean propolis was a different kind that was identified in 2015. It is derived from coniferous trees of the Pinaceae alongside Cupressaceae families. It mostly consists of diterpenes. Propolis from Greece as well as Cyprus is rich in aromatic chemicals and volatile compounds, that possess potent antibacterial qualities (Graikou et al., 2016).

Medical Benefits of Propolis

Propolis has long been known to offer health benefits, but scientists have only recently been able to demonstrate the substance's efficacy as a therapeutic agent. Recognizing its antirotting qualities, the Egyptians embalmed bodies with it. In Greece and Rome, it was utilised as oral disinfectant, natural antibacterial, and wound-healer (Cheng et al., 1996). Propolis' benefits were also valued by the New World's civilizations, who are known to have utilised it as an antipyretic by the Incas. Additionally, propolis was listed among the approved medications in the 17th-century English Pharmacopoeia. Propolis has been more well-known in recent years as a possible health food in several countries, such as the US, Japan, and the EU, where it has been prioritized as a food to enhance health and avoid diseases such as diabetes, cancer, cardiac disease, and inflammation. Researchers have been interested in propolis as a natural resource because of its many biological qualities, including antibacterial, anticancerous, antiviral and anti-inflammatory (Salleh et al., 2021).

Table 2: Different types of propolis, plant sources and bioactive components

Type	Origin	Source	Bioactive phytochemicals	Reference
Poplar	Subtropical Asia, Vinland, and Europe	*Populus* spp. of section *Aigeiros*, or *P. nigra* L.	Flavonols, flavanones, cinnamic acids and esters	(Bankova et al., 2005)
Birch propolis	Russia	*Betula verrucosa Ehrh.*	Flavonols and Flavanones	(Bankova et al., 2005)
Green propolis	Brazil	Specie of *Baccharis*, *B. dracunculifolia DC.*	Prenylated p-coumarics, diterpenes	(Weinstein et al., 2005)
Red propolis	Venezuela, Cuba	Specie of *Clusia*	Polyprenylated benzophenols	(Lopez et al., 2015)
Pacific propolis	Okinawa, Taiwan	Unknown	C-prenylflavanols	(Chen et al., 2003)
Canarian propolis	Canary Islands	Unknown	Furofuran lignins	(Graikou et al., 2016)

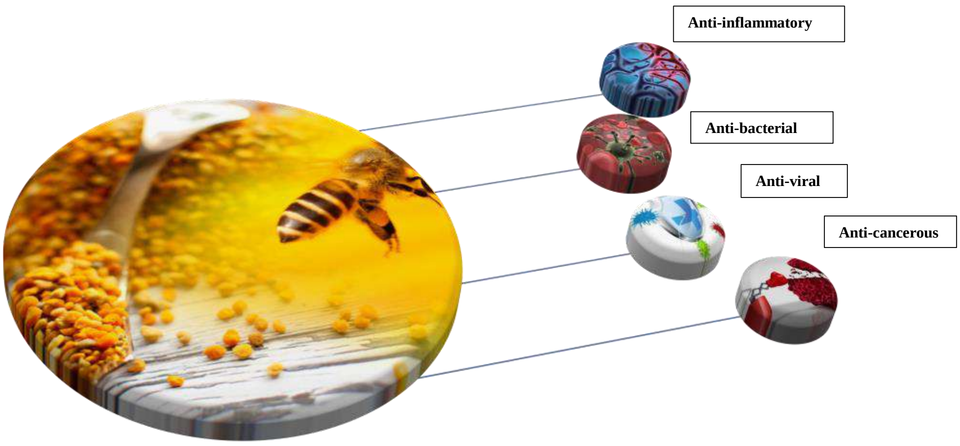

Fig. 3: Medicinal prospects of bee propolis

Abundance of Bioactive Components in Propolis Extract using Various Solvents

It's interesting to note that, despite variations in propolis concentration due to extraction methods, the biological activity of various extracts appears to be similar. Galeotti et al., (2018) showed that propolis, whether derived from the same raw material and dissolved in different solvents and liquids or solids, has a similar chemical composition, with variations in total polyphenols but equivalent antioxidant potency. Mašek et al., (2018) documented how the extraction process and solvent ratio affect the extract chemical profile. Maceration manifests the greatest amount of aromates while extraction by microwave-assisted technique resulted in extraction of surplus flavonoids. However, differences not proportionately impact on antimicrobial effectuality.

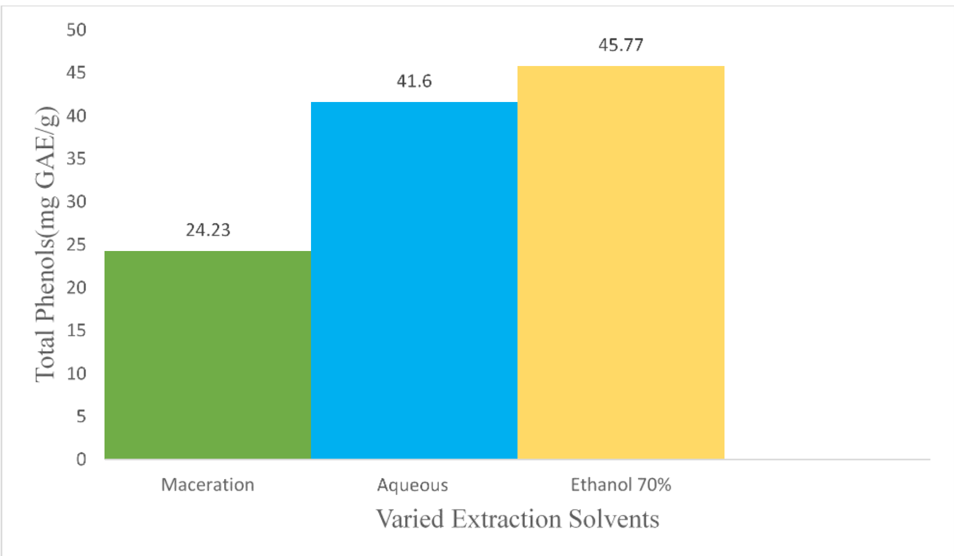

Fig. 4: Comparative abundance of Total phenolic contents in propolis using variable solvents

Prevalent Neurological Diseases

In 2006, neurological illnesses arose as a public health concern, highlighted by the World Health Organization, and it led to 63% of all disability-adjusted life-years (DALYs). This makes neurological illnesses a cause of temporary or permanent disability among the survivors and a leading cause of early death (WHO, 2021). Over 600 neurological disorders affecting the brain, spinal cord, or nerves have been identified, varying widely in seriousness from little headaches to severe and potentially deadly conditions like amyotrophic lateral sclerosis (ALS) or primary brain tumors (Victor et al., 2001). Age also affects the influence of risk factors, clinical presentation, and the natural course of neurological illnesses, most of which have a steeply rising prevalence as people age (Dumurgier et al., 2020). Followings are prevalent neurological diseases discussed by Deuschl et al., (2020)

1. Dementia among older individuals
2. Parkinson's disease and its associated conditions
3. Cerebrovascular accidents (strokes)
4. Seizure disorders (epilepsy)
5. Multiple sclerosis (MS)
6. Degenerative diseases affecting motor neurons
7. Cancers of the brain and nervous system
8. Inflammation of the membranes surrounding the brain and spinal cord (meningitis)
9. Recurrent severe headaches (migraines)

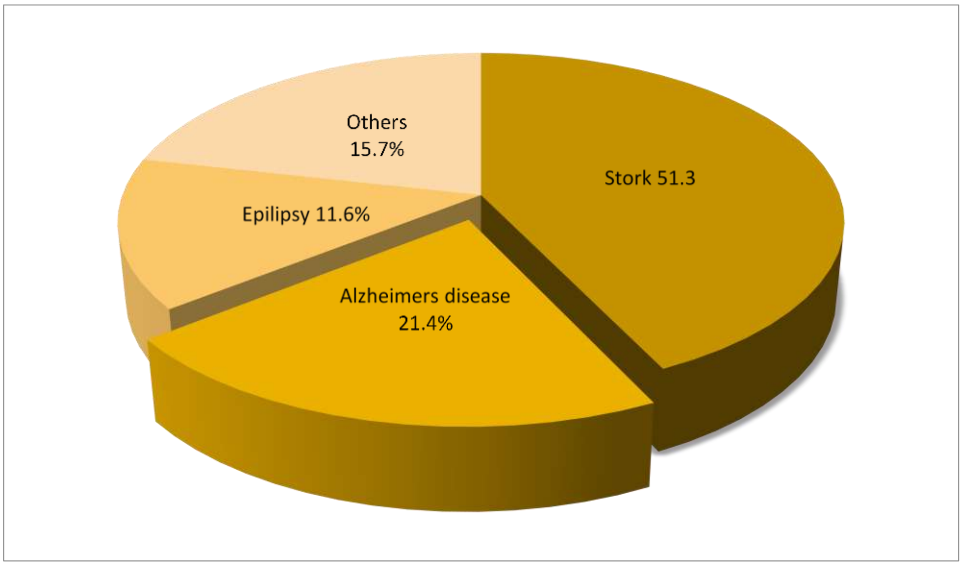

Fig. 5: Percentage abundance of neurological disorders globally

The Potential of Propolis in Treating Neural Diseases

Propolis, an organic substance of honeybees, due to its rich blend of compounds is renowned in traditional medicine. Pinocembrin and caffeic acid phenethyl ester (CAPE) are particularly notable for their diverse benefits across various bodily functions, among its many chemical components. Additionally, multiple studies have indicated that pinocembrin and CAPE, two constituents of propolis, show promise as beneficial treatments for central nervous system disorders (Menezes et al., 2021). Numerous organic compounds, including genisteins, naringins, pinocembrins, coumarics, artepillins C, caffeic acids, phenethyls ester, apigenins, chrysins, galangins, kaempferols, luteolins, genisteins, naringins, pinocembrins, and quercetins, are among the numerous biologically active components of propolis, which offer a wide range of bio-physiological and therapeucity, including antidiabetic, anti-inflammatory, antioxidant, and anticancer, as well as rheumatoid arthritis, chronic obstructive pulmonary disorder, CVDs, respiratory diseases, gastrointestinal disorders, and neuroprotective, immunomodulatory, and immuno-inflammatory effectvness (Zullkiflee et al., 2022).

Neurological Disturbance

Neurodegenerative diseases, neurological illnesses, and cognitive decline are significantly linked with oxidative stress and neuroinflammation. By decreasing the generation of reactive oxygen species (ROS) and reducing the expression of inflammatory agents and increasing the expression of antioxidants and neuroprotective molecules, propolis has promising benefits in controlling these processes. The dual action of it is what provides propolis the medicinal promise in these circumstances (Ni et al., 2017).

Ischemic Brain Injury

Stroke is a leading cause of disability and death worldwide. The potential neuroprotective properties of Iranian brown propolis (IBP) were investigated in a mouse model where there was a permanent blockage of the middle cerebral artery. The results suggested that IBP's neuroprotective effects during focal cerebral ischemia could potentially reduce the damage caused by ischemic brain injury (Bazmandegan et al., 2020).

Neuroinflammation

Neuroinflammation is a significant factor that results in the development of autism and is often characterized by abnormal cytokine levels in the brains of individuals having the condition. Maintaining a healthy gut flora through a diet rich in prebiotics can indirectly help regulate neuroinflammation. In a mouse model of autism, both propolis and bee pollen have been found to prevent neuroinflammation. Research focused on determining the neuro-inflammatory effects of propionic acid (PPA), a substance associated with autism. These findings indicate that supplementation with bee pollen and propolis improved dysbiosis in hamsters, leading to lower levels of endotoxemia and reduced inflammatory responses (Aabed et al., 2019).

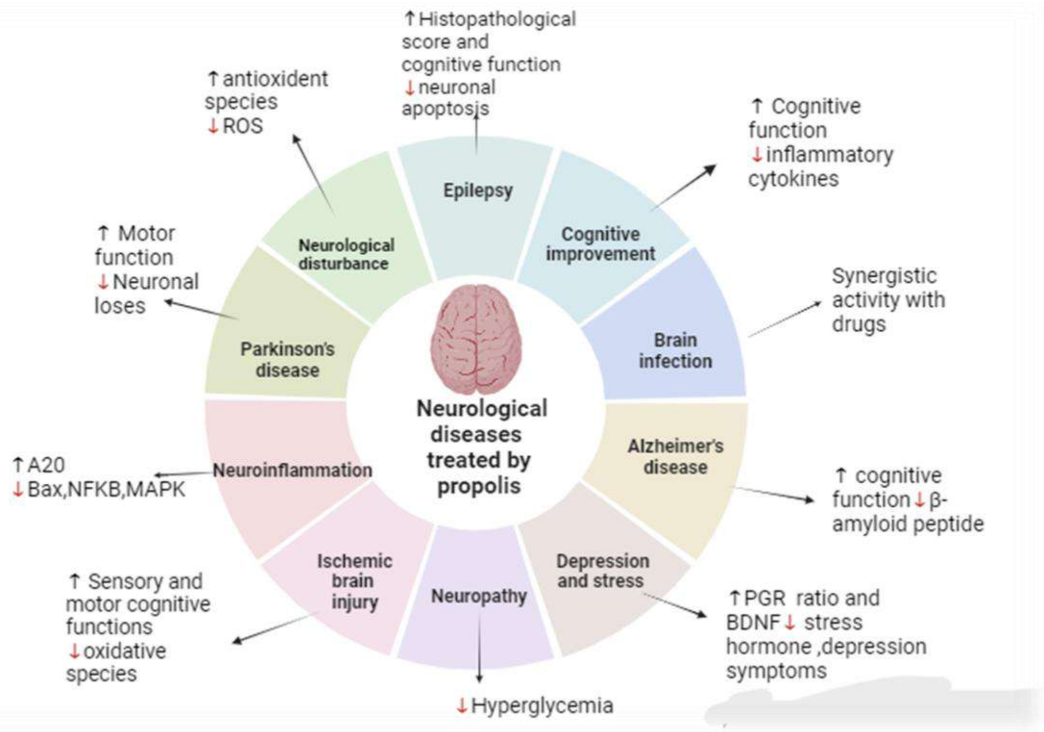

Fig. 6: Neurological Disorders treated using propolis

Neuropathy

Neuropathy being the most common complication of diabetes, signals a serious condition that requires immediate treatment. It is projected that by 2050, one-third of the 9.7 billion global population will have diabetes, with half of them likely developing neuropathy unless effective interventions are implemented (Boyle et al., 2010). Propolis and quercetin have potential effects on the body by reducing hyperglycemia and also offer combined benefits for diabetic neuropathy and potentially provide optimal morphological protection and neuroprotective advantages. These substances could serve as important adjuncts in regenerative medicine.

Their anti-inflammatory, antioxidant, and neuroprotective properties make them valuable natural remedies for alleviating the neurological impacts of diabetes. The combination of these two agents is expected to yield the most favorable morphological healing, positively influencing nerve function. As hyperglycemia is the primary source of pathogenicity, these supplements may serve as essential alternatives in regenerative medicine by aiding in glucose regulation and preventing chronic complications associated with the damage process, particularly in terms of blood sugar control (Türedi et al., 2024).

Depression

The effectiveness of Propolis in treating depression has not been extensively researched. A 2013 study utilizing Korean propolis investigated its antidepressant effects. The results of this study suggested that the antidepressant benefits were associated with restoring balance to the HPA axis by activating the glucocorticoid receptors (GR) and the CREB downstream routes (Lee et al*.,* 2013).

Parkinson's Disease

Millions of patients and their families face a threat to their quality of life due to Parkinson's disease. Studies suggest that royal jelly (RJ) and propolis hold the potential to enhance health by impeding the progression of debilitating age-related conditions. Based on previous animal research, whole propolis, PB, CAPE, whole RJ, chrysins, and its lipid derivative (HPO-DAEE) may counteract neuroinflammation, oxidative stress, and mitochondrial dysfunction. This action could potentially reduce damage to the neurons and improve motor symptoms associated with Parkinson's disease (Ali et al., 2020).

Table 3: Different propolis extraction techniques and the relevant losses and benefits

Technique name	Explanation	Losses	Benefits	Reference
Maceration	Traditionally, extraction solvents (ES) made of different EtOH and water mixes are used to extract crude propolis. Propolis tincture is often made by using twenty-five to sixty percent aqueous Ethanol as the ES at ambient temperature. Such an easy extraction maceration is the name of the process. It is carried out by adding aqueous ethanol to the unprocessed propolis pieces at a weight-to-volume (ES) ratio of 1:3–20. Typically, this combination is allowed to stand at room temperature for seven to thirty days in a closed vessel.	• Takes longer time for extraction • EtOH-relatively aggressive solvent • Products containing alcohol are not appropriate for young children, expectant mothers, or certain patients	• Performed at room temperature • Still used as cheap and simple extraction method • Utilization of this technique is dependent on a number of factors, including the sample's origin, its duration, and the liquid that is immersed.	(Suran et al., 2021) (Yıldırım, 2022)
Ultrasonically assisted extraction technique	The ideal parameters for extracting propolis' phenolic content using ultrasonically assisted technology are eighty percent ethanol and sixty-five-degree Celsius for twenty-five minutes.	• Low sensitivity	• The solid sample and solvent have a larger surface area of contact when the solvent diffuses more readily into the matrix of sample due to the mechanical action of ultrasonic waves • Requires less time as compared to maceration • Propolis extraction by using ultrasonically-assisted technique contains more phenolic content and more antioxidant activity.	(Bankova et al., 2021) (Yuan et al., 2019)
Soxhlet Apparatus	Many research groups have discovered that the highest yield and the highest levels of total flavonoids and phenolics were obtained from a 4 to 6-hour Soxhlet extraction using 100% ethanol at sixty-degree Celsius with 5:150 w/v increasing ethanol concentration leads to more extraction yield.	• Impact of potentially poisonous emissions during the extraction process • The use of flammable liquid organic solvents • The process is more expensive since the solvents used in the extraction must be extremely pure. • The potential for thermal breakdown of extracts is increased by high temperatures and extended extraction times	The primary benefits of the Soxhlet over maceration are: • Less amount of solvent • Solvent recycling • Shorter extraction times.	(Bryda et al., 2021) (Yusof et al., 2020)
Microwave extraction	For the first time, the microwave-assisted extraction (MAE) method was refined to extract polyphenols from raw or unprocessed propolis. Based on the response surface experimental design methodology, the optimal overall response was achieved at one hundred and six degrees Celsius for the extraction temperature, a solvent composition of about 80:20 (v/v), and a fifteen-minute extraction duration.	• The percentage of recovered active components decreased somewhat after microwave irradiation, most likely as a result of degradation processes.	• The extraction yield is increased • The extraction duration is shortened by the microwave-assisted extraction method • When it comes to extracting flavonoids from propolis, MAE exhibits a higher degree of selectivity	(Juodeikaitė et al., 2022) (Pellati et al., 2013)

Alzheimer's Disease

It is anticipated that Brazilian green propolis derived from *Baccharis dracunculifolia* may possess cognitive-enhancing properties. This type of propolis was shown to alleviate the memory and learning impairments induced by Aβ. Detailed analysis of gene expression indicated that Brazilian green propolis treatment suppressed brain inflammation and immune responses by targeting immune cells like astrocytes and microglia. These results propose that Brazilian green propolis could be a beneficial element in averting Alzheimer's disease (AD)-related dementia. Additionally, it exerts an anti-Alzheimer's impact by reducing inflammation in glial cells and immune responses (Ito et al., 2023).

Which Extraction Technique is more Effective and Acceptable?

Ultrasonically assisted extraction (UAE) technique was discovered to be the most accelerated extraction process having reduced energy usage, and improved phytochemical recovery from annatto seeds. Owing to the mechanical action of ultrasonic waves, the sample matrix of plant and solvent molecules have improved surface contact. Thus, accelerated release of phytochemicals was observed by using ultrasound, alteration, and disruption of the physical and chemical properties of plant materials, and strengthening of the solvent's mass migration into plant cells occurs. A study found that the UAE approach yields more in less time-thirty minutes as compared to that of the maceration method, which produced lesser yields in about one hundred and twenty minutes. Moreover, the UAE method is a faster process and requires comparatively less solvent. So, UAE is a preferable extraction technique (Bitwell et al., 2023).

How to Get Propolis Essential Oil?

By using hydrodistillation for four hours in a Clevenger-style apparatus, the crude propolis, the essential oils from the dry residue (EODR), moist residue (EOMR), and crude propolis (EOP) were recovered. For distillation, the samples were diluted five times in distilled water. To determine the extraction yield, the volume of the essential oils was measured. Before being used, the samples were kept in amber flasks at four-degree Celsius (Ikeda et al., 2021).

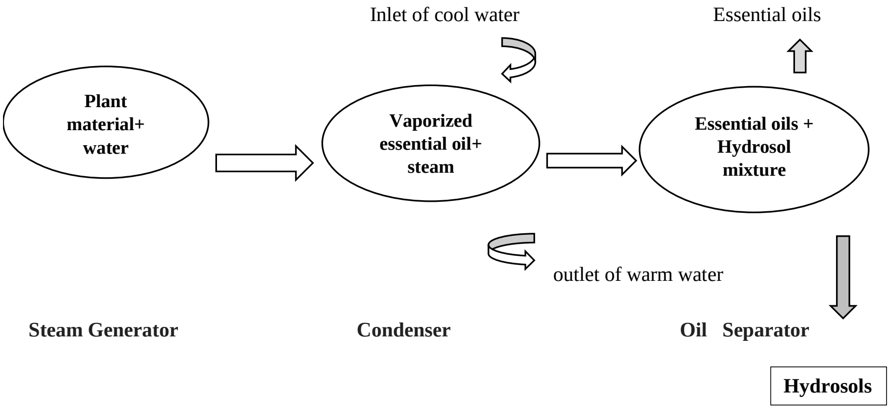

Fig. 7: Schematic diagram for essential oil extraction

Composition of different Groups of Compounds in Propolis Essential Oil

Investigations were conducted into the chemical makeup and in vitro antioxidant activity of propolis essential oil (EOP), which was gathered from 25 different places throughout China. The extraction of EOP was carried out by steam-distillation extraction, and its chemical makeup was determined by utilizing GC/MS. Additionally, the antioxidant activity of EOP was evaluated. According to the findings, 406 compounds were discovered in EOP. Cedrols, γ-eudesmol, benzyl alcohols, phenethyl alcohol, 2-methoxy-4-vinylphenols, 3,4-dimethoxy styrenes, and guaiols were discovered to be the primary components of Chinese EOP. A linkage between EOP and color was also discovered, and principal component analysis indicated a strong relationship between EOP compositions and their sources (Chi et al., 2020).

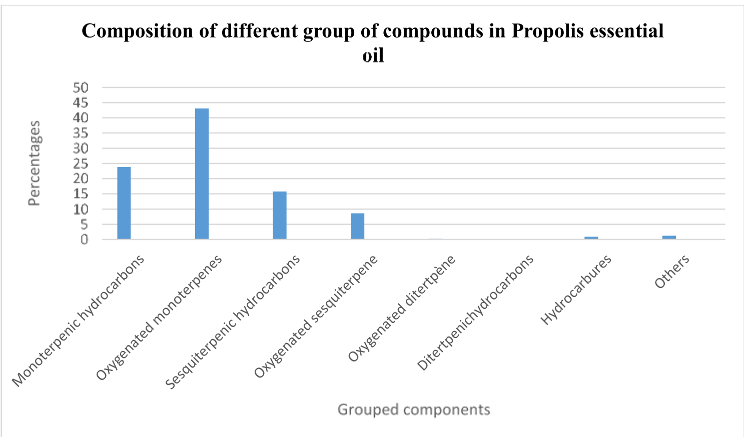

Fig. 8: Composition of different group of compounds in Propolis essential oil

Conclusion

Propolis is a resinous bee product and has been used for its medicinal properties for centuries. It is significantly efficient in treating various ailments including neurological disorders. Propolis is a complex substance and its chemical composition depends on the plant's origin and source. Despite these variations, the health benefits include antioxidant, antimicrobial, and anti-inflammatory attributes. These properties make it a promising candidate for treating various neurological ailments like Parkinson's disease, stroke, and Alzheimer's disease. Moreover, investigations are required to fully understand the effectiveness of propolis for treating neurological disorders. Propolis has beneficial use in the near future unfolding efficient therapeutic effects against neurological disorders and other ailments.

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Chapter 28

Traditional Chinese Medicine for the Treatment of Sepsis

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ABSTRACT

This chapter provides a detailed overview of sepsis, which is a severe systemic inflammatory response to an infection causing significant tissue injury and organ failure as well as high mortality rates. It starts with outlining what sepsis is, why it is relevant in clinical practice, and explaining how sepsis and septic shock occur through an extensive process involving systemic inflammation, endothelial dysfunction, immune response suppression, impaired mitochondria function, and multiple organ dysfunction. The chapter also discusses the variety of symptoms of sepsis which do not make it easy to diagnose in the early stage and can progress to septic shock. Based on this groundwork, the chapter brings TCM perceptions into discussion thus defining sepsis as a syndrome that affects the balance within the body including Qi, blood, and the Yin-Yang balance. In TCM, sepsis is not considered as a single disease but rather as a manifestation of toxic heat or pathogenic factors that interfere with the normal functioning of the body. Diagnosis from the TCM perspectives such as Heat Toxin Invasion and Qi and Yin Deficiency are discussed in the following sections as well as treatment approaches that include herbal medicine prescriptions, acupuncture, and supplementary treatments. Some of the TCM compounds and their active monomers are discussed in detail with reference to their activities such as anti-inflammatory, immunomodulatory, and organ pro-tection. The curative effects of various Chinese medicine compounds, Xuebijing Injection, Shenfu Injection, Shengmai Injection, and Huanglian Jiedu Decoction are discussed in the management of sepsis. The chapter also examines the interaction of TCM with Western medicine, focusing on the ability of herbs to boost the effectiveness of antibiotics and on the potential of acupuncture in promoting immune system stability and organ repair. Lastly, the chapter reviews what is currently known about the involvement of TCM in sepsis treatment while stressing a global approach that uses both scientific and traditional medicine. Seeking to enhance patient survival, this multifaceted concept is designed to provide a higher level of familiarity with sepsis and its implementation in clinical practice.

KEYWORDS		
Sepsis, Risk factors, Cardiovascular Diseases, Conventional Methods, Chinese Medicine	Received: 01-Jun-2024 Revised: 04-Jul-2024 Accepted: 09-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Traditional Chinese medicine (TCM) has been used extensively in Eastern countries for the treatment of infectious disorders for more than 2,000 years (Han et al., 2024). Numerous TCM preparations have been shown to improve organ dysfunction brought on by sepsis by lowering oxidative stress, suppressing the inflammatory response, enhancing immunity, and preserving cellular homeostasis, according to both anecdotal and scientific data. Sepsis treatment is an area in which traditional Chinese medicine (TCM) has amassed a great deal of experience. The ingredients in traditional Chinese herbal medicine have the ability to eliminate heat and toxins, kill bacteria, control immunity, and aid in the restoration of the neuroendocrine system (Song et al., 2023).

Sepsis is characterized by the host's out-of-control and abnormal response to infection presenting with acute organ dysfunction and in serious cases, death. Although modern science has made great strides in the discovery of new techniques for treating various diseases, sepsis is still a pressing issue in today's world and has high rates of mortality and morbidity (Wayland et al., 2024). Traditional interventions mainly focus on the administration of antibiotics, fluids, and supportive measures in the respective organs. However, the complexity of the sepsis pathophysiology and the increasing prevalence of antibiotic-resistant bacteria raised questions about consolidation of strategies and the identification of other adjunctive therapies that can resolve the issue (Chiscano-Camón et al., 2024).

A schematic view of the Treatments in Traditional Chinese Medicine (TCM) in understanding and studying the TCM way of treating diseases has been popular for thousands of years and has a distinct approach to individual methods of treating several diseases such as infective and inflammatory diseases. TCM involves many approaches such as herbal remedies, point stimulation by needles, Moxibustion, and Qi Gong. These all are based on the harmonizing of body energies and the promotion of body self-healing mechanisms (Zhao et al., 2019).

Over the last several decades, there has been increasing focus and research on the use of TCM approaches to manage sepsis. There has been research done on the effects of certain herbs and acupuncture strategies that have proved to affect immune system reactions, inflammation levels, and organ functionality in septic patients. Some TCM treatments appear to be effective when tested in experiments and clinical trials and thus may be helpful when used in combination with conventional medical therapy.

Thus, this chapter discusses traditional Chinese medicine, both from the historical point of view and according to the achievements of modern science regarding sepsis treatment. In this chapter, we sought to briefly review the core TCM concepts applied to sepsis care, review various herbal formulas used in clinical care, and summarize current studies evaluating their efficacy and mechanisms. This chapter discusses the application of TCM approaches in combating sepsis with the intention of helping working professionals in the healthcare setting and researchers to enhance the care and outcomes by embracing the unexplored complementary therapy, where necessary while molding sepsis management in a comprehensive healthcare framework.

Understanding Sepsis and its Clinical Significance

A complicated illness known as sepsis is linked to severe organ dysfunction and a high mortality rate. It arises from a dysregulated host response to an infection. Understanding the symptoms that are present is crucial because this illness requires immediate treatment. Sepsis is a disorder that is highly prevalent and continues to be one of the primary causes of death worldwide. Sepsis diagnosis and treatment have been made faster in the last 30 years because of a significant body of research and enhanced clinical procedures. To further improve this procedure, a new definition was created in 2016 that placed more emphasis on identifying organ dysfunction in the setting of infection (Levy et al., 2012). In 2017, the World Health Assembly and WHO issued a resolution to enhance sepsis prevention, detection, and management, making sepsis a global health priority (Reinhart et al., 2017).

The prognoses of sepsis syndromes vary throughout the clinical scale. The most serious sepsis consequence, septic shock, has a significant fatality rate. The immune system's pro- and anti-inflammatory branches activate in response to an inciting agent. Monocytes, macrophages, and neutrophils are also activated. These cells interact with the endothelium via pathogen recognition receptors to produce cytokines, proteases, kinins, reactive oxygen species, and nitric oxide. The endothelium, which is the main location of this reaction, sustains microvascular damage as well as triggers the complement and coagulation cascades, which worsen vascular damage and cause capillary leak (Nguyen et al., 2006). The clinical manifestations of sepsis and the transition from sepsis to septic shock are caused by this series of events. The degree of morbidity and/or mortality that the patient experiences ultimately depends on the capacity to balance pro-inflammatory responses to eliminate the invasive microorganism with anti-inflammatory signals established to manage the overall inflammatory cascade. Sepsis-related mortality has been greatly and favorably impacted by the prudent and timely administration of antibiotics, the use of sepsis care bundles, and the use of early goal-directed therapy. The most effective therapeutic method for managing and treating sepsis, meanwhile, is still early detection.

Etiology of Sepsis

According to the EPIC II study, defined in 2009 among the European ICUs, gram-negative bacteria were implicated in sepsis syndrome with higher frequency than other pathogens, 62%, while gram-positive bacteria were found in 47% of the cases. The relative frequency of the latter may be attributed to higher overall performance indices of invasive procedures and nosocomial-associated infections as noted by (Mayr et al., 2010). The most prevalent bacteria in patients are Staphylococcus to about 20%, Pseudomonas about 20%, Escherichia about 16% (Vincent et al., 2009) Infection is most commonly seen in the respiratory (42%), bloodstream (21%), and genitourinary tract (10%)(Mayr et al., 2010) . These data need to be discussed in the context of the knowledge about the fact that over a third of patients never switch cultures.

Site of infection and bacterial strain were also shown to influence the mortality rate in a gargantuan record review study described by (Cohen et al., 2004). Here overall with gram-negative infections, reported increases in overall mortality in the respective populations were recorded. Yet, the gram-positive bacteremia with Acinetobacter or pneumonia with Staphylococcus had a mortality rate of 40% and the highest mortality rate of 70% was by Pseudomonal pneumonia. The attended sepsis syndromes acquired in the hospital include MDR bacterial pathogen infections contributing up to 25%; MRSA and VRE infections; viruses and parasite conditions; and other sepsis-causing cases detected between 2- 4%(Annane et al., 2003).

Risk Factors

Risk factors that predispose to sepsis include

- Kidney failure or liver failure
- Trauma
- Hemodialysis
- Indwelling catheters
- Prolonged hospitalization
- Extremes of age
- Indwelling catheters
- Malignancy
- Use of corticosteroids
- Immunosuppressed state
- Burns
- Malignancy

Kidney failure or liver failure
- Major surgery
- Diabetes

Epidemiology of Sepsis

It was established that the rate of this disabling condition is increasing by approximately 9% every year (Martin et al., 2003). Sepsis and severe sepsis have increased over the last decade from 600,000 to more than 1,000,000 hospitalizations per year from 2000 through 2008 (Elixhauser et al., 2006). Alongside this has gone an increased index of healthcare costs, thereby making sepsis the costliest healthcare-related affliction in 2009, constituting 5% of overall hospital costs in the United States (Torio and Andrews, 2006). It has therefore been on a decline with increasing mortality among sepsis patients, and improvement in the management of this condition through the Surviving Sepsis Campaign. The primary data was acquired by the Nationwide Inpatient Sample in the United States for the years 2009 to 2012; it was indicated that overall mortality has reduced from 16.5% to 13. A total of 8% are reported to have JIA; findings that are in concord with other researchers namely (Elfeky et al., 2017).

Nevertheless, severe sepsis continues to be one of the major causes of death in a hospital (Angus et al., 2001). Moreover, for severe sepsis, the mortality is between 15–25% and for septic shock, 40–50% of the patients will die from the associated complication. However, this mortality rate of sepsis syndromes lies in between thirty to fifty percent. Depending on age, color, sex, presence of co-morbid illnesses as well as organ dysfunction (Liu et al., 2014). For instance, the mortality among in-patients was best explained by simple severity scores, organ failure, and degree of organ injury, with risks from respiratory, cardiovascular, hepatic, and neurologic failure being high (Elfeky et al., 2017).

Clinical Manifestations of Sepsis

Sepsis has a rather infinite list of symptoms that can be subjected to changes in accordance with the primary site of infection, age, or presence of chronic diseases. The presenting symptoms are fever, chills, tachycardia, tachypnea, and altered mental status. Such symptoms are inherent to the body's general inflammatory response to the infection. Symptomatic progression of sepsis is characterized by worsening of clinical signs and some complications such as hypotension with or without septic shock, oliguria or anuria attributable to acute renal failure, respiratory distress which may culminate into ARDS, and coagulopathy like DIC. Hypotension that does not respond to fluid overload due to sepsis termed septic shock has a mortality ranging between 40-60 %. It is a clinical condition that exists in a certain range of pathophysiologic processes, ranging from SIRS through the use of MODS before death.

The earliest signs of inflammation are heralded by the following (Giustozzi et al., 2021):

- Fever, which is a temperature more than 38C, or hypothermia – a temperature less than 36C.
- Tachycardia, meaning, a heart rate of more than 90 beats per minute.
- Tachypnea as defined by a respiratory rate greater than 20 breaths per minute.
- Leukocytosis (WBC greater than 12000 cu mm) / leukopenia (WBC less than 4000 cu mm) with or without bandemia (more than 10%).

Any four out of the following clinical signs are used in determining SIRS and the presence of at least two out of the four is enough. Following that, SIRS with infectious sources are adequate to meet the clinical criteria for sepsis (Bone et al., 1992).

Pathophysiology of Sepsis

In hypotension also, tissue demand is not met by tissue oxygenation, and the patient is now defined to be having severe sepsis. As flap circulation and oxygenation to peripheral tissues are reduced, there will be cellular and metabolic implications that involve change of metabolic reactions to anaerobic ones in which lactic acid is formed. This may be related to other symptoms of tissue hypoperfusion like pre-renal renal azotemia or transaminitis.

In the second stage of sepsis, hypotension that was due to sepsis may not improve when fluid loading is applied to the patient; this is described as septic shock. Regarding the classification, it is necessary to mention that septic shock is a distributive type of shock. Since bacterian endotoxins stimulate the action of inflammatory mediators (histamine, serotonin, super-radicals, lysosomal enzymes) the capillary permeability is increased most intensively at the same time as the peripheral vascualr resistance is diminished. This results not only in a reduction of after-load but also it leads to pre-load reduction as a result of the third spacing of fluids. The consequent decrease in stroke is first balanced by an increase in heart rate, that is, compensated septic shock. As a result, the patient has a hyper-dynamic circulation which belongs to septic shock.

In clinical examination, the precordium is active with tachycardia and strong peripheral pulsation. Their body temperature is elevated, and their flash cap refill is decreased. This is described as warm shock, and it has been reported that up to 90% of patients with penetrating cardiac injuries die before reaching the hospital. With the advancement of shock, high levels of catecholamine result in an increase in peripheral vascular resistance as the body tries to divert the blood away from the non-crucial organs such as the GI tract, kidneys, muscles, and skin to the vital organs, especially the brain and the heart. This is described as cold shock. Thus, it is important to understand the etiology and progression of septic shock, to provide the right measures to manage this condition (Arina and Singer, 2021).

Pathological Mechanism Underlying Sepsis and Septic Shock

Sepsis is a pathophysiological process that occurs through multiple immune, inflammation, coagulation, and metabolism pathways. The pathophysiology process includes a series of events following the body's attempt to respond to infection through inflammation, coagulation, and oxidative stress, which result in tissue impairment and organ failure.

Infection and Immune Response

The development of sepsis involves initial contamination with pathogens, which may be bacterial occasionally viral, or fungal. These pathogens are acknowledged by the innate immune system through pattern recognition receptors (PRRs) including Toll-like receptors (TLRs) which detect pathogen-associated molecular patterns (PAMPs). The activation of these receptors tends to induce the immune response soon; it is accompanied by the production of pro-inflammatory cytokines like the tumor necrosis factor-alpha (TNF-α), interleukins (IL-1, IL-6), and interferon-gamma (IFN-γ). This response is critical for containing the infection, however, in sepsis, it is overactivated and uncontrolled (Marques et al., 2023).

Sepsis and Cytokine Release Syndrome

The release of cytokines is related to a state of systemic inflammatory response syndrome (SIRS), which leads to endothelial dysfunction, increased permeability of blood vessels, and edema of the tissues. This is commonly known as a cytokine storm and leads to severe systemic inflammatory response which can affect nutrient supply in organs and can be the cause of MODS. The uncontrolled inflammation also causes the activation of the coagulation and the complement systems, which makes the clinical course of sepsis even worse (Daniel et al., 2022).

Endothelial Dysfunction and Coagulopathy

Endothelial damage is regarded as another factor that plays a key role in sepsis pathophysiology. Endothelium, comprised of cells that line the interior surface of blood vessels, has a significant responsibility in the preservation of vascular stability and balance. Conditions that exist in sepsis, include activation and injury of endothelial cells by pro-inflammatory cytokines, which results in the expression of adhesion molecules, increased leukocyte adhesion to the endothelium, and increased permeability of the vasculature. This leads to the filtration of fluids into the interstitial space and the development of edema and hypoperfusion. Also, initiation of the coagulation process may result in microvascular thrombosis and thereby promote organ ischemia. Sepsis is associated with a condition referred to as disseminated intravascular coagulation which is caused by the formation of clots in various parts of the blood vessels and may lead to bleeding because of the utilization of clotting components (Walborn et al., 2019).

Immunodepression and Complicated Infections

After the first phase of the hyper-inflammatory response, septic patients develop immune paralysis which includes apoptosis of immune cells, reduced Major Histocompatibility Complex (MHC) expression, and increased levels of anti-inflammatory cytokines like IL-10. This immunosuppressive phase makes the patients prone to developing secondary infections by opportunist pathogens and could further compromise the resolution of the primary infection. It is important to strike a balance between pro-inflammatory and anti-inflammatory reactions, as the former may result in chronic inflammation and unfavorable outcomes (Pei et al., 2022).

Impaired Mitochondrial Function and Energy Metabolism

Sepsis has been shown to cause severe impairment in organ function and a key factor traditionally described in this process is mitochondrial dysfunction. The issue of elevated ROS and NO during sepsis impairs mitochondrial metabolic coupling to oxidative phosphorylation and causes cellular energy depletion. This metabolic derangement leads to the development of organ failure especially in tissues with high energy demand such as the heart, kidneys, and the brain. Furthermore, it is well established that sepsis causes metabolic derangement such as hyperglycemia and lactate accumulation, which not only worsens tissue injury but also impairs tissue function.

Multi-organ Dysfunction and Failure

These pathophysiological processes culminate in multi-organ dysfunction syndrome (MODS), a condition in which more than one organ system derails, frequently in concert with each other. Lungs are often the target organ of infection and injury, and acute respiratory distress syndrome (ARDS) remains a prevalent and formidable complication. The kidneys, liver, heart, and CNS are also targets and an individual suffering from this disease can develop AKI, hepatic dysfunction, myocardial depression, and septic encephalopathy. MODS is related to a high mortality rate and having MODS is an essential clinical predictor of severe sepsis and a poor prognosis (Srdić et al., 2024).

Treatment of Sepsis and Septic Shock

The assessment of sepsis also remains an important clinical problem even though significant progress has been made in anti-infective therapy and advanced life support. Due to high medical costs and potential complications, including renal insufficiency and cognitive dysfunction, sepsis is a public health concern on the international level (Singer et al., 2016). Furthermore, it has been established that approximately thirty-eight percent of sepsis survivors have post-intensive care syndrome with complaints of physical and cognitive dysfunction as well as impaired organ function. Progression of the existing chronic diseases, original damage, and immune dysfunction explains the worsening health state after sepsis. Since intense and unmodulated inflammation is considered to be the primary factor that triggers the development of sepsis and multiple organ failure, new anti-inflammatory agents are actively sought for treating sepsis. However, clinical trials that tried to modulate cytokine responses, including TNF-α antagonists and TLR4/MD2 antagonists, did not bring about a reduction in the mortality of septic. Given the lack of effective pharmacological management strategies for sepsis and related organ dysfunction, CAM and supplemental therapies are explored to identify novel therapeutic strategies for the treatment of sepsis (Opal et al., 2013).

Complementing conventional treatment, TCM is being widely accepted globally in the management of diseases due to its effectiveness and low side effects. For instance, a systematic review with meta-analyses published in the last 2 years showed the effectiveness of TCM in improving immunity and reducing fever and other symptoms of COVID-19 (Kang et al., 2022). Indeed, TCM provides a number of advantages in the treatment of inflammatory diseases like sepsis, which is qualified as a fever disease of exogenous origin' in TCM. As to TCM theory, the fundamental concepts of septic treatment are eliminating heat and detoxifying, removing heat from the internal organs, activating blood circulation, eliminating blood stasis, and reinforcing, and protecting the body to consolidate detoxification. Numerous publications, including clinical trials, demonstrate that TCM acts through anti-inflammatory actions, modulating the immune system, and preventing oxidative stress. Strong evidence also proves the possibility of the use of TCM compounds, herbal extracts, and EA in the prevention as well as treatment of heart-, brain-, lung- and intestine-involved diseases. Thus, this review intends to sum up the effects and working of TCM compounds, herbal extracts, and electroacupuncture in sepsis and sepsis-associated multiple organ injury (Kang et al., 2022).

Sepsis from Traditional Chinese Medicine Perspectives

Being an Integrative Medicine practice originating from China, TCM views sepsis as a different model compared to the modern biomedical approach. Sepsis is not recognized by TCM as a single disease but as a deeply complex one expressed in terms of Qi, blood, Yin, and Yang. Sepsis in TCM is understood according to the theories of disease pathogenesis, differentiation of syndromes, and regulation of Qi and blood (Zheng et al., 2021).

TCM Pathophysiology of Sepsis

In TCM, sepsis can be regarded as toxic heat or pathogenic invasion that could penetrate through the body's defensive barrier. The condition is frequently linked with heat, dampness stagnation, and blockage of Qi and blood. One key aspect of TCM is that sepsis is a result of the interaction of internal and external pathogens that create imbalances in the body's various organ systems (Cheng and Yu, 2021).

Heat Toxins

Sepsis is traditionally linked with the concept of heat toxins, referring to the Western medicine definition which features inflammation. It can cause fever, delirium, and worsening of the patient's status in the shortest possible time due to these heat toxins.

Qi Deficiency

In sepsis, it is credited that the body's vital energy, the Qi, is deficient, especially in chronic sepsis or in elderly patients. This deficiency diminishes the ability of the immune system to protect the body against disease and heal itself.

Blood Stasis

Another important concept in sepsis from TCM is the idea of stagnation of the blood or blood stasis. This is similar to the microvascular thrombosis and shutdown in circulation that are seen in sepsis.

Yin and Yang Imbalance

It was postulated that this is due to a sharp disparity between Yin and Yang, with Yin being the 'cooling', 'nourishing' energy and Yang as the 'warming', 'activating energy'. This puts the body in an internal conflict, leading to high fevers, chills, and instability in physiological parameters.

TCM Diagnostic Patterns

In TCM, the diagnosis of sepsis mainly depends upon the differentiation of patterns into eight different categories depending on the nature and intensity of symptoms, pulse, tongue coating as well as the constitution of the patient. The following are common TCM patterns observed in sepsis (Xing et al., 2019):

Heat Toxin Invasion

It is accompanied by high fever, thirst, irritability, delirium, and a loud, hard pulse. This pattern can be affiliated with the initial stage of inflammation in the septic process.

Qi and Yin Deficiency

Some of the signs and symptoms may include fatigue, weak pulse, night sweats, dry mouth, and a low-grade fever. This pattern is typically observed when sepsis progresses or in situations where the patient had sepsis for a longer period of time.

Damp-Heat Accumulation

Some of these manifestations include thick and greasy tongue coating, lethargy or feeling ‘weighed down’, fullness in the stomach region, and icterus or yellowing of the skin. The formation of this pattern indicates that sepsis is accompanied by dampness and heat in the gastrointestinal system.

Blood Stasis with Heat

Expressed by rigid, stabbing, acute, and localized pain, purplish tongue, and dark and clotted menstrual blood in females. This pattern suggests a severe condition where there is stagnant blood flow together with heat, the latter worsening the organ's damage.

TCM Therapeutic Approaches

While effectively treating sepsis, TCM employs principles of herbal medicine and acupuncture together with other interferences whose purpose is to drain pathogenic factors and restore harmony. It is a unique treatment plan that may involve several aspects of the disease depending on the pattern diagnosis of the patient (Wang et al., 2024).

Herbal Medicine

The TCM herbal formulas are intended for eliminating heat and toxicity, strengthening and regulating Qi, and removing blood stasis. Some of the widely utilized herbs are Huang Qin (Scutellaria baicalensis), Jin Yin Hua (Lonicera japonica), and Lian Qiao (Forsythia suspensa) which possess anti-inflammatory and antimicrobial effects (Fu et al., 2024).

Acupuncture

Acupuncture is used to control the circulation of Qi and blood in the body, tonify the defender's Qi, and treat the clinical manifestations. Acupoints are then chosen depending on the patient’s pattern and symptoms; points such as LI4 (Hegu) for fever and inflammation and ST36 (Zusanli) for strengthening the immune system and increasing energy (Xian et al., 2023).

Moxibustion and Cupping

These modalities sometimes are adopted as transformations to eliminate dampness and cold pathogen factors as regarded responsible for disturbing the free circulation of Qi and blood in the body. In most cases, they are used in combination with herbal remedies and acupuncture (Zhang et al., 2024).

Integrating Traditional Chinese Medicine with Conventional Sepsis Management

A series of studies have been conducted to determine ways through which TCM can be incorporated into regular sepsis management. Research has indicated that specific TCM herbs and preparations may boost the efficacy of antimicrobials, suppress inflammation, and modulate immunity. Acupuncture has also been explored for its potential immunomodulatory effects and organ protection in septic individuals (Mousavi et al., 2016).

Herbal Medicine as an Adjunct to Antibiotics

Certain Chinese herbs have been identified to have additive effects when used together with antibiotics, meaning that the amounts of the latter that will be needed would be smaller and this would help to mitigate the chances of bacteria becoming resistant to the antibiotics.

Acupuncture for Immune Modulation

Unlike conventional medicine approaches, acupuncture could offer immunomodulating effects that may decrease high inflammation rates, as well as address dysfunction in affected organs in sepsis cases.

Holistic Patient Care

TCM has a comprehensive view of the patient and does not merely focus on the management of sepsis. Patients may get advice on their diet and lifestyle as well as other counseling that may be needed to assist them in overcoming their various challenges.

Current Research and Evidence-based Application of TCM Compounds for Sepsis Treatment

TCM compounds are prescriptions that combine two or more ingredients to provide synergistic effects that are beneficial to multiple targets. Components of Traditional Chinese Medicine (TCM) herbs interact with one another through the mutual compatibility of diverse chemical compounds, reducing toxicity and negative side effects while boosting therapeutic results (Cheng et al., 2021). Numerous traditional Chinese medicines (TCM) have shown promise in treating organ damage associated with sepsis. These include Xuebijing injection, Shenfu injection, Huanglian Jiedu decoction, Dachengqi decoction, and Xijiao Dihuang decoction. A brief explanation of these compounds and their therapeutic effects for the treatment of sepsis has been shown in the following table (Song et al., 2023):

Therapeutic Effects of Traditional Chinese Medicine Compounds for Treatment of Sepsis

Category of TCM Compound	Name of Compound	Components/Origin	Therapeutic Effects	Mode of Action
TCM Compounds	Xuebijing Injection	Carthami flos, Paeoniae radix rubra, Szechuan lovage rhizome, Angelicae sinensis radix, Salviae miltiorrhizae	Anti-inflammatory improves survival in sepsis models	Inhibits NF-κB and MAPK pathways; reduces inflammatory cytokines. Decreases IL-6, TNF-α improves renal perfusion, survival rate varied.
	Shenfu Injection	Ginsenosides, Aconitine alkaloids	Antioxidant, anti-inflammatory, protects tissue morphology	Inhibits MEK/ERK pathways; regulates apoptosis and immunity. Enhances cellular immunity, improves clinical symptoms in septic patients.
	Shengmai Injection	Panax ginseng, Ophiopogon japonicas, Schisandra chinensis	Enhances myocardial metabolism, immune function	Activates AMPK signaling; improves mitophagy. Improves myocardial function, and prolongs survival in sepsis models
	Huanglian Jiedu Decoction	Rhizoma coptidis, Radix scutellariae, Cortex phellodendri, Fructus gardeniae	Anti-inflammatory regulates lipid homeostasis	This formula addresses both inflammation and lipid metabolism, crucial for managing systemic inflammatory response. Inhibits TLR4/MyD88/NF-κB pathway; neutralizes LPS activity
	Dachengqi Decoction	Rheum palmatum, Magnolia henryi, Citrus aurantium, Natrii sulfas	Anti-inflammatory reduces vascular injury	Dachengqi Decoction targets multiple aspects of inflammation and injury, contributing to improved outcomes in sepsis and related conditions. Inhibits TLR4/NF-κB pathway; regulates PI3K/AKT signaling
TCM Monomers	Tanshinone IIA	Salvia miltiorrhiza	Anti-inflammatory, neuroprotective	Tanshinone IIA provides broad anti-inflammatory effects and neuroprotection, making it useful in treating inflammatory and neurodegenerative conditions. Inhibits NF-κB and MAPK pathways; reduces cytokine production
	Astragaloside IV	Astragalus membranaceus	Anti-inflammatory, neuroprotective	Astragaloside IV supports immune function and protects against organ damage, which is beneficial in conditions involving systemic inflammation. Activates Nrf2; inhibits NF-κB/NLRP3 inflammasome
	Glycyrrhizin	Licorice root (Glycyrrhiza glabra)	Anti-inflammatory, improves survival	Glycyrrhizin modulates critical inflammatory pathways, which helps improve survival and reduce inflammation in sepsis. Inhibits HMGB1 expression and MAPK/NF-κB pathways
	Triptolide	Tripterygium wilfordii Hook. F.	Anti-inflammatory, vascular protection	Triptolide's ability to regulate inflammation and protect vascular function makes it valuable in treating cardiovascular and inflammatory diseases. Inhibits NF-κB and MAPK pathways; reduces cytokine levels

	Artemisinin	Artemisia annua	Anti-inflammatory, immunoregulatory	Artemisinin offers anti-inflammatory and cognitive protective effects, making it useful in managing sepsis-related complications. Activates AMPKα1; inhibits NF-κB pathway
Flavonoids	Apigenin	Fruits, vegetables	Anti-inflammatory, antioxidant	Apigenin's anti-inflammatory and antioxidant properties are important for liver protection and general inflammatory conditions. Inhibits NF-κB translocation; enhances PPARγ
	Salidroside	Rhodiola Rosea	Anti-inflammatory, antioxidative	Salidroside's ability to reduce inflammation and oxidative stress makes it beneficial for protecting various organs from injury. Enhances Sirt1 expression; inhibits NF-κB
	Baicalein	Scutellaria baicalensis	Anti-inflammatory, antioxidative	Baicalein provides neuroprotective and hepatoprotective effects, which are valuable for managing inflammatory and liver conditions.
Phenols	Resveratrol	Grapes, berries	Antioxidant, anti-inflammatory	Resveratrol's dual role as an antioxidant and anti-inflammatory agent supports organ function and reduces oxidative damage. Inhibits NF-κB and MAPK pathways
	Paeonol	Paeonia suffruticosa	Anti-inflammatory protects against AKI	Paeonol helps mitigate kidney injury and inflammation, which is crucial for managing acute kidney injury. Inhibits NF-κB signaling; modulates macrophage phagocytosis
Alkaloids	Berberine	Cortex phellodendri, Rhizoma coptidis	Anti-inflammatory protects intestinal barrier	Berberine's impact on inflammation and barrier protection supports its use in treating conditions involving systemic inflammation.
Acupuncture	General Effects		Pain relief improves circulation, balances energy flow	Acupuncture is widely used for its ability to alleviate pain and support general well-being through the regulation of bodily functions. It Stimulates specific points to regulate bodily functions

Conclusion

This chapter has offered an in-depth analysis of sepsis which is a life-threatening and multifaceted condition involving a host's injurious response to infection leading to organ dysfunction. Sepsis is characterized clinically by fever, tachycardia, tachypnea, confusion and organ dysfunctions, and septic shock in severe cases. The pathophysiologic processes include immunity, inflammation, endothelial dysfunction, coagulation, immunosuppression, and mitochondria dysfunction, leading to the failure of more organs. TCM, on the other hand, presents sepsis in a different context as a toxic heat syndrome or pathogenic invasion with disturbances in Qi, blood, Yin, and Yang. Some common TCM diagnostic patterns include heat toxin invasion, Qi and Yin deficiency, damp-heat accumulation, and blood stasis with heat. TCM treatment aims at rebalancing, cleansing heat, eliminating toxicity, nourishing Qi, and eliminating blood stasis with the help of herbal medicine, acupuncture, moxibustion, cupping, etc. Recent studies have revealed that there is potential for combination therapy of TCM and conventional approaches to manage sepsis, which suggests that TCM herbal preparations may improve the efficacy of antibiotics, suppress inflammation, and boost immunity. Acupuncture has also been investigated for the purpose of regulating the immune system and enhancing the operations of individual organs. This can include not only treatment of the specific conditions that are associated with sepsis, such as cardiovascular disease or acute kidney injury, but also patient-assisted solutions regarding diet, exercise, and mental health. While further research supports these interventions, the combination of TCM with orthodox medicine in the treatment of sepsis could constitute a more holistic approach to the treatment of sepsis, the outcome of which would be better patient prognosis and a possibility of lowering sepsis mortality rate.

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Chapter 29

Evidence-Based Alternative Veterinary Medicine

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ABSTRACT

Evidence-based medicine, or EBM in veterinary practice is the integration of clinical experience and client values with best available scientific information. Alternative veterinary medicine (AVM) encompasses a wide range of non-conventional therapeutic modalities such as Acupuncture, nutritional therapy, homeopathy and herbal medicine to chiropractic care etc. It is obligatory to follow predesigned protocols during the implementation of EBM in AVM. Those pathways in question, that of developing a clinical question; gathering data and critically analyzing the best available evidence to use in practice whilst still considering local context before assessing results. Obstacles to EBM for AVM include the need of individualized treatment strategies, insufficient research and variations in practitioner experience. The future will likely involve both increased coverage of evidence-based-medicine (EBM) principles in practitioner education and further research into AVM modalities, as well as efforts to integrate co-operation between conventional medicine practices with those from the services offered by alternative practitioners.

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KEYWORDS		
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INTRODUCTION

Definition of Evidence-Based Alternative Veterinary Medicine

In the continuously evolving field of veterinary medicine, both animal lovers and professionals are depending upon the complementary and alternative methods to deal with health issues and welfare of animals(McKenzie, 2012). These modern alternative ways provide a better approach in comparison to traditional veterinary care practices (Magalhães-Sant'Ana et al., 2023). They are mostly based in centuries old rituals, customs and holistic beliefs. The crux of evidence based alternative veterinary medicine (EBAVM) is mainly one of these strategies that comes out as a model of deep research and applying the evidence in veterinary and human practice (Bergh et al., 2022).

Basically, EBAVM joins the contemporary scientific research, clinical expertise and conventional knowledge with the sole objective to optimizing animal health outcomes (Simoneit et al., 2011). We portrayed many facets of EBAVM in this introductory investigation, explaining its foundations, techniques, guiding concepts and practical uses (Zhou et al., 2020). The main goal in searching the diverse array of evidence based alternative therapies is to provide prudent insights into the dynamic relationship between innovation and tradition in veterinary practice (Yang et al., 2016).

Before we discuss the direly needed and prevailing alternative therapies in veterinary medicine, it is important to clarify the underlying main ideas of EBAVM. EBAVM places a strong emphasis on the critical evaluation of data analysis from rigorous and thorough scientific research and clinical trials, as opposed to anecdotal or belief-based methods (Weiermayer et al., 2022). This critical analysis of data regarding EBAVM provides a logical and knowledge approach to veterinary health care by acting as the basis for judgements about alternative therapies. By the application of same analysis to alternative therapies as to conventional procedures , EBAVM brings efficacy, transparency and accountability in the field of modern day holistic animal medicine(Johnson et al., 2018).EBAVM connection to integrative thinking, which goes beyond the division between alternative and traditional modalities, is one of its key distinguishing characteristics that makes EBAVM very important in current era for dealing with current animal health and treatment domain(Johnson et al., 2018).

The increasing interest in evidence-based medicine in the field of human health care where its origin actually started. A parallel move movement advancing for a same paradigm shift towards evidence-based medicine practice evolved within the veterinary community as the main principles of evidence-based medicine gained popularity among medical professionals. Veterinary clinicians started looking at the alternative therapies through the prism of evidence-based investigation after realizing the shortcomings of conventional methods and felt the necessity for the more robust scientific foundation to upgrade the veterinary health care (Fox et al., 2018).

With advancing time, chiropractic adjustments, herbal medicine, acupuncture, nutritional supplements and a diverse range of many other alternative treatment therapies and procedures have been included in the multidisciplinary and dynamic area of EBAVM (Cooper et al., 2012). These ways are diverse, but they mainly stick to the principles of ongoing improvement, advancement and empirical confirmation. The search for scientific evidence is restricted to only laboratory and controlled clinical trials in the field of evidence based veterinary treatment. Instead, it encompasses a wide range of evidence sources, such as expert opinions, case studies, customer feedback and observational studies (McCabe et al., 2009). Medical and veterinary health practitioners can develop a thorough grasp of the effectiveness, security, and suitability of alternative therapies in practical contexts by combining different types of data from different sources. With the help of analysis and integrative approach, veterinarians can clearly and confidently unravel the complex world of clinical decision making, enabling them to their patients the exact and best possible care (Holst et al., 2024).

By carefully analyzing the available data, clinical procedures, and moral issues related to complementary and alternative medicine, we hope to promote a better knowledge of this rapidly developing discipline. Veterinarians can leverage the power of alternative modalities to improve patient outcomes and care quality by adopting the concepts of evidence-based inquiry and integrative thinking (Keller et al., 2024).

This chapter will provide a detailed and thorough examination of procedures, tenets and uses of evidence based alternative veterinary medicine, as well as its potential to advance veterinary medicine and welfare in a variety of species and settings (Neal and Greenberg, 2024). By intricately analyzing the available data and moral issues related to complementary and alternative medicine and clinical procedures, we hope to promote a better knowledge of this rapidly emerging discipline. Veterinarians can use the power of the alternative veterinary medicine to improve patient prognosis, outcomes and quality care by adopting the concepts of evidence-based medicine and integrative thinking (Ghimire et al., 2024).

It is important to recognize the inherent difficulties and conflicts that emerge with incorporating alternative therapies into conventional veterinary practice as we start our analysis and investigation into evidence based veterinary medicine (Bueno de Mesquita et al., 2024).

Importance of Evidence-based Approach in Veterinary Medicine

It is not possible to underestimate the importance of using an evidence-based approach in veterinary practice. This prudent approach forms the basis for ensuring that patients who are animals, receive care that is efficient, safe and morally sound. Veterinary clinicians can optimize the patient prognosis and outcomes to improve the quality of care by making well informed judgements about diagnostic and treatment methods based on empirical evidence taken from rigorous scientific research, observational studies and clinical trials (Whittaker et al., 2024).

Decreasing the hazards linked with uncertainty and variability in veterinary clinical practice is one of the main benefits of evidence-based approach in veterinary medicine. Contrary to belief based or traditional approaches, which might be swayed by old experiences or personal prejudice, evidence-based medicine depends upon a sequential methodical assessment of factual data to inform clinical judgement (Rosso et al., 2024).

Veterinary practitioners are also more equipped to analyze the effectiveness and safety of diagnostic procedures, preventive care and therapeutic interventions where they can use evidence-based approach (Biermann et al., 2024). Veterinarians can evaluate the drawback and benefits of various interventions and select the best course of action for every patient by combing evidence-based data from different sources, such as peer reviewed literature, clinical trials and expert consensus (Groves et al., 2024). This evidence-based decision-making approach ensures that treatment therapies are both clinically and financially beneficial while also enhancing and improving the quality of care and encouraging the rational use of resources (Sargeant et al., 2020).

An evidence-based approach is necessary for developing and shaping veterinary medicine under the umbrella of research and innovation, as well as for improving patient health care and welfare. Evidence based research advances veterinary science by creating new knowledge and upgrading current procedures. This paved a way for advancements (Pun et al., 2020).

An evidence-based approach emphasis on transparency and accountability in veterinary practice is another important advantage. Veterinary practitioners can improve communication with coworkers, clients and regulatory agencies by recording the data and reasoning behind clinical decisions and evidence sources that supported them. Collaborative decision making and informed consent between clients and veterinarians further enhances confidence in empirical veterinary treatment. Moreover, veterinarians can decrease the possibility of legal and moral issues related to patient care by abiding to evidence based guidelines and standards of practice (Busch et al., 2021).

Understanding Alternative Veterinary Medicine

Scope

Deviating from conventional and traditional methods, alternative veterinary medicine consists of a wide range of therapeutic ideologies and approaches. Basically, holistic care of animals is the main goal of alternative veterinary medicine, which takes into account their emotional, mental, and spiritual health. Alternative veterinary medicine has more encompassing stance, considering animal as a whole creature with energies and interrelated systems, in contrast to conventional veterinary health care, that mainly focuses on diagnosis and treatment of certain diseases and symptoms. This holistic viewpoint highlights the significance of harmony, balance, and vitality in fostering health and healing because it acknowledges the complex relation that exist between the mind, body and environment (Sharma et al., 2018). The discipline of alternative veterinary medicine is diverse and broad, incorporating different therapeutic models such as chiropractic adjustments, acupuncture, herbal therapy and more (Duarte et al., 2023). For example, acupuncture is an old Chinese medicine practice that dates back more than 3000 years. Its main goal is to increase healing by stimulating the passage of qi throughout the body by inserting tiny and fine needles into particular Açu-points. It is used in veterinary medicine to treat a variety of conditions, such as gastrointestinal problems, neurological abnormalities, chronic pain and musculoskeletal illness. Similar to this chiropractic care deals with manual adjustments to re-align and mobilize the spine and musculoskeletal system in order to provide the body back its functionality, mobility and equilibrium (Koh, Xie, et al., 2017).

Another compulsory component of alternative veterinary medicine is herbal medicine, which utilizes the healing qualities of plants to strengthen and enhance the body natural healing processes. The main part of alternative therapy is nutrition, with a prime focus on natural, dietary supplements and whole meal to promote optimum vigor and health. Veterinarians can help in immune system betterment, illness prevention, and longevity promotion by feeding animals a balanced diet full of essential nutrients, phytonutrients and antioxidants. Another well liked complementary therapy is massage therapy that gives a hands-on method of reducing stress, elevating wellbeing and promoting better circulation and general wellbeing. Massage therapy helps to make animals of all breeds and ages feel relaxed by using mild manipulation and pressure techniques on joints, muscles and soft tissues. This helps in relieving discomfort, increase mobility and lower stress levels (Rastogi et al., 2015).

The purpose of energy healing procedures and techniques like Healing touch and Reiki is to bring the body, spirit and mind back into balance, symmetry and harmony. All thigs considered alternative veterinary medicine encompasses a wide range of therapeutic modalities and ways that are united by means of a dedication to provide a patient centered and comprehensive care. It provides natural and safe means of bringing health and healing in animals by addressing the root causes of imbalance and sickness rather than only treating the apparent symptoms. Alternative veterinary care can supplement traditional therapies and provide more options for large animal and pet owners to seek integrative and holistic care for their companion animals, even though it might not be appropriate for every ailment or patient (Pacheco et al., 2021).

Different Types of Alternative Therapies used in Veterinary Medicine

Many alternative and complementary therapies are available in the discipline of veterinary medicine, giving comprehensive methods for addressing the health and welfare of patients with animals. These approaches include a variety of modalities, each with its own peculiar concepts, uses and methods. A greatly used alternative therapy is acupuncture, traditional Chinese medicine derived ancient therapeutic technique. The sole purpose of acupuncture is to increase and harmonize the flow of qi and facilitate healing by inserting tiny needles into different points of body. It has many applications regarding many conditions of body. Acupoint stimulation is mainly involved in the release of endorphins and neurotransmitters, which have the effect in improving circulation, easing pain and lessening pain (Bergh et al., 2021).

Another prudent alternative therapy in veterinary medicine is chiropractic care, which deals with spine alignment, musculoskeletal system and mobility. Chiropractic adjustment's main goal is to treat musculoskeletal dysfunction and bring back appropriate biomechanical function through manual and digital manipulation techniques such as spinal adjustments and joint immobilization. Chiropractic care can assist animal patients feel better overall, decrease pain and perform better by aligning vertebral subluxations and optimizing nervous system function. Animals with musculoskeletal injuries, spinal misalignments and mobility problems mainly arthritis, sports related injuries and intervertebral disc disease are benefitted greatly from this therapy (Haq et al., 2017).

One more essential component of alternative veterinary care is herbal medicine, which promotes the body healing by using active compounds in plants. Herbal treatments are mild. Natural and gentle way to support animal health and wellness. There are many ways for their administration which includes physically, orally or as a part of nutritionally balanced diet. Every herb has different pharmacological qualities that can be combined to treat a variety of ailments and health issues. In veterinary medicine, it is the frequently used to treat a wide range of chronic and acute illness, such as immune system imbalances, skin diseases, digestive disorders, and respiratory infections (Li et al., 2017).

Another alternative therapy that has emerge as a more popular in veterinary medicine is homeopathy, which works on the principle of **"like cures like"** and uses extremely diluted medicines to encourage body natural healing process.

Homeopathy is a greatly individualized type of therapy because medicines are chosen mainly based on symptoms and constitution of every particular animal. This way of treatment offers noninvasive and gentle choices for treating a variety of chronic and acute diseases. They are be administered topically, orally or by inhalation. With a very low chance of adverse effects or medication combinations, homeopathy is largely used to treat behavioral problems, anxiety, digestive problems and musculoskeletal discomfort in animals (Doke and Dhawale, 2015).

Another branch in the discipline of alternative veterinary medicine is nutritional treatment, which stresses on the value of healthy diet and appropriate nutrition in increasing and avoiding illness in animal patients. Veterinarians can enhance immune system, promote general wellbeing and optimize organ function in animals by feeding them a diet in critical nutrients, antioxidants and essential phytonutrients. Minerals, amino acids, vitamins and fatty acids are example of nutritional supplements that can be used to treat specific health issues and nutritional deficits in patients that are animals. Additionally, therapeutic diets and rational dietary adjustments can be customized to match each animal's specific nutritional requirements, providing animals with good nutrition which makes their health and preventive care more better (Zeng et al., 2015).

Acupuncture is another widely used alternative therapy in veterinary care that helps to reduce stress, improve circulation and overall well-being of animal patients. Massage techniques, which involve applying pressure to the muscles, joints and soft tissues can include effleurage (stroking), petrissage (kneading or rubbing), friction and compression; this manipulation aims at causing a relaxation response in order for patients to experience less discomfort thus facilitating greater movement. Massage therapy can help animals that are recuperating from surgical treatment or injury and also those experiencing arthritis, persistent pain, stiffness due to age. Moreover, massage combined with these techniques can strengthen the bond between animals and their caretakers as it supports care givers in providing modulated comfort measures to facilitate emotional attachment services (Arlt and Heuwieser 2010).

Energy healing methods comprise yet another category of alternative therapies employed by the veterinary profession, including Reiki Healing and Therapeutic Touch. Basically, these healings work on bringing back energetic balance in the systems of our body and also harmony between all aspects that we are (mind/body/spirit). These non-invasive practices use the channeling of universal life force energy which help to bring about deep relaxation, reduce stress and support healing. Through a gentle non-invasive technique, energy healing procedures can treat animal patients (small and giant forms) for physical, mental or behavioral diseases by aligning the body's chakras. In addition, energy medicine techniques are easy to apply within the veterinary model and may upgrade the level of care delivered to an animal patient as a complement or adjunctive therapy with standard treatments (Kinter et al., 2021).

In summary, the multitude of complementary and alternative therapies offered by veterinary medicine offer an expansive collaborative tool to support animal patients in better health throughout their lives. They give pet owners, seeking compassionate, holistic and tailored care for their animal friends more possibilities. From acupuncture and chiropractic adjustments through herbal medicine, homoeopathy, nutritional therapy, massage therapy to energy healing modalities. With a focus on long-term wellness, Alternative therapies take the time to uncover what may be contributing to an animal's imbalances and disease processes rather than just focusing on symptom management. This highlights the importance of holistic care to keep animals in optimal health, which requires looking after their body (as discussed above), mind and spirit as well (Millis and Burge, 2023). The pictorial view of integrative alternative veterinary medicine approach is given in Figure 3.1.

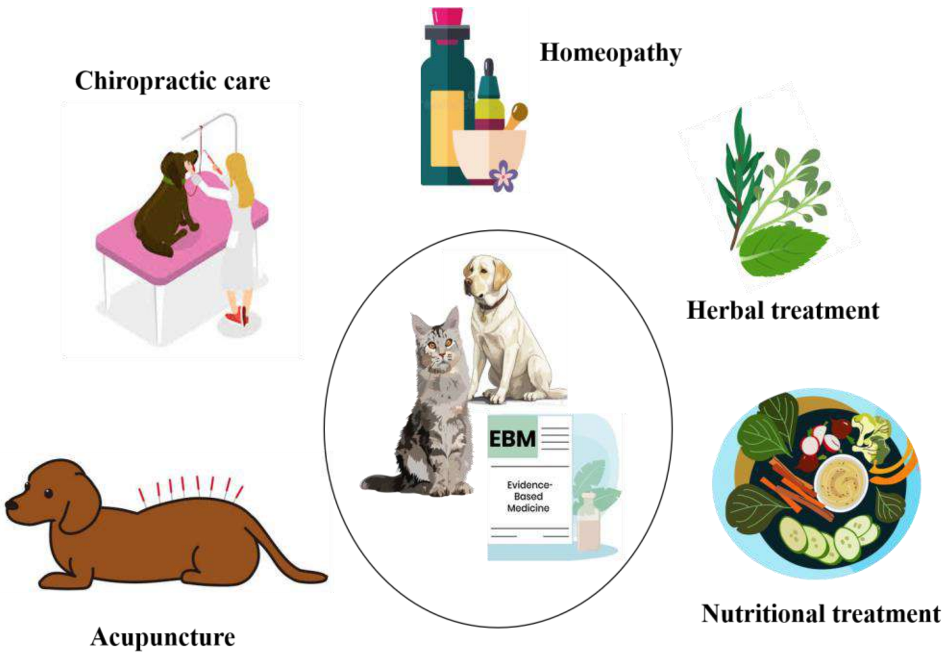

Fig. 3.1: Integrative Alternative Veterinary Medicine Approach

Historical Background and Evolution of Alternative Veterinary Medicine

In prehistoric societies, when healers and veterinarians used natural remedies, holistic beliefs and maternal healing practices to treat animals, the roots of alternative veterinary medicine can be traced back. Save recognizing the interconnectedness of humans, animals and environment ancient peoples in societies like Egypt, Greece to China to India all developed various practices for healing that spoke not only to our physical appearance but also spiritual health. These early systems of care for veterinary patients set the stage for what are now considered alternative healing approaches by identifying and treating root causes of disease and imbalances (Rastogi et al., 2011).

One of the most ancient applications of other veterinary medicinal practice is perhaps that which arises to become knowable from drunken China for over 3,000 years is **Acupuncture**. The use of plants in veterinary treatment dates back to the times of act healers and herbalist similar to those found today, RX, herbaceuticals were based on amazing medicinal qualities that many contemporary people have almost forgotten. Many ancient societies have used herbal therapies, such as in Egypt, Greece and India for treatment of infections and gastrointestinal or musculoskeletal problems. People had passed down through the generations, knowledge about medical plants and every culture developed involve traditions custom-made in medicinal plants as well herbal cures and handling (Bellavite et al., 2005).

In Middle Ages Europe, opposition to veterinarians remained largely tacit and the practice of veterinary medicine consolidated as a specialized field with the establishment of veterinary guilds or colleges in many countries. Meanwhile, alternative medical practices which kept their popularity still prevailed as orthodox veterinary medicine focused on diseases identification and medications to combat illnesses (Gong et al., 2014).

Alternative veterinary medicine has evolved over the years due to changes in societal norms, advancements of science and healthcare needs are at an all-time high. With integrative and holistic care increasing in importance, veterinarians are incorporating alternative therapies into their practices along with traditional treatments. Moreover, a substantial volume of clinical research is now available in the field documenting safety and efficacy as well as mechanisms underlying activity enabling some alternative-medicine interventions to be science-based veterinary therapeutics. The traditional philosophies of healing that recognize the body, mind and spirit as interdependent factors in health and well-being in animal patients have remained at the heart of alternative veterinary medicine (Johnson, 2018).

The Role of Evidence in Alternative Veterinary Medicine

Importance of Evidence-based Practices in Veterinary Care

The importance of evidence-based practices in veterinary medicine cannot be overstressed as they form the sole basis for delivering safe, effective and ethically acceptable care to animal patients. Evidence-based practices are driven by rigorous scientific research, clinical trials and empirical data deployed for use in the sanctity of patient care during workforce decision-making. This process can ensure that treatments are appropriate and ethical for each individual case. Veterinary patient care likely can be improved by veterinarians adhering to evidence-based guidelines and standards of practice allowing for optimal outcomes while minimizing adverse events (Robinson et al., 2022).

One of the primary benefits care evidence-based procedures in veterinary medicine is to reduce the risks associated with uncertainty and variability clinical practices. In comparison to other types of approaches, Evidence-based approaches differ from anecdotal or belief-based approaches, which could be influenced by tradition the type II error (Shurtz et al. 2017). Furthermore, veterinarians can more critically evaluate the safety and efficacy of diagnostic tests as well as therapeutic interventions and preventive measures using evidence-based approaches. Thus, veterinarians can integrate the available information (i.e., clinical trials data-review of peer-reviewed literature and expert-consensus) to assess what methods are likely have a favorable risk to benefit ratio for an individual patient. This approach maintains evidence-based decision making to create therapy solutions that enhance the delivery both in clinical effectiveness and cost-effectiveness whilst improving quality of care through encouraging responsible resource use (Batt-Williams and Wade, 2022).

Both in patient care and for the sake of advancing veterinary medicine through innovation and research, evidence-based methods are necessary. Evidence-based research results in a new knowledge to veterinary science that supports and improve existing practices which ultimately change the way diagnosis are performed (Huntley et al., 2016). Ultimately, the use of evidence-based strategies will ensure that veterinary patients receive only the best and safest care. The use of empirical evidence to guide clinical decision-making by veterinarians can enhance animal patient care, lead to better patient outcomes and lower the numbers of adverse events. Moreover, evidence-based practices foster innovation and research in veterinary medicine by enabling the field to be at its best with respect to disease prevention strategies, treatment methods and diagnostic tools. Nevertheless, given that the overall purpose of veterinary medicine is to supply ethical, reliable and high-quality care for animal patients so we must be using evidence-based methods (Janicke et al., 2020).

Challenges in Evaluating Evidence for Alternative Therapies

The confusion comes because alternative therapies are unusual in veterinary medicine, and there many kinds of evidence to consider when assessing the efficacy. One of the critical problems is the lack of well-defined methods and designs in research for complementary/alternative therapy. Whereas conventional treatments are often the subject of systematic reviews and randomized controlled trials (RCTs), many alternative therapies lack scientific validation. Such reasons could arise from methodological issues such as study design, sample size, not blinding and a control group. In addition, many alternative therapies are individualized treatment plans and use an overall approach to assess their efficacy by existing research methods and standards difficulty (Lin et al., 2021).

Another challenge comes from the diversity of evidence sources for complementary and alternative medicines, such as expert opinion, case studies, observational studies or anecdotal accounts-preclinical research. These information resources may have less rigor and scientific validity than controlled clinical studies, but they can provide valuable insights into the safety, efficacy or mechanisms of action of alternative medicines. In addition, individual biases and understanding of the world as well as cultural context can greatly influence how evidence base supporting alternative medicines are interpreted leading to differences in treatment effect responses and practice behaviors (Baglioni et al., 2020).

In addition to, assessing this by means of drugs meant for substitute utilization is likewise impeded through the placebo effect and the place out therapeutic outcomes being subjective. Most alternative therapies are based on subjective measures such as owner assessments, pain scores and quality of life measurements (Moreau et al., 2014). (Hartwigsen, 2023). Further, integrating alternative therapies into accepted veterinary practice raises a host of logistical and regulatory concerns that include issues such as training/certification, licensure/credentialing, scope-of-practice and reimbursement. While some alternative therapies (e.g., acupuncture) may be endorsed by professional organizations and considered legitimate adjunctive treatments, other forms of health care lack regulatory oversight or standardization in practice leading to differences with respect to training, qualifications and competency among practitioners. Furthermore, incorporation of alternative ways into mainstream veterinary science would require a shift in culture practice attitudes and reimbursement models that is not easy to achieve due the barriers for implementation as well as adoption. In summary, the evaluation of evidence for alternative therapies in veterinary medicine is a complex process that requires an understanding of both potential benefits and challenges to this type novel modalities as well as an open scientific attitude combined with stringent data mining and interdisciplinary team effort (Hartwigsen 2023).

Criteria for Assessing the Quality of Evidence in Alternative Veterinary Medicine

For alternative veterinary medicine, a number of important criteria must be taken into account when evaluating the quality of evidence to ensure valid and reliable results that are relevant. The choice of methodology and research design used to generate evidence is one criterion which matters due importance. Randomized controlled trials (RCTs) are considered the gold standard for assessing treatment efficacy, largely because they randomly allocate people to a trial arm or control group. Additionally, systematic reviews and meta-analyses of RCTs and well-conducted cohort studies may provide valuable information about the effectiveness, safety aspects and hypothesized transitivity inference for alternative treatments. This third standard - the transparency and repeatability of research techniques and findings, is also essential. Critically assessing the quality of study results involves clear reporting of study methods, participant characteristics, treatment regimes, outcomes and statistical analyses (Prache et al., 2022).

Evidence-Based Alternative Therapies

Acupuncture

Acupuncture is a more than 3,000-year-old Traditional Chinese Medicine practice that involves placing fine needles into specific points on the body called acupoints. The (theoretical) premise of the treatment is that, by stimulating these acupoints you can unblock energy flow - or qi - in meridians across body to restore internal harmony and balance. The idea is that acupuncture fixes these imbalances, thus inducing healing. According to traditional Chinese medical philosophy, the passage of qi can be obstructed or imbalanced giving rise to different disorders (Huntingford and Petty 2022).

Explanation of Acupuncture and its Principles

Along with anecdotal evidence, empirical studies have given ample proof to the use of Acupuncture in veterinary practice. There are a number of research trials which support the use of acupuncture both in cases where these is pain, inflammation and also for overall well-being. Acupuncture is helpful for countless animals including the dog, cat or horse as well exotic varieties (Xie and Holyoak, 2021).

Scientific Evidence Supporting the Efficacy of Acupuncture in Veterinary Medicine

In dogs and cats, acupuncture is commonly used to treat neurological disorders (such as paralysis or nerve dysfunction) and musculoskeletal problems including hip dysplasia, osteoarthritis, and intervertebral disc degeneration. In addition, acupuncture is also able to improve the overall health and well-being of companion animals; relief stress and anxiety as well as chronic pain management. Acupuncture in horses is used for enhancing performance, faster recovery after an injury and relief from musculoskeletal pain caused due to problems such as back issues; navicular syndrome or laminitis. In horses, acupuncture can even be effective for treating gastrointestinal diseases and reproductive issues, as well as various respiratory conditions. Exotic animal acupuncture for chronic illnesses (Holyoak and Ma, 2022).

Applications of Acupuncture in different Animal Species

So, in conclusion, acupuncture is a great technique used for thousands of years with growing substantiation of its therapeutic value scientifically within veterinary medicine. This science-based medicine can help to sooth the animal, reduce pain and inflammation in several conditions by stimulating specific acupoints through which balance and harmony are reestablished within the body. As a safe and effective form of adjunctive gold standard treatment, acupuncture has few side effects or adverse reactions allowing it to be used in most animals with many illnesses. Acupuncture is an ancient healing art that will play a larger and more significant role in integrative veterinary care as research into its mechanisms and applications matures (Mier, 2021).

Herbal Medicine

Overview of Herbal Medicine and its use in Veterinary Care

Herbal medicine is one of the traditional ways of healing that exist for thousands of years in many different civilizations also called as Botanical Medicine, and sometimes named Phytotherapy. Herbal medicine in veterinary care refers to the use of plant-derived medications for prevention, treatment or mitigation involving various veterinary health issues (Silveira et al., 2020). Unlike conventional pharmaceuticals, which often consist of isolated synthetic molecules, herbal remedies are composed of mixtures of several bioactive compounds (phenolic acids, alkaloids and flavonoids) and terpenoids acting in synergy to elicit therapeutic effects. Veterinary Herbal Medicine Veterinary herbology, similar to human herbal medicine, is dedicated at assisting the body's natural state of health and well-being. It is grounded in holistic health and natural healing (Cheng and Han, 2020).

Research Evidence Supporting the Efficacy and Safety of Herbal Remedies

A large body of research evidence has emerged over the last decades, supporting both the effectiveness and safety of herbal treatments pointing to their potential as adjuncts or replacements for conventional medicine. Many clinical trials have established the efficacy of medicinal plants in a multitude of common health problems from colds to chronic pathologies such as arthritis and diabetes. You know how ginkgo biloba has been proven to enhance the cognitive functions and memory of dementia patients, or that turmeric patting curcumin possess potent anti-inflammatory as well as antioxidant prowess. Great number of commonly used herbal remedies also has a proven safety profile, as they cause less frequent mild adverse events than synthetic pharmaceuticals (Liu et al., 2021).The safety margin of standardized extracts of St. John's wort for the treatment of mild to moderate depression has been observed to be similar or better than that reported for conventional antidepressants Moreover, stringent quality control and evidence-based guidelines are helping establish practices in which herbal medicine can be integrated into modern healthcare systems (Canenguez et al., 2022).

Due to their ability of improving the immune system and reducing the severity, duration and symptoms of airway infections even more under lens with Elderberry as herbal remedies unglazed popularity. Moreover, the worldwide herbal products market continues to be driven by burgeoning consumer interest in natural and holistic health remedies (Wieland et al., 2021). The already mainstream use of herbal remedies in health maintenance e.g echinacea is likely to become even more popular as scientific research continues (Burlou-Nagy et al., 2022).

Examples of Commonly used Herbs in Veterinary Practice and their Therapeutic Benefits

Research has shown that hundreds of herbal treatments are healing for animals, and more evidence continues to support their safety instead of pharmaceuticals. The herbal medicines have many uses in the treatment of some diseases, such as musculoskeletal disorders, gastrointestinal symptoms, dermatological problems including decreasing skin moisture content on eyelids can be reduced with using Aloe Vera Gel extract from medicinal plants for that purpose (Romero et al 2022).

In veterinary medicine, further support for known herbal and herb formulations used as adjuvant therapy can be found in the systematic reviews or meta-analyses. As with any fields of herbal medicine, many plants are both safe and effective enough to be recommended for use in veterinary care. One such herb is the popular chamomile *(Matricaria chamomilla)*, which has anti-inflammatory and sedative effects on sleep (Zhu, 2020).

Chiropractic Care

Introduction to Chiropractic Therapy for Animals

Chiropractic care for animals is also known as veterinary spinal manipulation therapy, or VSMT. The manually applied approach to medicine focused on identification, management and prevention of musculoskeletal problems related conditions. Using manual manipulation techniques, chiropractic therapy for animals aims to correct alignment and mechanics of the musculoskeletal system as well as vertebral column. Derived from chiropractic practice and founded on the premise of centralizing both health and overall well-being in terms of neurological function with respect to spinal integrity (Maldonado et al., 2022). Chiropractic care of chiropractic animal patients is directed to the diagnosis and treatment (correcting) vertebral subluxations, joint limitations, and muscle imbalances for prevention of pain reduction as well as part of sports training enhancement along with general health maintenance (Elmets et al., 2021).

Evidence-based Research on the Effectiveness of Chiropractic Care in Animals

The utilization of chiropractic care in animals, especially veterinary medicine is becoming more recognized with its possible therapeutic effects. Research in the form of evidence-based practice has proven that it helps animals -- e.g.

increasing quality and pain free life feasible (Maldonado et al., 2022). Chiropractic adjustments have been found to alleviate musculoskeletal pain in studies among animals with disorders like arthritis, intervertebral disc disease and sports injuries. In addition, chiropractic care helps aid the body in its natural healing process by keeping proper alignment and function of the spine/joints. Several studies on canine and equine subjects have produced strong evidence for enhanced gait and posture during chiropractic care. Finally, the synergistic effects achieved by combining chiropractic care and traditional veterinary treatment can lead to better overall health (Marziani et al., 2018). Chiropractic therapy is appealing for the non-invasive nature of this approach to pain management and improved quality of life, especially in senior pets. Advanced imaging techniques using MRI and ultrasound have confirmed additional positive changes in anatomy secondary to chiropractic care. The evidence base for veterinary chiropractic is growing, and it has gained acceptance as a legitimate aspect of overall animal health (Du Plessis et al 2017).

Case studies illustrating the use of Chiropractic Techniques in Veterinary Medicine

Over recent years, the evidential research into animal chiropractic has been growing progressively. Case studies provide examples of where and how chiropractic principles are applied in veterinary medicine giving specifics regarding the clinical application and outcomes associated with chiropractic care for animals. These case studies often report a variety of clinical injuries and animals that benefit from chiropractic care, as well as the numerous ways veterinary chiropractors use in treatment (Maler 2023). From chronic back pain in a horse improved following chiropractic adjustments, to improvement of mobility and QOL for a dog with hip dysplasia after several adjustments- case studies could serve as an example. Case studies contribute to the growing scientific literature around chiropractic care in veterinary medicine by documenting clinical case notes, care plans and results for individual patients (Halle and Granhus 2021).

Integrating Evidence-Based Alternative Therapies into Veterinary Practice

Considerations for Integrating Alternative Therapies into Conventional Veterinary Care

Veterinary practices considering integrating evidence-based alternative medicines into their care of animal patients should be prepared to deliberate over a number of issues in order to provide safe, efficient and morally-responsible care. The first step in considering their integration with conventional veterinary care is to evaluate the evidence base for alternative treatments -the quality and reliability of research studies, clinical trials as well as observational data. Alternative therapy should be judged critically by veterinarians according to its scientific basis, including study design with sufficient number of animals included, randomization (and concealment), double-blinding or not blinded observations as well as the presence of a control group and subsequent application of intent-to-treat-analysis. In addition, the benefits of alternative therapies need to be compared and balanced with a patient's requirements, medical history as well as treatment objectives. Professionals can offer a more comprehensive and customized treatment method through the incorporation of non-scientific complementary therapies with traditional veterinarian medicine to help maintain animal health based on evidence (Bai et al., 2022).

Collaborative Approaches between Conventional and Alternative Veterinary Practitioners

Second, motivational methods are necessary to facilitate interdisciplinary communication and collaboration among conventional as well as alternative veterinary practitioners. The ability of various veterinarians with different training programs and specializations to work together allows them the freedom to learn from one another as well, promoting an integrative view that combines all perspectives for a more holistic approach in veterinary care. Building evidence-based treatment protocols, referral networks and educational opportunities to help conventional veterinarians offer safe, effective integration of alternative therapies within traditional veterinary practice requires collaboration among both our colleagues in either camp. In addition, collaboration may assist in establishing the regulatory frameworks and clinical ethics to permit veterinary medicine with treatment alternatives (Matthew et al., 2020).

Ethical Considerations and Informed Consent in Offering Alternative Therapies to Animal Patients

Third, using alternative medicines on animal patients opens up a can of ethical worms-and the need for informed consent. All veterinary professionals should obtain balanced and realistic information on the risks, benefits and uncertainties associated with alternative medicine so clients have all necessary facts to make informed choices about their pets' care. A full discussion about treatment options, outcomes of those interventions and their costs should follow in order to assure that all clients are well informed (Stanossek and Wehrend 2022). Veterinarians are also subject to ethical principles, professional standards and legal requirements controlling the practice of veterinary medicine with regard to patient welfare, client communication and confidentiality. Practices can be applied fairly reaching highest standards of expertise, integrity and responsibility prioritizing consent together with ethical considerations when delivering (De Paula Vieira et al., 2020).

Future Directions and Challenges

Emerging Trends in Evidence-based Alternative Veterinary Medicine

There are a variety of trends and issues that will likely shape the future progression of evidence-based alternative veterinary medicine. One such emerging key trend in veterinary medicine, on account of higher consumer demand and growing perceived benefits from holistic approach is to adopt alternative therapies with traditional approach. This interaction led to the formation of imaginative treatment plans and synergistic research partnerships between various specialties, marrying well-established practices with alternative modalities in an attempt to optimize patient outcomes. There are problems associated with the integration of alternative therapies within veterinary care that include the need for standardized research methodology, training programs and regulatory frameworks to ensure they are safe, effective and ethically applied (Sridhar et al 2023).

Research Gaps and Areas for Further Investigation

While there have been significant advances in evidence-based alternative veterinary treatment, as a profession we still face a plethora of unanswered questions and directions for future research. The lack of high-quality scientific evidence for most complementary therapies is ascribable to concerns regarding trial design, sample size and methodological rigor. Additional research is needed to assess the long-term safety, efficacy and cost-effectiveness of alternative therapies as well. In addition, comparative studies to define the efficacy of different modalities are needed. In addition, research is needed to develop standardized treatment response outcome measures, identify biomarkers of therapy responsiveness and elucidate the mechanisms by which alternative medicine work (Lyons et al., 2022).

Addressing Skepticism and Misconceptions Surrounding Alternative Therapies in Veterinary Medicine

A further significant argument faced by veterinary medicine is that of dispelling the myths and skepticism surrounding them in alternative therapy. Even as these methods are becoming more accepted and commonly practiced, many veterinarians, pet owners and regulatory bodies remain skeptical about some alternative treatments. Some of the skepticism is linked to concerns about a lack of an evidence-base, variable standards in practice and risks associated with CPT - (e.g., Memon et al. 2016); Progressive education is needed for stakeholders on the basics, evidence base and safety of alternative medicines to promote informed choice and trust in veterinary care. Another solution could be helping veterinarians, researchers and legislators to communicate more openly that functions as a team bringing together two models of treatment in the name of animal health can lead us through these loopholes (Mortada, 2024).

Conclusion

For the veterinary profession, evidence-based practice is vital in order to deliver quality care for animal patients. More informed decisions by veterinarians, based on experimental evidence derived from sound scientific research including clinical trials and observational studies, should result in better patient outcomes and a higher quality of care. This can be achieved through evidence-based practice, which leads to the standardization of care protocols and reduces in variance in practice patterns as well as minimizing risk for errors or adverse results. It also empowers vets to critically appraise the safety and effectiveness of interventions, ensuring that patients are given treatments which are both cost-effective and evidence-based. EBVAM promotes ethical, responsible and open decision-making in veterinary care that translates into confidence and trust for patients, coworkers as well regulatory bodies. facilitating adherence to evidence-based norms and standards of practice among veterinarians.

Finally, because the evidence base for each alternative veterinary therapy is incomplete and beset with controversies or gaps from data that are difficult to assess scientifically (or even replicate), more reliable research across various practices of interest has potential beneficial advancements other than simply increasing options, enhancing outcomes and elevating standards of care in animal patients. Veterinarians need to engage through an evidence-based collaboration with other disciplines that would help develop new holistic animal healthcare strategies, identify areas which require further research and enhance our knowledge related to symbol of alternative medicine. The welfare of animals and the advancement in veterinary medicine must be promoted through continued evaluation, investigation, and training in alternative medicines.

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Chapter 30

Ethno-veterinary Practices for Disease Control in Pakistan

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ABSTRACT

Ethno-veterinary Medicine (EVM) is fundamental to traditional alternative medical practices in many developing countries, including Pakistan. Traditionally, EVM has been used to control various animal diseases. Certain plant species have significant therapeutic value for treating various livestock diseases, and they are not just utilized as feed or fodder. Common livestock ailments treated and controlled using Ethno-veterinary Practices (EVPs) in ruminants are flu, ringworms, inflammations, constipation, bloat, mastitis, pneumonia and wounds, genital prolapse, retention of fetal membranes, dystocia, tick and lice infestation, helminthiasis. In poultry, they include coccidiosis, fowl cholera, avian influenza, and some other respiratory and gastrointestinal problems. Among the practices, medicinal plants like *Aloe vera* (Aloaceae), *Aerva javanica* (Amaranthaceae), *Brassica campestris* (Cruciferae), *Calligonum polygonoides* (Polygonaceae), *Eruca sativa* (Cruciferae), *Oryza sativa* L. (Poaceae) and *Acacia modesta Wall.* (Fabaceae) have emerged as the most commonly used botanical plant for livestock diseases. Conventional medications are stored in bottles, paper, cloth, and other containers. They are administered through various routes; the primary ones are topical, oral, and respiratory. Ethno-veterinary medicine practices can be used in Pakistan to articulate potential applications in modern veterinary medicine because of their low cost, local availability, and fewer side effects. This chapter was compiled to highlight the role of EVM in animal disease control in Pakistan.

KEYWORDS
Ethno-veterinary practices, Alternative medicine, Animal diseases, Pakistan

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INTRODUCTION

Ethnoveterinary medication (EVM) is a field of medicine that safeguards the health of animals and treats illnesses in line with traditional ideas, methods, and practices. Plant-based ethnoveterinary remedies are used extensively worldwide because raising farm animals is a fundamental component of most people's livelihoods (Rehman et al., 2022). It continues to be essential in many rural regions of the globe for assuring the health of farm animals and, therefore, the survival of pastoral or agro-pastoral groups. Ethno-veterinary knowledge (EVK) consists of many forms of expertise and practical abilities: ecological expertise of pastures; ethno-climatological understanding of climate forecasting; knowledge of harvesting and cultivating and supplying animals with unique fodder plant life. These practices are considered authentic for animal well-being, as well as for growing animal-based meal products (i.e., dairy products, meat, eggs, honey, and other bee products). Also, they include recruitment and use of natural remedies and other natural remedies when animals are sick, ways of managing whole animal breeding systems, and so forth (Aziz et al., 2020). Nowadays, natural medications are given greater attention globally due to minimum/low risk factors compared to synthetic drugs. Pills are unavailable in rural regions, or their supply is erratic. Many stock raisers either underdoes to save money or overdose because they do not understand the instructions for use. Imported drugs are expensive (IIRR. 1994).

Moreover, plant-based veterinary medicines or formulations are very inexpensive. Present-day drugs derived from plant-based substances were traditionally used to treat humans and animals. Plant-based ethnoveterinary herbal medication is one of the options for artificial drugs and the most sustainable approach that is easily tailored to rural farm animals for the remedy of animal illnesses in Pakistan (Abidin et al., 2021).

The agro-livestock industry plays a significant role in Pakistan's economy, with around 43.5% of individuals linked to this industry contributing 21% to the gross domestic product (GDP). Pakistan is the world's third-largest milk producer, highlighting the importance of livestock. Many Pakistani livestock producers are impoverished and face financial constraints, making it difficult for them to purchase modern allopathic medications, leading to poor animal productivity and health. In such situations, ethnoveterinary medicine can be considered as an alternative to conventional pharmaceuticals, helping in poverty reduction by enabling people to treat their animals using local resources. In study conducted in Namibia's Omusati and Kunene areas, Eiki et al. (2022) investigated the use of ethnoveterinary medicines for treating livestock diseases. They identified 15 plant species from 10 plant families used as veterinary medicines, with formulations typically utilizing fresh ingredients. The most common method of administration was oral, followed by topical application.

Diarrhea can be treated using *Ziziphus mucronata*, *Combretum collinum*, and *Colophospermum mopane*. Mastitis can be treated with *Z. mucronata* and *Salvadora persica*. *Aloe esculenta* can be used to cure skin infections. Eyes diseases in cattle, goats, and sheep could be treated with *Ximenia Americana* and *C. imberbe*. *Grewia flavescens, Acacia nilotica,* and *A. erioloba* were used to cure retained placentas. *Fockea angustifolia* roots were used to cure anthrax (Rehman et al., 2022). There is a wide variety of EVM treatment principles, according to the cause of the disease. They include cauterization, bleeding, fuzzing, and minor surgeries; crushed leaves, tobacco leaves and fish waste, and oil for skin ailments; wooden splints for fractured limbs; meat and grains; grazing/browsing on certain plants; the use of different ashes including bone ashes, tree tar, wood oil, mineral springs, seawater, sulfur, motor oil, bone marrow oil, sour milk.

The treatments are based on the idea that all living creatures should live in harmony with their environment and must balance hot and cold, work and play, wakefulness, and sleep. The remedies differ between communities, but many are routine treatments for several people. The same remedy is often applied to both animals and humans. The practices in an area are closely linked to the local flora and fauna (Raziq et al., 2010). Many factors inhibit the growth of the livestock sector in Pakistan, including policy issues, rapid deterioration of rangelands, unhygienic eating practices, poor marketing systems, inadequacy of extension services, and insufficient resources. There are several fatal animal diseases in Pakistan, including foot and mouth disease (FMD), hemorrhagic septicemia (HS), bovine viral diarrhea (BVD), and black quarter (BQ). Farmers do not regularly vaccinate their animals against these fatal diseases, which lowers dairy production. The consequences of livestock diseases are generally seen as direct impacts only, but they can be complex. The diseases affect the productivity of animals and deprive farmers of their possible daily earnings. These fatal diseases lead to morbidity, resulting in short- or long-term product loss (Aziz et al., 2020).

Historical Development of Ethno Veterinary Practices

Herbs, medicinal plants, and other traditional practices are vital in managing human and animal health. Herbs and medicinal plants are sources of medicinal substances and emerging modern medicines; they play a crucial role in revolutionizing conventional medicine. Herbs thus form an essential basis in drug development and are a natural blueprint for developing new drugs or phytomedicines to control and treat livestock diseases. Ethno veterinary practice generally consists of local indigenous knowledge and methods used to care for, treat, and manage livestock health. Natural options, especially plant-based products or herbs that are locally available and readily accessible, are the drugs of choice for most resource-poor smallholder farmers, especially women. There is also growing concern about microorganisms causing drug-resistant diseases due to overuse and misuse of conventional drugs. That is why there has recently been a paradigm shift towards a focus and increased demand for organic farming practices worldwide for animal health management. Herbs and medicinal plants offer a practical choice as they have a broader spectrum of action (Ndlovu et al., 2023). Alhaji Eggi Sule was one of the first ethno veterinarians to establish a medicinal plant garden in the early 1990s to improve access to medicinal plants and preserve rare species in Cameroon.

Traditional veterinary practices have been around for a long time and were the only medicine available until the 19th century. The world center of veterinary and other medical knowledge in the early Middle Ages was Arabia. With the spread of Islam, some of this knowledge reached Africa and was adopted by breeders. Ethno-veterinary medicine was practiced as early as 1800 BC when the Babylonian king Hammurabi formulated laws on veterinary fees for treating cattle and donkeys. Ethno-veterinary medicine (EVM) has been experiencing a resurgence for over a decade, and several reports have been published. Recognizing some effective ethno-veterinary medicinal products has supported this growing interest in traditional practices. Until 1989, ethno-veterinary practices were mainly carried out individually, with little coordination. In 1989, the Cameroon Ethno Veterinary Council was established (Menegesha A. 2020).

Preparation and Uses of Ethnomedicinal Plants in Livestock in Pakistan

For centuries, Pakistani local culture has been based on raising livestock. Livestock health care typically entails various methods, such as biomedical pharmaceuticals, traditional knowledge, and herbal remedies. Pakistan's rural areas had limited access to modern therapeutics in the past. Biomedical pharmaceuticals have been on the rise in recent years as the infrastructure has improved. However, most rural areas rely on ethnoveterinary practices because of their cost and ease of availability. The lack of formal education in the field has been demonstrated to impact people's knowledge of and use of medicinal plants in other parts of the world. Recent studies on medicinal plants show the widespread use of plants such as *Pinus gerardiana*, *P. wallichiana*, and *Withania coagulans* because they work better than pharmaceuticals. Initially, the plant was only used medicinally by humans, but because of its positive effects, people soon began using it to treat animal illnesses (Ahmad et al., 2015). In Pakistan, diseases that affect livestock are seasonal and frequently epidemic. Because seasonal changes also bring changes in the vegetation and fodder, livestock are particularly vulnerable. The locals classified digestive disorders based on various symptoms, including diarrhea, stomach pains, and digestive issues. Worm infections are typically brought on by drinking unclean water, grazing pastures frequently, and keeping livestock in enclosures contaminated by the waste material of infected animals. In Pakistan's hilly regions, irregular surfaces and steep inclines are more likely to cause skeletal and muscular issues.

Moreover, animals frequently climb and feed on trees in the semi-arid vegetation, which increases the risk of falls. In some parts of Pakistan, mange is also a common dermatological disease. Other common diseases, including foot and mouth disease (FMD) and contagious pleuropneumonia, are also prevalent in some areas (Ahmad et al., 2015). The table below documents the different common livestock diseases that can be treated using ethnoveterinary practices, plant part preparation, and route of administration. It primarily emphasizes the significance of EVPs in Pakistan.

Table 1: Common ethnoveterinary practices used for livestock ailments in Pakistan.

Sr. No.	Ethnoveterinary Practice Product	Family	Vernacular Name	Life Form	Therapeutic Value/ Ailment	Ethno-veterinary uses
1	*Aconogonon molle* (D. Don) H. Hara	Polygonaceae	*Chukro*	Herb	Enterotoxaemia, Dysentery (PPR),	Mashed uncooked roots are given orally. After boiling in the water, roots, and molasses in solution form are fed orally.
2	*Aconogonon rumicifolium* (Royle ex Rab.) H.Hara	Polygonaceae	*Panchoola*	Herb	Enterotoxaemia	Mashed uncooked roots are given orally.
3	Aloe *[Aloe Vera]*	Aloaceae	*Zargya*	Herb	Diarrhea, Newcastle, Duck disease, and Fowl Cholera	Leaves dried, Crushed, fluid squeezed, mixed with salt, and soaked in water for chickens to drink.
4	*Aesculus indica* (Wall. ex Camb.) Hook. f.	Hippocastanaceae	*Bunkhouse*	Tree	Indigestion	Fruits are mashed and fed to the cattle. Seeds are also given orally as a tonic, especially to the horses
5	*Ajuga bracteosa* Wall. ex Benth.	Lamiaceae	*Jan e Adam*	Herb	Internal heat	Uncooked roots are given orally to the cattle.
6	*Angelica archangelica* var. himalica (Clarke) *E. Nasir*	Apiaceae	*Murchar*	Shrub	Indigestion, Dyspnea	The roots of the plants are cooked, and molasses is added. This increases internal temperature and relieves pain.
7	*Angelica cyclocarpa*	*Apiaceae*	*Norman canon*	Shrub	Indigestion (locally known as Dood da Mala), Indigestion caused by the cold, Dehydration	Cattle are cured by being given uncooked roots with the addition of molasses. The same roots, cooked, are given to the cattle.
8	Ginger *[Zingiber officinale]*	Zingiberaceae	*Adrak*	Herb	Respiratory diseases (Prevention and cure), immunity booster	Rhizome Soaked in water mixed with feed and orally administered
9	**Aralia cachemirica** Dcne.	Araliaceae	*Chooryal*	Shrub	Lower milk production	Mashed and uncooked roots are given to the cattle as a tonic, increasing milk production.

10	*Berberis lycium* Royle	Berberidaceae	*Sunmbal*	Shrub	Weakness of bones and treatment of internal fractures	The root and stem bark is peeled off, dried, ground, and then combined with rice, maize flour, and butter as a tonic.
11	*Bistorta amplexicaulis* var. amplexicaulis (D. Don) Green	Polygonaceae	*Chiti Masloon*	Herb	Skeleto-muscular, Gastrointestinal, Liver	Cooked roots (decoction) are used as a tonic to the feeble cattle.
12	*Bistorta amplexicaulis* var. speciosa (Meisn.) Munshi and Javeid	Polygonaceae	*Bari Masloon*	Herb	Skeleto-muscular, Gastrointestinal, Liver	Cooked roots are given to the feeble cattle as a tonic.
13	*Capsicum annuum* L.	Solanaceae	*Rattian Marchan*	Shrub	Strangles (Kannar)	Cotton cloth is kept on hay and burnt. Dried fruits of Capsicum annuum (locally called Rattian marchan) are ground, and the powder, in combination with sugar, is also poured on the fire. Smoke and fumes produced are forcibly inhaled by animals (horses, mules, donkeys). Consequently, copious discharge from nasal cavities occurs, and animals become healthy.
14	*Cedrus deodara* (Roxb. ex D.Don) G.Don	Pinaceae	*Pluddar*	Tree	Dermatological	After heating the wood's chopped parts, the resin extracted from *Cedrus deodara*'s trunk is applied to the affected skin to cure/manage ectoparasites. Burned mobile oil is also used for the same purpose.
15	*Curcuma Longa L.*	Zingiberaceae	*Liddhar*	Herb	Prolapse of Uterus	Roots of *Curcuma longa* (Haldi) is cooked in ghee and are also fed orally.
16	*Dipsacus inermis* Wall. ex Roxb.	Dipsaceae	*Pilha*	Herb	Placenta Expulsion, Prolapse of Uterus	About 1–2 kg of roots is mashed, cooked in water, and given orally to expel the placenta as post-delivery treatment in cattle. This has shown quick results, and the placenta has been removed. Cooked roots of *Dipsacus inermis* (Pilha) are also used.
17	*Azadirachta indica* A.Juss	Meliaceae	*Neem*	Tree	Lice infestation and Helmenthiasis	500 g leaves boiled with 1 L water and applied topically/ 500 g leaves brewed in 1 L water and drenched.
18	*Geranium wallichianum* D.Don. ex Sweet	Geraniaceae	*Ratanjoog*	Herb	-	Cooked roots are given to the cattle as a tonic.
19	*Helianthus annuus L.*	Asteraceae	*Gul e Aftab*	Shrub	Skeleto-muscular	Crushed seed (Powder) is given to weak cattle orally as a tonic to the general weakness.
20	*Hylotelephium ewersii* (Ledeb.) H. Ohba	Crassulaceae	*Loonslooni*	Herb	Over dozed Salts	The whole mashed uncooked plant is fed to the goats and sheep.
21	Indigofera heterarchy var. heterantha (Wall. Ex Baker) Ali	Papilionaceae	*Kainthi*	Shrub	Dewormer	Mashed uncooked roots are given to the young cattle as dewormers.

22	Lavatera cachemiriana var. cachemiriana S. Abdin	Malvaceae	*Dang Sonchal*	Shrub	Constipation	Cooked roots are used to treat the animals
23	Ligularia amplexicaulis DC.	Asteraceae	*Mata Khaish*	Herb	Endo-parasitic problems	Crushed uncooked roots are given orally to the young cattle to expel worms from the abdomen. It increases digestion and helps the young ones to graze fresh grass.
24	*Phaseolus lunatus Linn.*	Papilionaceae	*Mooth*	Climber	Goat Pox (Thandian)	Seeds (Mooth) are fed after boiling in water so that a blister should appear on the outer surface of the animal.
25	*Punica granatum L*	Lythraceae	*Darru*	Shrub/ tree	Nephritis	Other than the Alum (Phatkri), the outer fleshy part of the fruit of *Punica granatum* (locally known as Darru) is dried, ground, mixed in yogurt, and fed orally.
26	*Rheum webbianum* Royle	Polygonaceae	*Chootyal*	Herb	Indigestion, Constipation, and pain	Indigestion, Constipation, and pain
27	*Rhodiola himalensis* (D. Don.)S.H.Fu.	Crassulaceae	*Bugomasti*	Herb	Dewormer	Aerial parts are crushed and fed to the young cattle as dewormers.
28	Onion *[Allium cepa]*	Liliaceae	*Piaz*	Herb	Respiratory diseases, antibiotic, immunity booster, antipyretic	Bulb Mixed with either aromatic ginger, brown sugar, vegetable oil or garlic and give it to chickens with feed
29	*Rhodiola pinnatifid* Boiss.	Crassulaceae	*Bugomasti*	Herb	Dewormer	Aerial parts are crushed and given to the young cattle as dewormer
30	*Rhodiola sp*.	Crassulaceae	*Bugomasti*	Herb	Dewormer	Aerial parts are crushed and given to the young cattle as dewormer
31	*Rumex acetosa L.*	Polygonaceae	*Sufaid Hoola*	Herb	Cough, Indigestion, and Constipation	Cooked roots are used. Roots are buried under the fire in ash and used to expel retained placenta as a post-delivery complication and also on cough.
32	*Rumex nepalensis* Spreng.	Polygonaceae	*Hoola*	Herb	Cough, Indigestion, and Constipation Placenta expulsion	Cooked roots are Used. Roots are buried under the fire in ash and used to expel retained placenta as a post-delivery complication and also on cough. It is also used to cure dyspnea (Dhansna).
33	Garlic [*Allium sativum*]	Alliaceae	*Thoom*	Herb	Respiratory diseases, antibiotics, immunity booster	Bulbs Mixed with either aromatic ginger, brown sugar, or garlic and given with feed to chickens
34	*Saussurea lappa* (Dcne.) Sch. Costus (Falc. Lipsch.)	Asteraceae	*Kuth*	Herb	Dewormer	Crushed roots are given uncooked to the sheep and goats. The cattle start eating after the treatment.
35	*Sedum trullipetalum* HandT.	Crassulaceae	*Loonslooni*	Herb	Over dozed salt	The uncooked, mashed whole plant is given to the goats and sheep.

36	*Taraxacum laevigatum* (Willd.)DC	Asteraceae	*Hand*	Herb	Placenta expulsion	Mashed uncooked roots are given to cure the post-delivery complication.
37	Trigonella foenum- graecum Linn.	Fabaceae	*Sinji*	Herb	prolapse of uterus	Trigonella foenum-graecum (Maithi) is boiled and fed orally to the animals.
38	*Thymus linearis* Benth	Lamiaceae	*Ajwain/ Bun jamain*	Herb	Indigestion (Malla) and hemoglobinuria (Rut Mortrna)	The whole plant is decocted with milk, maize flour, and molasses and orally fed to the animals.
39	*Brassica campestris L*	Brassicaceae	*Sarson*	Herb	Manage	A sufficient quantity of seed oil mixed in an equal quantity of kerosene and applied topically.
40	*Urtica dioica* L.	Urticaceae	*Kairi*	Herb	Vesical palpation with irritation, causing plant	Urtica dioica (Kari), leaves are practiced, which irritates the birth canal, and eventually, the animal is set into a heat cycle called Repeat Breeding (Na Thairna).
41	Verbascum thapsus L.	Saxifragaceae	*Gadikan*	Herb	Injury	Leaves are cooked and given to the cattle.
42	*Viburnum cotinifolium* D.Don.	Caprifoliaceae	*Ukloon/ Guch*	Shrub	Constipation	Tips of the plants are collected while sprouting and are given uncooked orally to the horses and buffalos.
43	*Capparis decidua*	Capparaceae	*Kierra*		Gastrointestinal disorders, Antiparasite	The plant is burned, and then the burned twigs are ground to fine powder, mixed with whey, and given to animals for flatulence. To relieve ticks and mites, ash obtained from the wood of the the plant is mixed with one liter of water and administered topically.
44	*Viburnum grandiflorum* Wall. Ex DC.	Caprifoliaceae	*Ukloon/ Guch*	Herb	Constipation	Sprouting tips of the plants are collected, mashed, and given to the horses and buffalos uncooked.
45	*Zea mays* L.	Poaceae	*Makai (locally known as Linga da Malla)*	herb	Indigestion	Young plants of Maize (Makai) dried under shad are boiled, and the hot plant parts are tied on the backs of animals (cows and buffalos).

Source: (Rafique Khan et al., 2021), (Farooq et al., 2008), (Ndlovu et al., 2023), (Dilshad et al., 2008).

Advantages and Disadvantages of Ethnoveterinary Practices

The majority of farmers relied on EVPs to manage livestock ailments. As a source of contemporary medicine (drugs), EVPs have many benefits, including affordability, accessibility, local availability, cultural appropriateness and effectiveness, ease of animal metabolism of plants and plant extracts, and user-friendliness. EVPs have much to offer and can be an affordable and easily accessible substitute for expensive imported medications for both standard and more chronic ailments like colds, skin diseases, worms, wounds, reproductive disorders, nutritional deficiencies, and mild diarrhea. The knowledge of ethnoveterinary medicinal plants is widespread; much like other fields, it has been the subject of numerous studies, reports, conferences, and workshops (Menegesha A, 2020).

Although local homeopaths with experience and knowledge of traditional systems of treatment possess valuable traditional knowledge of ethno-veterinary practices, their knowledge is rapidly disappearing and needs to be documented. Traditional doctors keep their knowledge secret, making it less prone to manipulation and less available to the general public. A common belief is that traditional doctors are "given by God" and skilled in a particular field and that knowledge of traditional medicines is passed down orally from the father to his favorite child, typically a son, or obtained through various spiritual practices. Certain families and social groups guard the knowledge of traditional healing (Menegesha A, 2020).

Conclusion and Recommendations

Many livestock diseases, including diarrhea, endoparasitic issues, wounds, coccidiosis, respiratory illnesses, and reproductive disorders, can be controlled by herbs, medicinal plants, and traditional methods. The chapter demonstrated that rural farmers employ a range of herb species in addition to other traditional practices to treat livestock diseases. Traditional medicine provides an excellent alternative healthcare option, that is affordable for farmers, environmentally friendly, locally available, antimicrobial resistant, and has no drug residue with fewer side effects. Additionally, with more research, including lab testing, these herbs may be utilized to create less hazardous alternative conventional medications. Based on this conclusion, the following recommendations should be considered to advance the current directions and future perspective of ethnoveterinary practices in Pakistan. Attention must be paid to conserving these herbs and plants as urbanization, along with a lack of knowledge about these medicinal plants, plays a role in their extinction. The government should be careful in conserving the knowledge of EVPs, establish standards for it, train individuals, and disseminate the knowledge, as knowledge about the traditional medicinal system is limited to herders, farmers and elder community members. Ethnoveterinary knowledge is transmitted horizontally within the community, particularly among elderly individuals who typically have a robust social network, as well as vertically from parents and grandparents to offspring. The knowledge gaps observed between villages may be explained by weaker contacts between villages. Due to modernization, the younger generation is ignorant of this historical treasure and shows no interest in it. Farmers awareness of the preservation and correct use of ethnomedicinal plants is also crucial. It is essential to conduct phytochemical and pharmacological studies to identify the active ingredients and evaluate the botanical plants' ability to treat the intended veterinary illnesses in vitro or in vivo; Legislative procedures that support the use of ethno-veterinary medicine should be developed, as well as a national drug policy for herbal remedies.

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Chapter 31

Therapeutic Impacts of Traditional Chinese Medicine in Peripheral Neuropathies

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ABSTRACT

This chapter presents an insightful and in-depth discussion of Traditional Chinese Medicine, understanding the core concepts and theories involved under the umbrella notion of traditional Chinese Medicine and the versatility of its applications for various diseased conditions. The discussion further delves into the understanding of the disorders of peripheral neuropathy and their associated causes. Peripheral neuropathy is the collection of neurological disorders, including any peripheral nerve defect surrounding the whole body. The significance of peripheral neuropathy is demonstrated in this chapter by indulging in the associated etiology, signs and symptoms, and different forms of peripheral neuropathies affecting millions of people across the globe. While keeping in view the importance of peripheral neuropathy and understanding its mechanism to get better treatment overcomes, this discussion goes further towards the current pharmacological options utilized for this painful condition and the diverse side effects associated with these medications leading towards the application of Traditional Chinese Medicine for the treatment of Peripheral neuropathy. Among the vast therapeutic applications of Traditional Chinese Medicine, Peripheral neuropathy is one of the significant ones. Different practices of Traditional Chinese Medicine have been utilized for years to treat this condition, and its therapeutic significance has been highlighted by the underlying mechanism it has on peripheral neuropathy as it focuses on multiple targets rather than conventional pharmaceutical medications that focus on single targets.

KEYWORDS		
Neuropathies, Traditional Chinese Medicine, Peripheral neuropathy, Acupuncture, Moxibustion, Tuina	Received: 04-Jun-2024 Revised: 06-Jul-2024 Accepted: 09-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Traditional Chinese Medicine is regarded as a scientific, regulatory model that is the foundation for the systematic healthcare system created via clinical experience. In treating illnesses and improving health, TCM uses theories and methods. These include acupuncture, moxibustion, Chinese herbal medicine, dietetics, and other non-pharmacological therapies, including Tuina, in other words, known as manual therapy, and Qigong and Taijiquan, in other words, traditional monitoring practices (Wu et al., 2023). Cutting-edge analytical techniques are currently used to study TCM and other conventional medicines to determine their potential as medical treatments, social impact, and general medical applications. TCM is an invaluable resource for knowledge and research material in pharmaceutical diagnosis. When applied to clinical settings, TCM emphasizes patterns and uses several Western medical concepts to understand the sick state of the human body. TCM can cure diseases effectively. TCM offers a complex mechanism of action but also benefits from a dispersed application point, gradual effect, and relative safety as compared to targeted therapy (L. Guo et al., 2023).

A neurological disorder known as peripheral neuropathy affects the motor, sensory, and/or autonomic nerves. It is brought on by irregular and abnormal nerve function that can have a variety of causes. Diabetes, alcoholism, HIV, poisons, aberrant metabolism, vitamin deficiencies, and unfavorable medication side effects are among some of these causes (Maiese, 2023). In traditional Chinese medicine, peripheral neuropathy is interpreted as qi and blood stagnation in progress, damp deposits, or renal yin/yang insufficiency. This pattern can have excess and deficiency, further differentiated by the involved meridians. Addressing the underlying cause or disease may also be essential, as these are significant contributors to the developed neuropathy syndrome. While CNS depressants and other medications are used to treat neuropathy in Western medicine, there is much more to know about how traditional Chinese medicine treats this condition. Since physical therapy exercises and pain relief medications are part of the current Western medical treatment for neuropathy, the condition still has a slow rate of symptom relief (Ziegler, 2023).

The primary focus of traditional drug research is on one active ingredient. In addition to lowering local medication concentration, systemic administration can result in difficulties and unfavorable side effects. In contrast, given their safety and lack of adverse effects, natural substances are gaining more and more attention and deserve consideration (Michalova et al., 2023).

Because of their multiple practices, a wide range of aims and objectives, and universal notions, the practices of TCM have long been used in clinical settings for an extended period. Along with this, herbal medications and extracts from plants and natural resources have gained proficient demand and popularity, growing progressively in the field of pharmacology all over the world (W. Guo et al., 2024). TCM has proven effective for various functional disorders with complex etiologies and conditions containing nervous system pathologies. TCM has shown to be an effective and distinctive therapy for the treatment of peripheral neuropathy due to the attributes of minimal side effects and complications in comparison with commercial drugs (Song et al., 2023)**.** This chapter provides an in-depth understanding of TCM for managing peripheral neuropathies and an insightful discussion of its underlying mechanism.

Overview of Peripheral Neuropathy

Peripheral neuropathy is a set of nervous disorders in which the peripheral nerves are damaged. This condition can have many etiologies, resulting in broad categories of signs and symptoms that depend on the underlying etiology. Peripheral neuropathy is the result of damage to the nerves found outside the brain and spinal cord, i.e. peripheral nerves (donné Gnonlonfoun et al., 2023). The disease frequently results in discomfort, numbness, and weakness, generally in the hands and feet. Peripheral neuropathies are among the most prevalent neurological conditions, affecting around 20 million people in the US alone (C. Li et al., 2023). They are a widespread problem throughout the world. Worldwide, the prevalence of peripheral neuropathy is estimated to be 2.4%. That number increases to 5% to 7% for individuals aged 45 years and older (Kavanagh et al., 2024). Peripheral neuropathy can be inherited or acquired. Acquired peripheral neuropathy can be caused by the following (Sahu et al., 2024):

- Trauma, or bodily injury to a nerve
- The Tumor Growth
- Hazardous substances and toxins
- autoimmune reactions
- deficiencies in nutrition
- The Use of Alcohol
- Disorder of the vasculature and metabolism
- Trigeminal neuralgia, commonly referred to as tic douloureux, is a kind of acquired peripheral neuropathy characterized by episodic attacks of intense, lightning-like pain on one side of the face caused by injury to the trigeminal nerve, the central nerve supplying the head and face.
- A previous viral infection, pressure on the nerve from a tumor or enlarged blood vessel, or, rarely, multiple sclerosis are the causes in some instances. However, it is often impossible to pinpoint a precise cause. Idiopathic neuropathies are the term used by doctors to describe neuropathies that have no recognized cause.
- The most frequent way that a nerve is injured is by physical trauma. Damage or abrupt trauma resulting from:
  - Crashes of vehicles
  - Falling and slipping
  - Injuries associated with sports.
- Metabolic neuropathies are commonly caused by systemic diseases, which include numerous conditions that impact the entire body. Endocrine and metabolic conditions may be among them.
- One of the leading causes of peripheral neuropathy in the United States is diabetes mellitus, which is characterized by persistently high blood glucose levels. People with diabetes with mild to severe nervous system impairment make up 60% of the population. (Chang & Yang, 2023).
- Unusual, elevated blood levels of hazardous substances resulting from kidney problems have the potential to cause significant harm to nerve tissue.
- Neuropathies can also result from hormonal abnormalities that interfere with regular metabolic processes.
- Alcoholism and vitamin deficits can result in drastic damage to nerve tissue. Niacin and vitamins B1, B6, B12, and E are necessary for normal neuronal function.
- The oxygen supply to peripheral nerves can be reduced by vascular injury and blood disorders, which can swiftly cause significant harm or even nerve tissue death (Tokuçoğlu & Diniz, 2023).

Types of Peripheral neuropathy

Peripheral neuropathies have many different forms.

1. Peripheral neuropathies that are Inherited include (Ma et al., 2023):

a. Charcot-Marie-Tooth disease affects the arms, hands, legs, and feet, affecting both sensory and motor nerves (the nerves that signal a muscle to contract).

b. Friedreich ataxia is characterized by gradual nervous system impairment and difficulties with mobility.

c. A mutation in the GAN1 gene can result in Giant Axonal Neuropathy (GAN), which impairs mobility and sensation by causing the nerve cell's messenger fibers, or axons, to swell and eventually degrade. Due to its progressive nature, GAN gradually grows worse. In their second decade of life, most children with GAN will require a wheelchair, with the majority exhibiting symptoms before the age of five. A small number of GAN children live into their early adult years. At present, there exists neither a cure nor a treatment to halt the advancement of this uncommon disease.

2. The peripheral neuropathies discussed below are Acquired, which means that the individual acquires them throughout their lifetime rather than having them from birth. Among them are (Kraus, 2024):

a. One debilitating side effect of cancer treatment is Chemotherapy-induced Peripheral Neuropathy (CIPN).

b. The result of the immune system accidentally targeting the body's nerves is Guillain-Barré syndrome.

c. Diabetic neuropathy affects individuals with diabetes. It may impact movement patterns, how you perceive and interpret temperature changes, and how your body controls bodily processes like blood pressure and respiration.

d. When the immune system targets the myelin sheath, the protective layer covering nerves, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) results. Progressive weakness and diminished sensation in the arms and legs are among the signs and symptoms of CIDP.

e. Compression or squeezing of the lateral femoral cutaneous nerve, a sensory nerve that covers the thigh, results in Meralgia Paresthetica.

f. Individuals with the disease frequently observe a patch of skin in that location that is touch-sensitive, occasionally painful, numb, or tingling. People's condition usually improves as they reduce weight or wear looser clothes. Pain may be reduced by medications designed to treat neurogenic pain, such as antidepressants or seizure medications. Surgery may be necessary in certain instances when the pain is severe or persistent. With lifestyle modifications, the disease will typically get better or go away independently.

g. A rare immunological condition known as multifocal motor neuropathy causes a progressive weakening of the hands' muscles, with the muscles affected varying from side to side of the body (Siao & Kaku, 2019).

Symptoms of Peripheral neuropathy

Peripheral neuropathy symptoms are rarely fatal; however, they can vary from moderate to severe. The nature and extent of the injury and the kind of nerve fibers impacted determine the symptoms. The onset of symptoms may occur over days, weeks, or even years. There are situations when symptoms improve independently and don't need any treatment. Peripheral neuropathy can produce pain in many ways. Neuropathic pain can occasionally worsen at night, interfering with sleep. It may be brought on by spinal cord signal processing issues that might result in intense pain from a light touch that is ordinarily painless, or it may be caused by pain receptors activating randomly without any recognized reason. It's known as allodynia (Kim et al., 2022).

Neuropathy affecting the motor nerves can cause the following symptoms:

- Weakened Muscles.
- Painful cramps
- Fasciculations (uncontrollably twitching muscles visible beneath the skin)
- Muscle shrinkage (atrophy)
- Symptoms associated with neuropathy in the sensory nerves include:
- Pain and sensation of tingling.
- Failure to feel movement and touch, especially from the hands or feet.
- Loss of reflexes.
- The inability to sense position can cause a person to be unable to coordinate complex movements like walking, button-pressing, or maintaining balance when their eyes are closed.
- Inability to feel pain or temperature changes (due to damage to small fiber nerves).
- Excess or insufficient perspiration.
- Temperature intolerance.
- Failure to expand and contract the small blood vessels that regulate blood pressure.
- Digestive symptoms infrequently.
- In rare cases, difficulties swallowing or eating (if there is damage to the esophageal nerves) (Colvin & Dougherty, 2015).

The mechanism underlying Neuropathic Pain in Peripheral Neuropathy

Neural plasticity, which results in somatosensory and pain-sensitive neurons in the brain and central nervous system, as well as peripheral sensitization of primary sensory neurons in the dorsal root ganglia and trigeminal ganglia, is the cause of peripheral neuropathy. Peripheral and central sensitization result from neuroinflammation, defined by the infiltration of immune cells, glial cell stimulation, and the generation of inflammatory mediators, such as inflammatory cytokines and chemokines, inside the neurological systems. Tumor necrosis factor- (TNFα), interleukin-1β (IL-1β), and interleukin-6 (IL-6) are examples of inflammatory cytokines that can quickly alter the activity of neurotransmitter receptors, including gamma-aminobutyric acid, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, N-methyl-D-aspartate, glycine, and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors. They can also directly cause central sensitization. This causes increased excitatory synaptic transmission and decreased inhibitory synaptic transmission in the circuits responsible for spinal pain. An essential feature of neuroinflammation is glial cell activation. Because it triggers the production of growth factors, chemokines, and inflammatory cytokines, it is crucial for the onset and maintenance of peripheral neuropathy. One of the main pathogenic mechanisms of peripheral neuropathy has been identified as glial cell-mediated neuroinflammation (Pacifico et al., 2023).

According to recent studies, glial cells in the peripheral nervous system, including Schwann cells and satellite glial cells, and glial cells in the central nervous system, like microglia and astrocytes, are linked to neuroinflammation and the development of peripheral neuropathy. Damage to the peripheral nerve causes a localized inflammatory response, which triggers the growth of behavioral hypersensitivity (Finnerup et al., 2021). The earliest immune cells to react to damage to a peripheral nerve are Schwann cells. Numerous immune cells, including neutrophils, mast cells, macrophages, and T cells, are drawn to injured peripheral nerves. These cells both directly and indirectly activate the nociceptors by inducing the production of proinflammatory mediators. Proinflammatory mediators released by these cells both directly and indirectly stimulate nociceptors. Activated Schwann cells enhance the production of chemokines and cytokines associated with inflammation post-nerve injury through membrane channels and receptors by acting on the appropriate receptors on nerve fibers and neurons (Fiore et al., 2023). The pro-inflammatory mediators are significant in neurons' pain signaling and excitability. Stem cells stimulate the regulation of the regeneration of axons after nerve damage by generating neurotrophic factors such as nerve growth factor and ciliary neurotrophic factor. However, these neurotrophic agents may simultaneously elicit an inflammatory response. The DRG contains neurons, immune cells, vascular endothelial cells, and satellite glial cells. Gap junctions directly connect satellite glial cells to the cell bodies of primary sensory neurons, encircling them intimately. Upon nerve damage, activated satellite glial cells proliferate. Satellite glial cells cause inflammation using purinergic receptors on their membranes(Davies et al., 2020). Adenosine triphosphate (ATP) is the activator of P2 receptors, which are further divided into G protein-coupled metabotropic P2Y receptors (P2YRs) and ionotropic P2X receptors (P2XRs)(Yang et al., 2023). Purinergic receptor expression on satellite glial cells is elevated due to inflammation and peripheral nerve injury. This encourages the production of inflammatory cytokines and the activation of satellite glial cells. Eventually, inflammatory mediators increase neuronal excitability by altering the expression of proteins, ion channels, and receptors in neurons. This exacerbates nerve damage by increasing pain signaling. For instance, pro-inflammatory cytokines TNF-α and IL-1β raise pain by causing an increase in sodium channel activity, which in turn causes an increase in neurons firing ectopically (Ameenudeen & Srinivasan, 2023).

Satellite glial cells express receptors in response to nerve damage, and inhibiting these receptors reduces inflammatory cytokines' release, reducing neuronal excitability. P2 × 7R also contributes to inflammation by regulating transient receptor potential vanilloid 1 (TRPV1). Furthermore, peripheral inflammation and nerve damage may aggravate TRPA1 action in satellite glial cells, resulting in inflammatory and neuropathic pain. Because ATP is produced by both the activation of satellite glial cells and the excitation of primary sensory neurons, purinergic transmission mediates the connection between satellite glial cells and neurons in the DRG after nerve damage. Peripheral neuropathy has been linked to increased expression of P2X4 receptors in microglia. It has been shown that P2 purine receptors, such as P2X3, P2X2/3, P2X4, P2X7, P2Y1, P2Y2, P2Y6, and P2Y12, are involved in neuropathic pain (Madaan et al., 2022). One potential NPP mediator is ATP produced by astrocytes and the spinal dorsal root ganglion (DRG). In spinal cord DRG and nodose ganglion neurons, P2X3 and P2X2/3 receptors are highly expressed. The P2X3 and P2X2/3 receptors of peripheral primary sensory nerve fibers may be the trigger point of Peripheral neuropathy, as the released ATP activates them following tissue damage. Microglia are the primary source of expression for P2X4 receptors. The dorsal horn and spinal DRG microglia both have highly expressed P2X7 receptors (Rawish & Langer, 2022).

Diagnosis and Treatment of Peripheral Neuropathies

Peripheral neuropathy is often identified based on the patient's history (i.e., symptoms), examination results that support the involvement of nerve fiber types, and results from ancillary techniques such as blood tests, nerve conduction studies, and electromyography. Blood testing can indicate uncontrolled immune system activity, infections, diabetes, vitamin deficiencies, liver or kidney malfunction, and other metabolism disorders. The presence of atypical immune cells or proteins in CSF fluids is less frequently examined. NCS measures signal strength and speed along significant motor and sensory neurons. They can assist in detecting damage to the nerves and determine if the symptoms are brought on by myelin sheath or axon disease (Lamotte & Sandroni, 2022).

Currently, available treatments for PN include both medications for CNS depression and analgesics. Some antidepressants, such as tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors, and some anticonvulsants, such as gabapentin and pregabalin, along with topical lidocaine, are advised as first-line treatments for Peripheral neuropathy based on randomized clinical trials. Tramadol and opioid analgesics are recommended as second-line treatments. Nonetheless, tramadol is suggested as a second-line treatment, and they are occasionally used as opioid analgesics (De Souza et al., 2023). They do, however, occasionally serve as first-choice medications. However, due to ineffectiveness or the possibility of intolerable side effects (such as drowsiness, fainting, oedema, and ataxia), those treatments only provide moderate relief. Even with the use of recommended drugs for their disease, patients with Peripheral neuropathy typically experience relatively intense pain. Moreover, the clinical use of Peripheral neuropathy pharmacotherapy is severely constrained by the potential for tolerance development as well as the hazards of addiction and misuse. There is currently no known medication that can reverse Peripheral neuropathy. It would, therefore, be advantageous to find new therapy options that are both highly effective and have little side effects. Herbal formulations have received increased attention recently in the realm of drug development, particularly those involving medicinal plants and herbal extracts from traditional Chinese medicine (TCM), which is becoming more and more popular around the globe. Compared to synthetic medications, TCM has fewer side effects and hazardous consequences, making it a unique tool for the clinical prevention and treatment of Peripheral neuropathy. Furthermore, TCM's multiple elements and goals transcend the drawbacks of clinical medications that focus on a single pathway. According to several studies, natural products may be a useful source of novel specialized molecules required for the management of illnesses associated with pain via controlling P2 receptors (W. Guo et al., 2024).

Introduction to Traditional Chinese Medicine

A vast range of speculative practices, principles, treatment protocols, and methods evolving and expanding with the time of more than 2000 years is somewhat known as Traditional Chinese Medicine. The history of traditional Chinese medicine can be used to trace the historical origins of acupuncture, Chinese herbal medicine, moxibustion, massage, bleeding, and cupping. China has used TCM and its related practice system for hundreds of years to treat and manage various medical conditions. Standard TCM practice generally uses a range of combinations of herbs, animal products, and minerals, together referred to as TCM formulations. One single active ingredient from a single plant, artemisinin (Artemisia annua), is an example. However, employing chemically uncharacterized formulations can make standardizing and carrying out repeatable research and clinical studies complex. The widespread use of TCM and other traditional medicines in monopharmacy-centered modern medical treatment settings has become increasingly challenging as a result. The application of recent approaches such as global systems biology and metabolomics to address these problems has significantly advanced the understanding of the physiological mechanisms and molecular constituents of TCM efficacy. Traditional Chinese Medicine and other relative protocols of classical, conventional treatment methods are investigated and evaluated to examine their capacity as therapeutic methods through advanced analytical techniques. This practice of TCM has provided beneficial and advantageous methods in the pharmacognosy domain (Fang et al., 2023). The two principal frameworks of Traditional Chinese Medicine norms and beliefs are the Five Phases framework and the theory of yin and yang. The chief practices involved in TCM include using Chinese herbal medicine, Acupuncture, Moxibustion, and Tai Chi, commonly referred to as Tuina. They also describe the activity of effects and functional powers involved in body function, such as the qi, the impact of active and resting fluids, or Jin ye, and the differential diagnosis of syndromes. According to ancient Chinese medicine, all things are composed of the same substance or qi. This ideology, which holds that everything that exists is symbiotically connected through the qi system, stands for harmony and wholeness as parts of the same paradigm. To live in harmony with the surrounding qi and balance the effects of the body's qi, also referred to as the Vital Force in the West, is one of the fundamental objectives of TCM. Ancient Chinese culture defined this as encompassing the energies of Earth, which include the energy of the land, the sun, moon, planets, and constellations, as well as the energies of Heaven, which include the impacts of location, the energy of the plants, soil, water, animals, and natural forms (Zhang & Li, 2021).

Theories of Traditional Chinese Medicine

A core concept in TCM philosophy is yin yang. These phrases in the Chinese language and culture indicate functional relationships and have many metaphorical interpretations. Examples of yang include hot, male, heaven, fire, strong, light, day, summer, active, and external. Examples of yin are typically cold, female, earth, water, weak, dark, night, winter, passive, and interior. In Chinese, Zang-fu refers to a generalization of how the human body functions and the anatomical components of the internal organs. The internal organs are divided into two groups in TCM, usually paired in yin-yang pairs per phase: Zang or solid organs, which are regarded as yin organs (liver, spleen, kidney, lung, and heart), and fu or hollow organs, which are considered as yang organs (small intestine and triple burner, stomach, large intestine, and bladder) (L. Guo et al., 2023).

The Five-element theory proposes that Earth, Metal, Fire, Water, and Wood are the five elements of Chinese medicine, and the body's organs symbolize them. According to the Zang-Fu Theory, these organs are yin and yang because they store energy and nutrients for the body. Traditional Chinese Medicine (TCM) employs the Five Elements Theory in various ways, and the systems of correspondences it suggests are linked to a broad spectrum of distinct nature and human physiological experiences and aspects. This correspondence includes tissues, organs, directions, colors, seasons, tastes, and climates. The following is a conceptual description of the functional activities associated with each Phase (Aplin-Houtz et al., 2023):

Wood represents potential creation; Fire represents potential transformation into function; Metal represents the rhythmical distribution of energy and a relative energy shortage; Water represents regeneration; and Earth promotes evolution and transformation. The primary mechanisms underlying these behaviors are associated with the total activity of the vegetative system, which is governed by neural pathways and transmitters. During the yang phases, sympathetic functions are more active. The parasympathetic (vagal) nervous system is comparatively more active during the yin phases (Mangan, 2023).

Traditional Chinese Medicine Treatments

Dietetics and Chinese Herbal Medicine

This area of TCM focuses on how foods and herbs can benefit the body. Among complementary and alternative medicine (CAM), the most popular therapy is herbal treatment, with many herbs utilized from traditional Chinese medicine. In Western society, CAM is becoming more and more popular and exciting. The prevalence of complementary and alternative medicine (CAM) in every nation appears to be correlated with socioeconomic, demographic, and health factors (von Schoen-Angerer et al., 2023). The study of Chinese herbal medicine is an intricate and broad area. Herbal medicine depends on the combined effects of all the ingredients in an herb or decoction, whereas Western medicine aims to isolate a single active element. Numerous effects, including anti-inflammatory, antioxidant, antipyretic, antidepressant, antibacterial, blood vessel wall relaxation, skeletal muscle relaxation, and anticonvulsant action, are possible with these combinations (Chen et al., 2023).

Acupuncture

The core concept of acupuncture, or Zhen, is the precise incorporation and management of needles of numerous lengths plus diameters into the skin at predefined acupoints. Acupuncture points are a mixture of blood, lymph, and several nerve types found inside a layer of loose connective tissue (mesenchyme) that punctures the superficial fascia, separating subcutaneous tissue from muscle. Acupuncture treatment can benefit many health conditions (Sun et al., 2023). The most widely recognized use of acupuncture is for the management of bodily pain. There is further evidence that acupuncture may help prevent headaches, migraines, allergic rhinitis, osteoarthritis in the knee, chemotherapy-induced nausea and vomiting, nausea and vomiting following surgery, and postoperative pain. (Zhang & Li, 2021).

Moxibustion

Lighting a Chinese mugwort (Artemisia vulgaris or argyi) tinder near or on top of a locus is the moxibustion method, sometimes called jiu. Nowadays, people in the West call artemisia tinder moxa, a word whose derivation comes from Japanese and means herb for burning. In traditional moxibustion, the tinder is shaped like a cone and applied to the skin in precise locations like acupuncture points. It can be used as a less aggressive heat treatment or as a counterirritant by blistering and scarring the skin when applied topically with a layer of salt or vegetable material between the skin and the cone. Another method is to cover and burn a needle that has been inserted into the body. Another method combines acupuncture with moxibustion by wrapping an implanted needle with a piece of moxa after it has been burned. Thus, the needle helps to transport the heat from the moxa to the surrounding tissues. Moxibustion creates antipyretic and thermolytic effects by activating polymodal receptors in the skin at zones that correspond to acupoints (Du et al., 2024).

Cupping

Another traditional method frequently employed in TCM is cupping. This method eliminates pathogenic elements from the body, such as wind, dampness, and cold. It also heals injuries or aching muscles caused by qi's stagnation. It helps with various lower back, shoulder, and leg pain conditions. On the other hand, it has also been documented to be an effective intervention in routine and emergency cases, including zoster, angina pectoris, acute asthma attacks, and poisoning-related abdomen discomfort (W. Li et al., 2024). Cupping is utilized to soothe swelling and torment in sprains and constrain stagnant blood from severe bruises by bloodletting. The systemic sensations of warmth and unwinding that are regularly experienced after cupping may be associated with the brain's expanded generation of endogenous opioids, which in turn leads to way better pain management(Lai et al., 2023).

What Is the TCM Perspective on Peripheral Neuropathy?

Peripheral neuropathy is treated by Traditional Chinese Medicine (TCM) through the focal points of blood circulation and the Qi (vital energy) stream within the body. TCM states that neuropathy is created when Qi and Blood don't adequately feed the appendages regularly because of essential lopsided characteristics or obstacles.

To viably create treatment strategies, the TCM approach places a solid accentuation on distinguishing the precise cause of disharmony, whether it be Qi and Blood Stagnation or the intrusion of remote pathogens like Wind, Cold, or Clamminess (Jing et al., 2024).

Blockages or Deficiencies that impair blood flow are frequently held responsible in TCM for peripheral neuropathy. Blood Stagnation and Wind-Damp Invasion are the two main patterns. Numbness and tingling sensations related to peripheral neuropathy are relevant to the wind-damp invasion, which results in muscle and joint pain. Blood stagnation causes lethargy and weakness due to obstructing and hindering the nutrient and energy flow. The practitioners can work better towards the objective of treating peripheral neuropathy by focusing more closely on these underlying mechanisms and patterns (Bo et al., 2012).

Applications of TCM Practices for Peripheral Neuropathy

Herbal Formulas from TCM for Peripheral Neuropathy

TCM practitioners can prescribe and recommend various formulae based on the underlying mechanisms and patterns diagnosed. Kusnezoffii aconite is suggested when the pathways are hindered by external factors such as wind, cold, and moisture. This herbal medicine is added to Xiao Huo Luo Dan, which heats the pathways and drags out the damaging energies (Nyirimigabo et al., 2015).

Regarding Blood Stagnation, Shen Tong Zhu Yu Tang with Peach Kernels improves blood flow and reduces discomfort. Shu Jing Huo Xue Tang also addresses the root causes of neuropathic pain and weakness by stimulating blood flow and removing dampness with Dong Quai. These recipes, which seek to enhance nerve function and restore equilibrium, are prime examples of TCM's holistic approach (Me and Qi, 2024).

Acupuncture for Peripheral Neuropathy

Neuropathic pain caused by peripheral neuropathy results from damage or any inconvenience to the nerves in the somatosensory nerve system. The median nerve, which extends from the forearm into the hand, can become compressed or inflamed at the wrist, resulting in carpal tunnel syndrome, a painful and incapacitating disorder that affects the hands (Pei et al., 2023). Acupuncture's potential benefits in treating carpal tunnel syndrome symptoms are documented in the literature (He et al., 2023)Various authors suggest that acupuncture may have benefits comparable to or superior to conventional treatment. Nerve conduction studies (NCS) may be a beneficial method for evaluating the quantifiable changes in nerves following acupuncture. (Chan et al., 2019) Evaluated the electrophysiological characteristics of the ulnar nerve and examined the effect of acupuncture and moxibustion by concluding that the stimulation on HT4 resulted in heightened latency and a significant increase in the reaction velocity during the continuous electric stimulations in which the stimulus intensity was reduced and the sensitivity as increased for achievement of maximum amplitude. (Meyer-Hamme et al., 2021) used the same assessment approach to discover that classical needle acupuncture significantly improved diabetic peripheral neuropathy (DPN) in patients with type 2 diabetes. Improvements in NCS values were also found to indicate structural neurodegeneration after acupuncture.

Conclusion

In a nutshell, this chapter highlights the in-depth understanding of peripheral neuropathy, which is described as a set of neurological disorders affecting the peripheral nerves and is amongst the most prevalent conditions in various parts of the world, affecting millions of people around the globe. This discussion further addresses the underlying cause or disease that may also be essential to examine the significant contributors to the developed neuropathy syndrome. While CNS depressants and other medications are used to treat neuropathy in Western medicine, there is much more to know about how traditional Chinese medicine treats this condition. Due to this, most of the individuals dealing with this neuropathy condition are moving towards the practices and therapies of traditional Chinese Medicine. The main reason behind this shift of the Western world from pharmaceutical and synthetic drug treatment towards Traditional Chinese Medicine is that conventional drug research primarily focuses on one active ingredient. In addition to lowering local medication concentration, systemic administration can result in difficulties and unfavorable side effects. In contrast, TCM practices have multiple complex targets, a wide range of aims and objectives, and universal notions and have long been used in clinical settings for an extended period. Unlike conventional analgesics, which focus on just one pathway, TCMs utilize a variety of components and targets, which can significantly increase therapy efficacy and help predict the dangers of Peripheral neuropathy. P2 receptors, notably P2X3, P2X4, P2X7, and P2Y12 receptors, which are particularly important for starting and maintaining neuropathic pain, are attractive potential targets for Peripheral neuropathy therapies. To reduce side effects and gain new insights into the pathogenic process of Peripheral neuropathy, research on the P2 receptor and related pharmacology may be beneficial. Due to TCM's multiple applications and distinct characteristics, combining TCM with Western medicine may enhance its ability to treat a wide range of diseases. Second, a possible area of concentration to pursue further TCM research is the prevention of diseases.

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Chapter 32

Treatment of Arthritis by Using Acupuncture

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ABSTRACT

Arthritis is a disease that can cause damage to the bone. More than a hundred different types of arthritis have been documented to date. The most common types of arthritis are Osteoarthritis and Rheumatoid arthritis. The signs and symptoms of arthritis include pain, swelling of the joints leading to debility, etc. Pharmacological medicines, including non-steroidal anti-inflammatory drugs, Opioids and disease-modifying anti-rheumatic agents, are commonly prescribed by clinicians for the procurement of arthritis. However, the long-term use of these medicines is associated with several side effects, including peptic ulcers, cardiovascular and gastrointestinal toxicities, etc. Acupuncture, a part of traditional Chinese medicine, helps treat pain associated with different diseases. It has been shown to reduce the signs and symptoms of arthritis. This book chapter explores the effect of acupuncture as a treatment for arthritis and the possible mechanism by which acupuncture reduces the pain associated with arthritis.

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INTRODUCTION

Arthritis can be defined as a disease that causes damage to joints. Up-to-date, hundreds of different types of arthritis have been recognized. They are further classified into non-inflammatory arthritis, including Osteoarthritis (OA); arthritis by an autoimmune process, including Rheumatoid arthritis (RA); arthritis due to deposition of crystals, including gout, pseudo gout and calcium phosphate disease, etc. (Radu and Bungau, 2021). OA, known as wear and tear arthritis, is the most prevalent type, particularly in East Asian countries (Shi et al., 2008). It is a prevalent degenerative condition of the articular cartilage characterized by hypertrophic bone change (bone hypertrophy) and osteophyte formation (Sinusas, 2012). Genetics, feminine sex, prior trauma, old age, mainly above 60 years, and obesity are some of the risk factors of OA. Pharmacological approaches for the treatment of OA include NSAIDs, corticosteroids, acetaminophen, opioids and hyaluronic acid (Manek and Lane, 2000). On the other hand, RA is a complex autoimmune disease with an unclear etiology that primarily affects the joints but can also show extra-articular manifestation, such as when it can affect connective tissue. 1% of the global population suffers from RA. The gradual start of symptoms is a common characteristic of RA; however, the disease steadily worsens over time. Though the immunological processes in the synovium and synovial fluid have been documented, the cause of RA symptoms remains unknown. Pathophysiology of RA includes synovial hyperplasia, synovial infection, genetics, impaired gut microbiota, environmental factors like pollutants, etc. However, the exact etiology remains unclear (Damerau and Gaber, 2020). Treatment options for RA include glucocorticoids, NSAIDs, opioids and disease-modifying management (DMRDs).

The long-term use of NSAIDs, which are selective cyclooxygenase (COX and COX-2) inhibitors, is associated with several Side effects, including cardiac failure, gastrointestinal toxicity and ulceration, rashes and dizziness. (Moura et al., 2018).. There are a limited number of studies which show the efficacy and safety of NSAIDs for the treatment of RA. On the other side, long-term use of opioids can lead to tolerance, less pain relief and opioid-induced bowel dysfunction (OIBD). Various complementary and alternative treatments for the reduction of pain associated with arthritis have been studied. A widely studied treatment option for OA (Zhu et al., 2020) and RA (Casimiro et al., 2005) is acupuncture.

The oldest Chinese medical technique, acupuncture, has been utilized to treat Arthritis and various pain disorders. It has shown to be quite effective at reducing pain, with minimal side effects. Numerous studies have examined the general pain-relieving effects of acupuncture, and it is reported that these effects are primarily achieved by controlling the levels of serotonin, endogenous opioids and norepinephrine as well as by blocking inflammatory cytokines, peripheral nociceptors, and CNS activation (Lee et al., 2019). Acupuncture can reduce visceral hypersensitivity, Enteric nervous system (ENS) activation (Hu et al., 2015) and brain-gut axis modulation (Li et al., 2015). Acupuncture is the process in which acupoints are stimulated by inserting tiny needles and manipulated through manual, electrical or other stimulations. The practice of electroacupuncture (EA), in which the needles are attached to an electrical stimulator that sends high-frequency or low-frequency impulses, or a combination of both, was developed in the 1950s. EA has been standardized regarding electrical stimulation frequency, voltage, waveform, and duration. Nevertheless, in most clinical investigations, MA is regarded as the standard therapy. This book chapter explores the effect of acupuncture as a treatment for arthritis and its possible mechanism.

Types of Arthritis

Arthritis is a generalized term for pain and swelling in the joints. The following are some of the types of arthritis.

Rheumatoid Arthritis

It is the most prevalent type of inflammatory arthritis, causing damage to bones and cartilage and leading to disability. It affects primarily joints, but some systems, like the pulmonary system, are also affected. Other extra-auricular effects of RA include vacuities, RA nodules, and systemic diseases. (Smolen et al., 2016). The manifestation of RA can be categorized in a number of ways, but often, the Disease develops slowly over several months before a definitive diagnosis can be made.

Epidemiology

1% of the global population is affected by RA, with a 2:15 ratio of males to females affected. While the disease can affect anyone at any age, people between the ages of 40 and 70 are most likely to get it, with the prevalence rising with age. Rheumatoid arthritis is found throughout the world; however, it is exceptionally uncommon in rural Africa and more common in several Native American tribes (the Chippewa and Pima). The prevalence of rheumatoid arthritis and socioeconomic status do not appear to be significantly correlated (Lee and Weinblatt, 2001).

Sign and Symptoms

The signs and symptoms of RA are variable, ranging from mild to severe. It includes swelling of joints, pain which starts early in the morning and generally lasts after an hour, synovial hypertrophy, deformity and fatigue. Pain is most commonly present in distal parts of joints rather than proximal and in PIP, ankle and wrist rather than shoulder, ankle and knee (Lee et al., 2001).

Diagnosis

The success of treatment depends upon early diagnosis, especially for patients with known risk factors for poor outcomes, including high disease activity, the presence of autoantibodies, and early joint injury. Patient history, Genetics, X-rays, CT scan, and Magnetic resonance imaging (MRI) can be done to properly diagnose and confirm synovial hypertrophy and RA.

Pathophysiology

- Genetics

Studies suggest genetics are responsible for about 60% of the population affected with RA.

- Histology

The pathogenesis of RA primarily depends upon an inflamed synovium. In this area, there is angiogenesis (formation of new blood vessels), hyperplasia, and the presence and recurrence of inflammatory leucocytes. Inflammatory cytokines (TNF-α, IL-1, IL-6) are significant histological features.

- Injury

Any injury to the joint, specifically in the elder patients, may lead to the onset of RA.

Osteoarthritis

OA is one of the most prevalent, chronic and degenerative types of arthritis, characterized by complex disorders of the entire synovial joint. It primarily affects joints and tissues and then gradually causes damage to articular cartilage. About 500 million of the global population is affected by OA, and it is believed to be the fourth major cause of disability with a significant cost of prolonged treatment(Yao et al., 2023).

Pathogenesis

- Altered structure of collagen and proteoglycan
- Meniscal structure degeneration
- Erosion of the articular cartilage
- Rush of Inflammatory cytokines and other mediator to the area
- This leads to a change in the synovial tissue and subchondral bone

- Bone sclerosis
- Synovial membrane thickness increased
- In the cartilage surface, gaps are produced

Sign and Symptoms
- Joint pain
- Joint stiffness
- Joint instability
- Bone change and joint deformity
- Muscle atrophy

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis is not a disease itself; it is a broad term used to refer to any arthritis that develops before age sixteen, lasts longer than six weeks, and has an unknown etiology. As such, the term refers to an exclusion diagnosis that covers all types of childhood chronic arthritis without a known cause (Ravelli and Martini, 2007).
Following are some of the sub-classifications of juvenile idiopathic arthritis

Systemic Arthritis

This subtype is quite different from other types due to its clinical features. It arises in boys and girls without a known age of onset, and the onset is little to rare in adults. The signs and symptoms include arthritis accompanied by fever for at least two weeks, abdominal pain, hepatomegaly and lymphadenopathy, and rashes on the skin. These signs may be severe when the temperature is high.

Oligoarthritis

It is a type of arthritis that can affect four or less than four joints during the first six months after the onset of the disease. The signs and symptoms include onset before six years of age, asymmetric arthritis, and the patient may develop a high risk of susceptibility to iridocyclitis. It occurs mainly in the legs, affecting the knee and ankle.

Other rare types of juvenile idiopathic arthritis include polyarthritis, enthesitis-related arthritis, psoriatic arthritis and undifferentiated arthritis.

Pharmacological Treatment of Arthritis

Treatment for arthritis includes non-steroidal anti-inflammatory drugs (NSAID), opioids glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs).

DMARDs

These are a class of drugs which reduce the progression of structural damage to the joints. The NSAIDs are not included in this class as they don’t have the effect of reducing structural damage.

DMARDs are further classified into two main groups, synthetic and biological, of which the synthetic has two types, i.e. conventional synthetic and targeted synthetic. The mechanism of action of traditional synthetic DMARDs is mainly unknown; in contrast, targeted DMARDs are produced to modify a specific target responsible for joint inflammation. Examples of targeted DMARDs include inhibitors of Janus kinase (tofacitinib and baricitinib) (Smolen et al., 2016)The recommended initial treatment for arthritis is glucocorticoids combined with conventional synthetic DMARDs like methotrexate. Some of the conventional synthetic DMARDs include sulfasalazine, leflunomide, and hydroxychloroquine.

Biological DMARDs are another class of drugs with different mechanisms of action, including TNF inhibitors (infliximab, adalimumab), inhibitors of IL-6 receptors (tocilizumab, sarilumab), co-stimulation blockers of T-cells (abatacept), and B-cell depletion (rituximab).

Side Effects of Pharmacological Treatment

There are several risk factors associated with the long-term use of NSAIDs, which are the inhibitors of COX-1 and COX-2, including cardiovascular and gastrointestinal toxicities, peptic ulcers, and incomplete pain alleviation. The reported side effects of opioids include tolerance, less pain alleviation and opioid-induced bowel dysfunction (OIBD). The side effects of conventional synthetic DMARDs are less than those of biological or targeted synthetic DMARDs. The side effects of DMARDs include gastrointestinal toxicity, an increase in the incidence of infections, tuberculosis reactivation and multiple sclerosis. This therapy is not recommended for patients who have recovered from a malignant condition within five years.

Due to the potential side effects of the drugs for the procurement of arthritis, complementary and alternative medicine (CAM) is gaining popularity among people with arthritis. Research indicates that a significant number of the population with arthritis use CAM in addition to traditional therapies like prescription drugs to manage their condition. This includes Ayurveda, yoga, herbal medicine, chiropractor, topical rubbing ointment and acupuncture. According to a study published in the National Library of Medicine, 90% of people with arthritis had used at least one type of CAM (Callahan et al., 2009). Another popular therapy for pain associated with arthritis is acupuncture.

Acupuncture

One of the oldest traditional Chinese medicines, acupuncture, has been used for over 3000 years to treat humans and animals. Acupuncture is often used for pain relief. Stress reduction is one aspect of total wellness that is being used increasingly. Acupuncture is described in traditional Chinese medicine as a tool to control the flow of qi, or chi, or chee, which is believed to move through your body along meridian routes. Acupuncture is the process in which acupoints are stimulated by inserting tiny needles and manipulated through manual, electrical or other stimulations. Acupuncturists think your energy flow can be balanced again by putting needles at specific points along these meridians. In contrast, many Western practitioners believe acupuncture needles are places where muscles, connective tissue, and nerves can be activated. For thousands of years, acupuncture has been used for the treatment of BI diseases. Under the theory of Chinese traditional medicine, RA is included in Bi or impediment disease. Many studies evaluated the effect of acupuncture as a treatment option for RA, OA and other types of arthritis. 30-60% of the patients suffering from RA use CAM as a treatment option. There has been an increase in the use of acupuncture in adult patients of RA from 1.2% to 1.5%. 41% of the patients suffering from RA use CAM in Israel, and in Korea, 51% of the new RA patients selected acupuncture for the treatment (Han et al., 2015).

Mechanism of Acupuncture

The exact mechanism of acupuncture is still unknown, but scientists have proposed several mechanisms for alleviating arthritis pain. These proposed mechanisms include an anti-inflammatory effect, immune function regulation, and antioxidant effect. The most explored mechanism is the Anti-inflammatory mechanism.

Anti-inflammatory Effect

Pain can be divided into two types based on its etiology. The first is inflammation or nociception, which occurs due to tissue injury, and the second is neuropathy, which occurs when nerves are damaged. Nociceptors' activation causes pain due to tissue injury, whereas neuropathy is caused by a dysfunction or a primary lesion in the nervous system. Inflammation has been thought to play a vital role in the pathophysiology of both types of pain. Exposure to inflammatory mediators, such as cytokines and chemokines, increases the excitability of sensory terminals and neurons, leading to increased pain sensitivity. Immune cells communicate through cytokines to maintain bodily homeostasis. Arthritis chronic pathogenesis involves activating immune cells, including innate, such as mast cells and macrophages; adaptive, such as T and B cells; and body cells, like endothelial cells etc. Cytokines released by these cells, including IL-6, IL-1β, TNF-α, IL-13, IL-4, and IL-10, play a crucial role in regulating inflammation and disease progression in arthritis (Xu et al., 2018). Many studies show that acupuncture alleviates pain by controlling the release of these cytokines. After acupuncture application, it was shown that the levels of these cytokines come to an average level that had previously increased during inflammation. Many studies show that acupuncture inhibits peripheral inflammation by expressing c-fos at the spinal level. Many spinal opioids, cytokines and serotonin are involved in acupuncture's antinociceptive effect as acupuncture decreases pain stimuli's input into the spinal cord with the help of these. These substances, including norepinephrine, dampen the activity of n-methyl d-aspartate receptors (NMDAR), thus inhibiting the input of nociceptive stimuli into the spinal cord and thus inhibiting pain (Zhang et al., 1996). During acute pain, acupuncture increases spinal opioids via μ-, δ-, and κ-opioid receptors, thus inhibiting pain. Acupuncture has been shown to increase spinal norepinephrine, decreasing glutamate release and reducing anti-NMDA receptor 1 (GluN1) phosphorylation, leading to pain relief. Furthermore, electro-acupuncture increased PWL, significantly reduced CFA-induced microglia activation, and controlled the up-regulation of TNF-α, IL-1β, and IL-6 in the spinal cord, preventing NMDARs from transmitting pain signals. According to reports on the supraspinal mechanism, acupuncture activates μ-opioid receptors in gamma amino butyric acid (GABA) energy neurons, which in turn suppresses GABA release in the rostral ventromedial medulla (RVM), hence causing the release of endogenous endorphins. Furthermore, electroacupuncture has been shown to reduce pain by inhibiting melanocortin four receptors, which attenuate IL1β and IL-1 receptor activation in the periaqueductal grey (Xu et al., 2018). Acupuncture has been shown to inhibit the nociceptive stimuli at local, peripheral and central levels.

Conclusion

Acupuncture is one of the oldest parts of traditional Chinese medicine, and it has been used widely to treat pain associated with different diseases. In this chapter, we explored arthritis, types of arthritis, signs and symptoms and the pharmacological approach for the treatment of arthritis. We also documented the potential side effects of pharmacological drugs for treating arthritis. We explored the impact of acupuncture on patients suffering from the debilitating disease of arthritis. We documented the mechanism of acupuncture for relieving the pain associated with arthritis. The published data has been revised, and we have concluded that acupuncture can be used as a sole or adjuvant therapy for treating arthritis.

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Chapter 33

Utility of Biomarkers in Traditional Medicine

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ABSTRACT

Biomarkers are significant part of traditional medicine playing vital role for a very long time in health maintenance, diagnosis, prevention and therapy. Alteration in their concentrations, intensities or nature characterizes the incidence, state and prognosis assessing therapy response. Development of biomarkers is a complex and extensive process with several steps including detection of an entrant biomarker, qualification of biomarkers, verification of biomarkers, research assay optimization, validation of biomarkers and commercialization. The omics- approaches have significantly enabled recognizing potential biomarkers. Validation is a significant process that evaluates performance and safety of a test, tool, or instrument. Clinical utility of biomarker is substantial for their productive clinical use to avoid downsides while usage. This chapter will bring significance of biomarkers in terms of utility in traditional medicine into light. Process of development of biomarkers, their clinical utility and potential challenges along with latest advancements in traditional medicine will be reviewed in this chapter.

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INTRODUCTION

A biomarker can be described as "a characteristic that is measured as a marker of normal biological processes, pathogenic processes, or responses to an exposure or intervention including therapeutic interventions. This can include molecular, histological, radiographic, or physiologic characteristics" (Babrak et al., 2019; FDA-NIH, 2021). Biomarker are naturally occurring biological structures or characteristic expressions generated by or in response of abnormal changes that can be detected in tissues and body fluids. Biomarkers can be constant or dynamic and are an essential fragment of biomedical studies and traditional clinical practice. Traditional medicine, including traditional Chinese, Korean, African or Iranian medicine, Ayurveda, Unani, medieval Islamic medicine, herbalism, ethnomedicine, ethnobotany etc., has an extensive history of harnessing therapeutic potential of herbs, spices, animal byproducts, minerals, other natural elements or compounds and other traditional rituals utilizing a combination of the information, skills and practices in various cultures grounded on the native theories, beliefs, opinions, views and experiences for diagnosis, prevention and therapy of physical or psychological ailments (Bhargavi et al., 2021). Biomarkers typically comprehended as quantifiable indicators of biological conditions and have grown significant grip in modern medicine. Nevertheless, their utility in traditional medicine is significantly developing interest for exploration. Previously disease diagnosis was mainly depended upon clinical signs, limited range of laboratory testing and, recently, incorporation of several imaging techniques. These confirmatory techniques are time consuming and require specialist expertise resulting life threatening delays in treatment and spread of disease. Numerous common examination assays and clinical tests, such as gauging cholesterol levels, blood pressure, or body temperature assisted as biomarkers for evaluating health statuses. In clinical trials, accurate traditional biomarkers are significant and accepted system of measurement to factually evaluate clinical standing, therapeutic effects and contrary events. Biomarkers are aimed to evaluate organs functioning, ailment's risk assessment, ailment's specific pathogenesis, severity of ailment, ailment outcome, and prognosis and treatment response. Traditional medicine is now a days utilizing biomarkers and newer technologies for drug development and diagnosis.

Applications of Biomarkers in Traditional Medicine

Biomarkers usually have clinical relevance in aspects of diagnostic values for origin and early detection of ailment, predictive values for therapy response and prognostic values for estimation of disease consequences and risk evaluation irrespective of therapy (Zhang et al., 2023). In precision medicine sensitive and specific biomarkers are clinically significant for there early detection of results (Lan et al., 2024). Traditional medicine usually deals with health from a general perspective, in view of the equilibrium of bodily energies. This normally explains ailments in terms of disproportions and commotions. Biomarkers can offer insights into these notions by connecting traditional imageries of ailment with calculable biological fluctuations. Their data can be incorporated for different techniques for better insight of biological regulatory mechanisms related to diseased states. Biomarkers have the capability to identify the initial events in the natural history, plummeting the level of mis-classification of disease and exposure while providing insights into disease pathogenesis, risk prediction, disease progression, prognosis and therapy response (Sharma et al., 2023).

Biomarkers are classified in different categories to make their utility more effective, on the basis of their characteristics and source, including susceptibility biomarkers, diagnostic biomarkers, monitoring biomarkers, prognostic biomarkers, predictive biomarkers, pharmacodynamic biomarkers, and safety biomarkers. The variety of biomarkers utilized to detect occurrence of disease or pathological condition and to identify disease subtypes are included in diagnostic biomarkers. They also be utilized as prognostic or predictive biomarkers. Monitoring biomarkers are investigated at several time intervals to monitor the ailment status, response to therapy or environmental interventions. They can be utilized in clinical trials, therapy initiation, drug development, risk assessment of disease and evaluation of drug pharmacodynamics. Predictive biomarkers are measured to predict the individual or population that are more likely to be affected by any pathogen, therapy or environmental factor, thus increasing survival rates and reducing adverse effects. Prognostic biomarkers are utilized to detect the probability of occurrence of clinical events, such as mortality or ailment occurrence, progression or reappearance, and consequent effect (favorable or unfavorable) of effecting agent in diagnosed individuals. This feature of biomarkers allows the identification of populations at higher risks. Another utility of prognostic biomarkers is in treatment choice and treatment safety. The safety of traditional medicine is of key importance, specifically keeping in view the potential for drug interactions and adverse side effects due to their long-term usage. Biomarkers can be utilized in safety monitoring of traditional therapies. Specific biomarkers can be tracked and can aid in detection of early signs of toxicity or side effects. Variations in biomarkers values or concentrations are measured as pointers of the development of ailment, therapeutic response and probability of side effects development. Safety biomarkers are evaluated for their levels prior or post exposure of effecting agent to detect or predict signs of toxicity and assess safety risk of particular therapy. Monitoring renal, cardiac and hepatic functions is crucial for many therapies for toxicity detection and therapy safety. Variations in the drug metabolism can alter its efficiency, reducing the response to the therapy or boosting toxicity risk in patients. Susceptibility or risk biomarker are utilized to measure risk of ailment occurrence such as genetic biomarkers can be measured to detect ailment prior to its symptom's onset. They are vital for the advancement of epidemiological investigations meant to evaluate the risk of developing an ailment, contributing to establish preventive strategies in clinical practice (FDA-NIH, 2021; Jiang et al., 2019; Zhang et al., 2023).

Genomic biomarkers presented the most recent substantial advances in ailment diagnostics, susceptibility, monitoring, prognostics, cancer and stem cell biology. They can detect genetic variants or particular mutations or alterations in genes contributing to the pathophysiology of ailment, numerous pharmacogenetic markers and estimate the risk factor of ailment, treatment plan and therapy response. DNA methylation biomarkers are very stable and easy to detect in saliva, plasma, serum, fecal matter, semen and urine even at their slight change in cells. DNA sequencing techniques are established enough that genomic biomarkers validation process is direct and assessment process is relatively low cost and convenient. RNA biomarkers can be utilized for disease diagnosis and prognosis. The transcriptome is characterized as coding ribonucleic acid transcripts (messenger RNA), non- coding ribonucleic acid transcripts (such as ribosomal RNA, small interfering RNA, transfer RNA, small nuclear RNA, microRNA and long-non-coding RNA) and its complements in body fluids, tissues or cells (Eckersall, 2019; Manzoni et al., 2018). They deliver dynamic understanding of cellular states and regulatory mechanisms than genomic biomarkers due to presence of their complements in cells. They are easily recognizable, more sensitive, specific and cost-effective than protein biomarkers. The transcriptome can pick up a more receptive state than DNA sequencing offering actively transcribed and regulated gene profile. Messenger RNA is the first well-studied RNA biomarker. It aids in the measuring presence and quantity of a transcript and analysis of genotype gene expression and protein isoforms. Multi-gene expression patterns, such as PAM50, work as biomarker for treatment effectiveness and prognostic biomarkers. Emerging extracellular RNAs (exRNAs) are non-invasive biomarkers, detectable in biofluids, lately utilized for early diagnosis, monitoring further development and therapy response assessment for tumors. Micro RNAs can effectively diagnose several diseases such as osteoarthritis, insulin resistance etc. and can easily be affected by oxidation and transesterification. RNAs circulating in serum are thought as one of efficient biomarkers in humans as well as in animals (Perera et al., 2022).

Traditional medicine usually uses remedies founded on centuries-old information and experience, but they are deficient of scientific explanations for their clinical use. Their scientific validation has been limited unlike modern medicine. Biomarkers offer a way to quantitatively measure the efficacy and mechanisms of these remedies. Biomarkers create a connection between traditional medicine and scientific validation leading to better understanding of mechanisms involved in traditional therapies and their clinical utility (Arcaro et al., 2023; Jansen et al., 2021). Biomarkers can aid in detection of the active agents in traditional therapeutics and uncover their effects on body and mode of action at molecular level, aiding traditional medicine practitioners to understand course of action behind their practices. This can also enable the development and improvement of the relation between traditional and modern medicine. Traditional medicine utilizes biomarkers primarily to evaluate and validate the quality and therapeutic potency of traditional drugs. Substances serving as biomarkers within the therapeutics and the individuals, either normal or with ailments, view as chemical fingerprints that deliver vital information about the authenticity, therapeutic potential, consistency and efficiency of therapeutics (Bhargavi et al., 2021; Lu et al., 2022). Biomarkers can also be utilized in drug development as targets. Biomarkers' incorporation into traditional medicine leads to discovery of novel and promising therapeutic agents and development of novel therapeutic strategies (Singh et al., 2020). Proteomics allows the single cell study while possessing the full spatial statistics of the cellular environment and provide exposure of intercellular intricacies like cellular receptor–ligand interactions leading to identification of activated pathways for therapeutics and biomarkers. Proteomic techniques such as mass spectrometry and its adjuncts, antibody techniques and liquid chromatography benefits from this trait to produce many protein profiles recognized as proteomes. Proteomes are the phenotypic expressions or endpoints of biological phenomenon, providing systematic information regarding biological responses and utilized as specific biomarkers or targets for therapy due to their high-resolution detection of differences (Sinha and Mann, 2020).

Level of metabolites in individuals varies and influenced by distinctions in gut microflora and environmental factors. Expression of metabolites have been recognized as possible biomarkers for toxicity evaluation and metabolic ailments (Gowthaman et al., 2021). As metabolome explains the end result of biochemical pathways carried out by proteomic entities, it can present more specific molecular explanation of individual's phenotype. Other omics can easily contradict due to epigenetics, and post-transcriptional or post-translational changes. While metabolomics is linked directly with ailment phenotype (Yang and Lao, 2019).

Under several physiological and pathological conditions proportion of variety of lipids tends to alter. Therefore, lipids can serve as potentially sensitive biomarkers and can promptly be measured in cell, plasma and serum. Lipid biomarkers have wide range of applications in traditional medicine, for instance, in detection of production efficiency of livestock, for keeping checks on toxicities of drugs, early detection of subclinical ailments such as mastitis, assessment of wildlife bulk mortality incidents, detection of hepatic and renal disorders on the basis of difference in levels of fatty acids and as substitution for digestive efficiency in poultry (Beauclercq et al., 2019; Koelmel et al., 2019; Svegliati-Baroni et al., 2019).

Multi modal incorporation for novel biomarkers detection for clinical utility is another rapidly developing new approach. Multiomics datasets assembled by researchers by incorporating varied assays from same sample set instead of focusing on single type of assay. Data obtained using multi-omics approach can disclose crucial biological information at many levels and provide understanding of on-going biological mechanisms behind biological state of interest. Findings or data from different omic-approaches when combined, provide a comprehensive visual of pathophysiological mechanisms causing ailment, establishing novel targets and therapy approaches (Subramanian et al., 2020). Multi-omics integrative analyses have multiple applications including study of nutritional and dietary ions and interpretation of controlling pathways for multifaceted disease characters. Researches are now focusing multi-omics approach for detection of sensitive and specific potential novel biomarkers for different ailments (Kornej et al., 2021; Park et al., 2021).

Traditional medicine greatly accentuates personalized therapy, customizing remedies according to the distinctive individual's characteristics and biological state. The personalized therapy depends on the relationship between intrinsic factors that are specific to individual and extrinsic factors that are environmental factors. Decision making for most appropriate treatment plan is the vital and most common mentioned purpose for biomarkers measurement. Genetic makeup and biomarker data is significant for customizing traditional therapies that suits individual's requirements, deciding dosage and therapy strategies and identifying patients at risk of adverse effects, thus helping in improving results and reducing adverse effects. Diagnostic biomarkers can contribute to improve personalized medicine and enhance the effectiveness of therapy response by identifying disease and its subtypes with varied prognosis and therapy responses (García-Gutiérrez et al., 2020).

Clinical Utility Assessment of Biomarkers

Clinical utility of biomarker is significant for their fruitful clinical use to avoid drawbacks while using biomarkers data for clinical interpretation of biomarkers. The most commonly used tactic for a newly detected biomarker projected as a risk predictor, is to compare it with existing prediction models that include different biomarkers. The criteria requirement for new prediction models to replace the existing one includes higher accuracy and higher diversity in risk types' detection than the existing models that allows the changes in therapy plans. Various statistical measures ought to be used to review the criteria fulfillment of new prediction model (Heilmann and Steiner, 2018). Clinical utility of new biomarkers can be evaluated in four steps. The first measure is to assess "global model fitness" for finding the best fit or parsimonious biomarker models. A model is preferred over models with same performance but higher number predictor variables. This can be evaluated by various methods including Akaike Information Criterion and Bayes the Information Criterion. The next measure is assessment of "Discrimination", which refers to the efficiency of discriminatory power of a biomarker model for recognition of diseased individuals from individuals not having the disease. Several gauges can be used for measuring discrimination, including C-statistic i.e., by comparison of area under the curve with existing model's area under the curve, Yates slope, the Brier score and the integrated discrimination improvement. Third measure is the "Calibration". Calibration refers to assessing the closeness of predicted ailment risks to the actual observed aliment risks by comparing the mean predicted risks to actual observed risks. Hosmer and Lemeshow chi-square test can be used to assess the calibration of a new biomarker model. The fourth measure is "Reclassification" of new predictor models to provide further clinically applicable information by a comparison among risk classification outcomes of a new biomarker model and an existing model. Discrimination manifestations do not provide knowledge regarding proportion of individuals categorized into high and low risk groups. Therefore, reclassification indices can evaluate the variations in predicted risk categories among new and existing models. Furthermore, scatter plots and bar graphs may effectually display clinically vital information regarding predictive performance. Another effective way to for the assessment of clinical utility of new predictive models or biomarkers is by calculating the number needed to screen (NNS) which is the indication of individuals required to be tested for identification of individuals at high-risk (Kim, 2012; McGeechan et al., 2008).

Diagnostic Functioning of Biomarkers

The diagnostic functioning of a biomarker assay depends on its sensitivity, precision and analytical execution which includes sample effects related to collection, handling, methodology and technical expertise. Higher sensitivity represents the lower false negative outcome rate while higher specificity represents the lower false positive outcome rate. Sensitivity can be calculated by dividing total true positive individuals by total diseased population. While specificity can be calculated by dividing total true negative individuals by total non-diseased individuals. Therefore, highly sensitive and highly specific diagnostic tests are helpful in ruling out a disease and confirmation of diagnosis more efficiently. Biological variability is an important perspective in the interpretation of the diagnostic functioning of a biomarker. It can be intraindividual and interindividual variations, both of which could be analogous or different amid healthy and diseased states. Biological variable also can determine the capability of biomarker to differentiate among healthy and diseased states of an individual. Bases of biological variation include periodic expression or secretion, disparity in gastrointestinal passage or irregular dispersal of cells expressing and discharging a biomarker and the absorption and half-life of a biomarker. Instituting the higher and lower limits of the reference ranges for a quantitative biomarker needs a large sample population because several biomarkers can differ with age, gender, body state or other environmental factors. Stratification may be necessary for such sample population that is founded on such variables (Heilmann and Steiner, 2018).

Digital Biomarkers

Digital biomarkers are newly introduced technology in the field of medicine. They are objective, quantifiable, physiological, and behavioral parameters that can be collected with help of wearable, transportable, implantable, or consumable digital devices. Traditional biomarkers are usually well rooted into clinical practice and research. They are mostly restricted in investigative complexity and range from being qualitative to quantitative. But they can be invasive, costly to determine and present a partial view of ailment. On the other hand, digital biomarkers are often less or non-invasive, modular, can yield qualitative and quantitative measurements, and usually cost-effective to measure. Value assessment of digital health techniques is complex. Digital biomarkers can play vital role clinically. Digital biomarkers can enhance diagnostic accuracy, improve therapy plans and aid in reducing clinical errors by providing timely and specific ailment related information (Motahari-Nezhad et al., 2022).

Surrogate Endpoints

Surrogate endpoints are the clinical markers that are not reliable measurement of clinical use but reasonably predict clinical benefit, can support approved drug or accelerate the drug approval for treatment or clinical trials and evaluate the efficacy of medication. Such biomarkers may include laboratory test data, physical symptoms or radiographic impressions. They are employed under situations where it is unrealistic or immoral to run clinical end point experiments. They are broadly used in oncology. The use of surrogate endpoints for clinical trials reduces the time and resources consumption. Many drugs have been approved by food and drug administration on the basis of surrogate endpoint. Estimating proportion of effect of treatment on surrogate endpoints is advocated as the validation of utility of surrogate endpoints or markers. Surrogate markers utilized for evaluation of treatment effect may not be useful for every diseased condition or therapy agent every time. Understanding this heterogeneity in utility of surrogate markers is crucial to make their use more beneficial in future (Parast et al., 2023; Wang et al., 2022).

Development of Biomarkers

Prior to utility, biomarkers require analysis, validation and verification, which involves understanding of their relationship with pathology that they are implicated to evaluate. The development of biomarkers in traditional medicine signifies a conjunction of ancient exercises with cutting-edge scientific studies. A biomarker's way from discovery to clinical usage is multiphase, extensive and complex process. Development process for biomarker includes recognizing the medical utility and recipient population, then following steps in sequence for selection and validation of the supposed biomarker with the aid of associated investigative procedures (FDA-NIH, 2021; Goldsack et al., 2020; Manzoni et al., 2018; Myers et al., 2017; Ou et al., 2021; Perera et al., 2022; Seibyl, 2023).

a) Selection of Traditional Practice

The preliminary step in developing biomarkers is selecting the traditional preparations or therapies that show possibility for scientific investigation. Traditional medicine practices like Ayurveda, Traditional Chinese Medicine, and others have used numerous natural ingredients and practices for centuries. Investigators initiate the selection process by identifying such remedies and their supposed benefits.

b) Discovery and Isolation of Biomarker(s)

Under biological change or pathological intervention, body cells respond by secreting materials in body fluids or surrounding tissues. Body fluids such as blood, urine, saliva, or endometrial fluids are employed to detect biomarkers for diagnosis by analyzing alteration in concentration of secreted materials. Discovery of biomarkers is the course of inspecting capable chemical compositions that have a possibility for high target affinity and selectivity. Compounds can be modified to attain various levels pharmacokinetics and pharmacodynamics during process of discovery. The discovery of putative biomarkers is the balanced and unbiased procedure by which different levels of certain biomarkers are found to exist in diseased or healthy conditions, usually by comparison of normal and diseased tissue. Investigators extract bioactive agents from traditional therapy mixtures to comprehend their mechanisms of action. This stage comprises advanced analytical systems to recognize and measure these agents. A variety of practices such as enzymatic tests, nanotechnology, single-cell next-generation sequencing, liquid biopsy, microbiomics, radiomics and other omics-approaches, mass spectrometry and its adjuncts, antibody techniques and liquid chromatography are presently being used to recognize novel biomarkers and authenticate their prognostic value. These techniques can picture state of body cells, tissues or fluids at piercing levels of cellular DNA or proteins and discover the finest characteristic marker for the disorder or state.

c) Qualification of Biomarkers

Qualification of biomarker is associated with the consistency of the biomarker. The biomarker essentially be steadily acquired to differentiate tissues such as healthy tissue from cancerous tissue using various methods. Biomarkers also required to show its differential levels in blood or plasma. In the qualification stage, biomarker sensitivity is of more significance than specificity. According to food and drug administration, the qualification process of biomarkers for drug development is collaborative. The Biomarker Qualification Program works with the researchers in supervising biomarker development. Multiple interested parties usually work collectively for this process. Under the 21st Century Cures Act , there are three stages for submission process, for the biomarker development for regulatory use, including submission of letter of intent, presentation of detailed proposal and then provision of comprehensive compilation of supporting evidence.

d) Verification of Biomarkers

The verification is an investigation of the biomarker in a larger number of blood samples. This step additionally approves biomarker sensitivity, but also instigates to consider biomarker specificity. As discovery efforts produce more candidate biomarkers than resources, a prioritization phase follows. Biomarkers of interest showing most significant alterations in specimen datasets are prioritized. Many of new biomarkers may not be able to achieve exclusive requirements needed for clinical validation. Verification stage aims to test the most of the candidate biomarkers with highest output. Verification determines if there is adequate evidence for potential clinical utility of a given candidate biomarker to permit more investment for validation. Similar assays are utilized for verification and clinical validation of biomarkers. ELISA is often employed due to its extraordinary sensitivity for quantifying the aimed analyte. Verification stage comprised of two levels of credentialing developing biomarkers.

Level one credentialing: This level demonstrates the mean plasma level of new biomarker among populations of cases and controls. Statistical tests are then applied for further assessment.

Level two credentialing: This is the pilot measurement of sensitivity and specificity of given biomarker in the chosen clinical setup to evaluate probability of success in larger clinical validation investigation.

e) Research Assay Optimization

Research assay optimization aim to alter biomarker test in order to improve it. These alterations may improve the test sensitivity and boost its capability to assess many samples rapidly.

f) Validation of Biomarkers

Validation is the method of determination of biomarker's assessment efficiency, prediction quality and epitomization for condition of interest. Internal validation founds a developing biomarker's performance in the data assessing through resampling techniques offering accurate prospects. External validation founds a biomarker's performance in an independent dataset from different timeframes, or geographic regions. Validity has various components such as sensitivity, specificity, analytical validity, and clinical validity. Sensitivity and specificity are essentially two sides of the same coin. A test is considered as specific if it provides a positive outcome only on the presence of biomarker and shows a negative outcome when the biomarker is absent. A test is considered as sensitive if it provides a positive result each time in the presence of biomarker in different individuals. A biomarker test lacks sensitivity if it detects biomarker in some individuals but may fail to identify in other individuals. Analytical validity represents the efficiency of a test to evaluate the given situation. This can be determined by comparisons of results to the results of best available tests known as gold standards. Clinical validity is another essential aspect of biomarker validation. It refers to the accuracy of test in predicting clinically significant outcomes. The validation process involves dealing with a variety of intrinsic features of biomarkers, its determinants, and the analytic technique. The final stage that is comprised of longitudinal studies, is attained after the determination of technical reliability of biomarker. A randomized, well-devised controlled study design is considered best for biomarker validation and provide the true unconfounded effects of biomarkers. Observational studies or uncontrolled studies can also be employed to gain vital information regarding health outcomes but can be subjected to bias. Prospective specimen collection, retrospective blinded evaluation design may be adopted in a condition in which specimens are gathered from an experimental unit that denotes the target population envisioned for biomarker to validate diagnostic, screening and prognostic biomarkers. There are numerous prospective clinical trial designs intended to validate the clinical utility of a predictive biomarker in a clinical setting such as enrichment designs, all-comer designs, subgroup designs and platform-type trial designs.

g) Commercialization

Biomarkers after validation in the laboratories may be commercialized, or made accessible for clinical utility. Before commercialization biomarkers must be further optimized to meet the tough and complex regulatory pathway needed for approval for their clinical use. The regulatory pathway to food and drug authority clearance or approval is reliant on the envisioned use of the test for biomarker.

Challenges and Future Perspectives

Many studies performed in various species focusing on wide range of conditions for diagnostic and monitoring aspects of new biomarkers. While numerous of them deemed pledging, many of the identified biomarkers facing challenges and still required to be developed and authenticated for their use in practice. Improper conduction or explanation of validation steps needed for approval of a biomarker for clinical use is one of the major challenges. Considerate analysis of such challenges will be beneficial for future of biomarkers pertaining their utility in traditional medicine. Identification of biomarkers till their validation for their clinical utility is a time consuming and costly process. A larger samples sizes are the requirement of authentic and extensive research studies for newly developed biomarker predictive models. Furthermore, interpretation of identified biomarkers into clinical utility needs additional time and finance. Maintaining the continuity is vital in the whole process and interruptions may compromise the eventual achievements of the process (Perera et al., 2022).

Development of biomarkers for utility in veterinary medicine face unique challenges such as, multiple qualification process for each relevant species, sample handling protocols and breed differences for values establishment. Perceptibly, omics platforms deliver unmatched application for biomarker discovery. With advanced equipment and speedily developing technology, establishing suitable protocols for collection of sample, processing and assessment is still not easy and consistent among research studies. A systematic consideration of various components is necessitated to have a standardized established methodology for each step. Focusing on different fields of sciences for each step to achieve well-established methodology is evident such as, for preparation of samples there is biochemistry, for instruments for processing and data analysis there are analytical chemistry and computational biology. Handling of samples while selection, collection and preparation, is a delicate process and any variation in this process can compromise the outcomes(Sinha and Mann, 2020). Using several markers of the similar type or a blend of different types such as proteins, DNA, RNA, lipids, and metabolites, will likely provide more evidence than the traditional measurement of a sole marker. Technical expertise, standardization and comprehensive reporting of experimental situations with species specifications and comprehensive explanation of sampling procedures and timing in relation to physiological state are essential to encounter several challenges (Shi et al., 2021). Computer based algorithms can be useful for integrating data from research studies and assemble it in the form of an atlas of biological agents. High potential of multi-omics comes with the challenge of storing and maintaining multi-dimensional bulk datasets, their quality control and standard statistical analysis leading to difficulty in making data findable, accessible, interoperable and reusable (FAIR principles). Supplementary quality control indicators that evaluate the datasets should be investigated for multi-omics as different omic-approaches differ in relation to accuracy. Therefore, consistent integrative assessment outcomes can only be illustrated when quality across platforms is similar (Conesa and Beck, 2019).

Other challenges encountered during development of biomarkers include biological variability, diagnostic accuracy and diagnostic performance of the biomarker. All analytes that are biochemical, show innate biological variability, an important factor to focus while inferring the diagnosis and acquiring values and strategies. Variations of either type, intraindividual variations or interindividual variations, can interfere with clinical performance of biomarker (Perera et al., 2022).

Conclusion

The utility of validated biomarkers in fundamental and clinical study along with clinical practice becoming routine, and their occurrence as endpoints in clinical trials is nowadays broadly recognized. Biomarkers allow improved understanding of pathological processes and pathways for therapy to combat disease. Biomarkers have numerous valuable applications in traditional medicine including ailment prevention and detection, individual's ailment risk determination, and disease monitoring. They can be well utilized to evaluate the safety or toxicity of a therapeutic regimen or certain ecological exposures. Biomarkers can improve the efficacy of existing medicines and aid in development of new medicines ultimately improving health outcomes.

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Chapter 34

Traditional Chinese Medicine (TCM) as an Alternative way of Treating Genetic Diseases

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ABSTRACT

Traditional Chinese Medicine or TCM is a complete practice with inherent logic, thought and consistency. It is a valued treasure for the mankind having distinctive benefits in treating or preventing diseases. Genetic diseases are caused due to abnormal variation in any gene. Many genetic diseases generally do not have a treatment. Some of these diseases have cures that can delay the development of disease or decrease the effect of these diseases on one's life. Use of Western medicine or synthetic drugs may give rise to sideeffects on the body. So, use of TCM can positively impact the body and aid in treating bysuppressing the symptoms of various genetic diseases.Various treatment methods usage like Acupuncture, Moxibustion, Cupping, Chinese Herbal Medicine, Dietary Therapy, Taijiquan, Qigong, and Tuina Therapyhave shown evidences preventing and controlling several genetic diseases. As mutations in certain genes result in specific genetic diseases, these TCM therapies can be used according to the causes and symptoms associated with these genetic diseases.

KEYWORDS		
Traditional Chinese Medicine, Genetic diseases, Acupuncture, Moxibustion, Qigong	Received: 21-May-2024 Revised: 22-July-2204 Accepted: 17-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

The main aim of the scientific community is to discover more efficient and economical medication for the cure of various chronic or other diseases. Ever since the creation of world, the nature has provided plentiful raw materials for the synthesis of medicine to the mankind. The major focus of the present-day medical research is to discover new treatment approaches based on the raw materials found in nature having variety of bio-activity and physio-chemical activity (Hu and Sun, 2017; Rayan et al., 2017). As Traditional Chinese Medicine (TCM) includes various natural products so, its study can be productive for the use of those natural resources.

Traditional Chinese Medicine (TCM) is a holistic or comprehensive approach to treat health issues of an organism (Gao et al., 2022). TCM is the earliest and classical medical approach popular in China and its surrounding areas (Su et al., 2012). It involves wide range of philosophical frameworks, modalities, and treatment regimens. In order to meet the modern standards, these treatment modalities and regimens have been evolved and modified with the passage of over 2000 years (Su et al., 2013; Wang et al., 2016; Gao et al., 2022; Gaur, 2024). Even though the modernized therapies are different from the past, the roots of Chinese herbal medicine, massage, acupuncture, bleeding, moxibustion, and cupping can be found in the history of classical Chinese medicine. Shang Dynasty Period, 1600 to 1046 BC, was the era when Chinese medicine was originated. It has gained recognition all over the world as a typical representative of complementary and alternative medicine (Zhang et al., 2017; Newman, 2020). In China, Chinese Medicine is referred as 中医 or zhōng yī means 'Chinese medicine'. It is modified to Traditional Chinese Medicine or TCM as it gained popularity in the West (Scheid, 2007).

Genetic diseases are the diseases that occur as the result of mutations or abnormal changes in the genome of an individual (Roth and Marson, 2021; Haspolat et al., 2023). Genetic diseases caused by mutation in single gene are known as 'monogenic diseases', while those by mutation in more than one gene are known as 'polygenic diseases' or 'multi-factorial inheritance diseases' (Pinnapureddy, 2015). Some genetic diseases are inherited from one generation to another, while some are the result of mutations or acquired changes in pre-existing genes. These changes can either be random or caused because of exposure to any environmental factor. Genetic diseases may give rise to various complicated and uncontrollable pathologies (Roth and Marson, 2021).

Due to abundant clinical practicein the past few years, TCM has emerged as a significant part in the field of medical science(Lin et al., 2022).The use of TCM has fewer to none adverse effects which has sparked the interest of several medical researchers. Moreover, TCM has multi-target effects as compared to that of synthetic drugs (Liu et al., 2022; Cao et al., 2024).

Comprehending Traditional Chinese Medicine (TCM)

Basic Principles of Traditional Chinese Medicine (TCM)

TCM is based on the principle that a person becomes sick when the life force energy (qi) is disrupted or imbalanced. The main aim of TCM is to rejuvenate the equilibrium within an individual by harmonizing Yin and Yang force energies (Gao et al., 2022).

Yin and Yang

Yin and Yang theory is one of the basic principles of TCM (Kim and Sue, 2009; Marshall, 2020). According to Chinese philosophy, everything in this world has Yin and Yang. These energies are contrasting yet interdependent. Although they are opposite and completely different from each other with respect of their nature, yet they are complementary. They are unable to survive without each other (Matos et al., 2021). Fig. 1 explains the interpenetrating and interdependent relationship of Yin-Yang pair.

Yin	Moon	Earth	Shade	Female	Rest	Water	Slow	Anterior	Weakness
Yang	Sun	Sky	Brightness	Male	Activity	Fire	Rapid	Posterior	Strength

Fig. 1: Correlation between Yin (阴) and Yang (阳).

The interpretation of 'Yin' and 'Yang' in the aspect of regulation is explained in Figure 2.

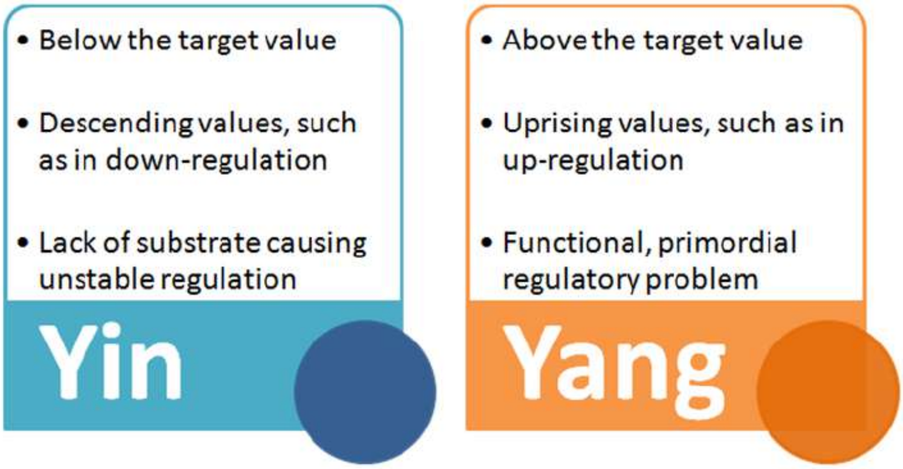

Fig. 2: Interpretation of 'Yin-Yang' in regulatory aspect

The interpretation of 'Yin' and 'Yang' in the medical aspect is explained in Figure 3.

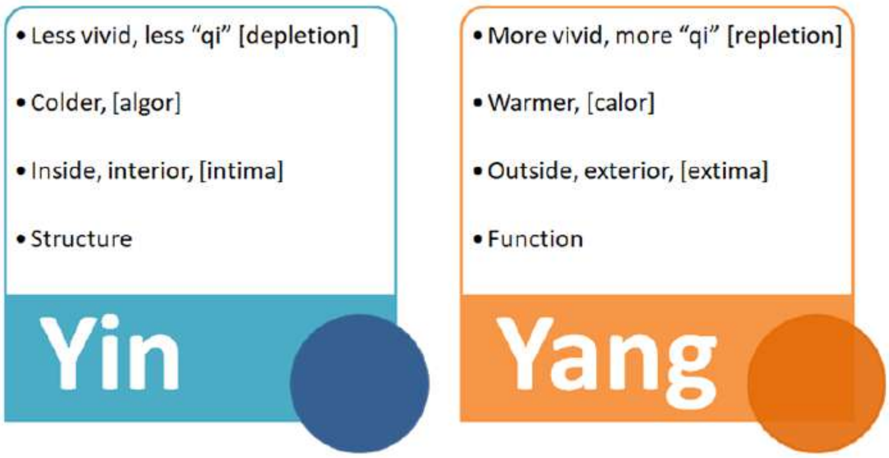

Fig. 3: Interpretation of 'Yin-Yang' in medical aspect

Understanding Ying and Yang theory is important to the application of TCM for diagnosing and curing various health problems. Treatment with TCM leads to the balance between Yin and Yang energies in every living being (Liu and Liu, 2011; Matos et al., 2021).

Qi

In English language, there is no word that can describe or explain "Qi". It is simply written as 'Chi' in English language. 'Qi' (*qì* or 气 in Chinese language) is generally translated as the 'life energy'. It is the vital energy that composes and holds together everything in the whole universe. It is the building block in nature. It is the breath that occurs as a result of inhalation and exhalation. On the basis of Classical Chinese Philosophy, Qi is not a tangible object that can be studied in a laboratory (Wager and Sue, 2009; Szmelskyj et al., 2015).

Qi is important for the existence of life. It performs various roles in body of an individual. Figure 4 shows some major functions of Qi or Chi.

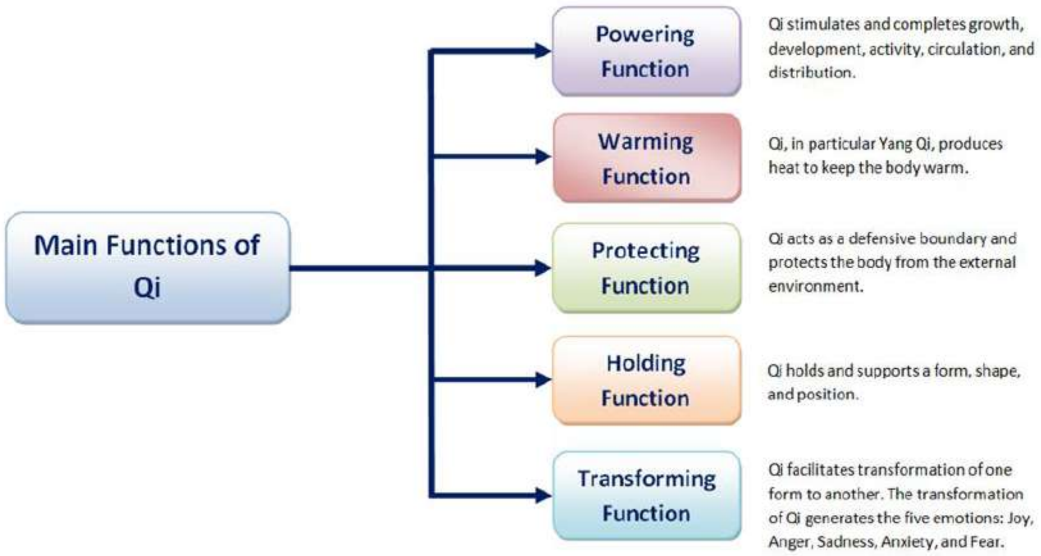

Fig. 4: Major functions of Qi

Unbalanced Qi (excessive or deficient Qi) may lead to diseases or various illnesses. There can be several reasons for unbalanced Qi. Figure 5 shows the reasons for the excessiveness and deficiency in Qi.

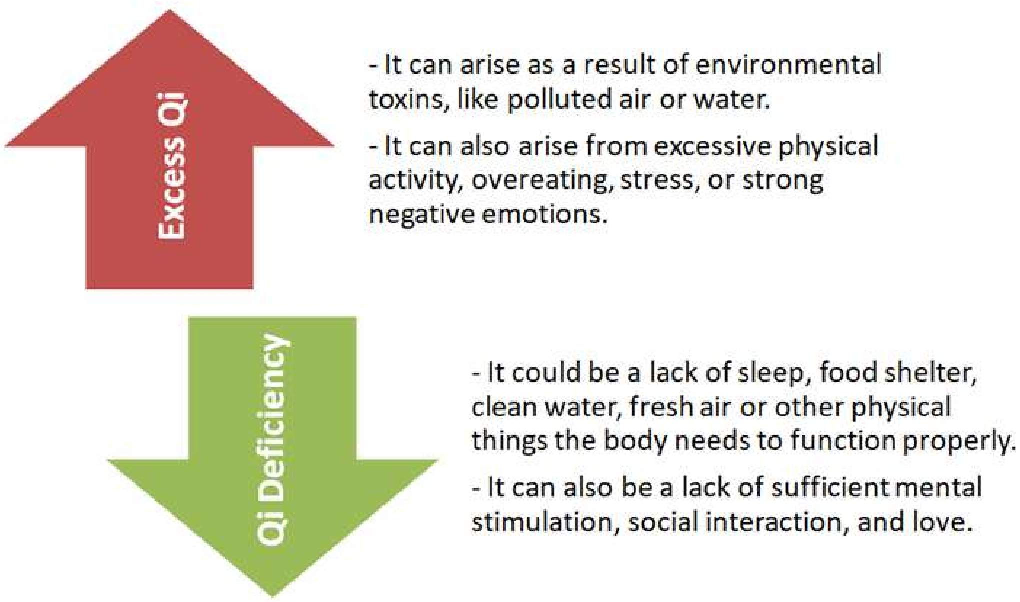

Fig. 5: Causes for unbalanced Qi

The Five Elements

In Traditional Chinese Medicine, Wood, Water, Earth, Metal, and Fire are the five elements that symbolize the five sense organs. This five elements theory has several practices in TCM and various correspondences such as internal or external organs, tastes, body fluids, seasons, directions, directions, etc. are correlated with particular natural and biological processes and qualities (Gaur, 2024).

Following table 1 elaborates some of the associated aspects of the five element theory.

Table 1: Associated factors of the Five Element Theory

Elements	Sense Organs	Yin Organs	Yang Organs	Fluid	Tastes	Seasons	References
Wood (mù or 木)	Eyes	Liver	Gallbladder	Tears	Sour	Spring	(Zhou et al., 2019; Marshall, 2020; Gaur, 2024)
Fire (huǒ or 火)	Tongue	Heart	Small intestine	Sweat	Bitter	Summer	(Zhou et al., 2019; Marshall, 2020; Gaur, 2024)
Earth (tǔ or 土)	Mouth	Spleen	Stomach	Saliva	Sweet	None	(Zhou et al., 2019; Marshall, 2020; Gaur, 2024)
Metal (jīn or 金)	Nose	Lung	Large intestine	Mucus	Pungent	Autumn	(Zhou et al., 2019; Marshall, 2020; Gaur, 2024)
Water (shuǐ or 水)	Ears	Kidney	Urinary bladder	Urine	Salty	Winter	(Zhou et al., 2019; Marshall, 2020; Gaur, 2024)

Diagnostic approaches in TCM In TCM, it is important to understand the pattern of disease during diagnosis (Zhang et al., 2017). This shows the physio-logical and patho-logical patterns of a living body. These patterns show the imbalance in the body systems that are marked out by the physician through systemic-analysis (Pei and Long, 2014; Marshall, 2020). Diagnosis in the field of TCM involved 4 basic and vital examinations; look, question, hear-smell, and palpate (Bob and Sionneau, 2001; Matos et al., 2021), in order to get a clearer image of the condition of the patient including physical and indistinct factors (Lee et al., 2017).Tongue diagnosis is the aspect that is investigated by looking, whereas, pulse diagnosis is investigated by palpating.

Tongue Diagnosis

In TCM, tongue is regarded as the mirror for the internal organs. It demonstrates the physio-logical and patho-logical patterns of one's body (Figure 6). The indicators of tongue include several parameters such as colour, size, body, movement, and shape of the tongue along with the changes in the form of the tongue including thickness, breaks, as well as teeth imprints. These parameters are associated with the health condition of a patient and should be analyzed.

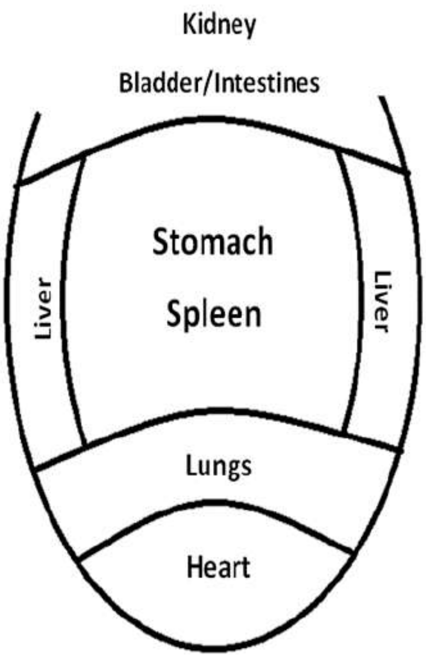

Fig. 6: Somatotopic arrangement of tongue in TCM diagnosis (Gholami et al., 2020)

Pulse Diagnosis

Pulse diagnosis is considered to be a factor that gives details regarding the condition of organs and relevant meridians through the palpation of the radial artery on wrist. The qualities of pulses are as significant as the rate of pulse. The qualities of pulses are generally characterized as slow, rapid, dull, strong, thin, rough, wiry, rigid, turbulent, smooth, deep, floating etc. (Lee et al., 2009; Tang et al., 2012; Bilton and Zaslawski, 2016; Matos et al., 2021). By these indicators of pulse enable the TCM practitioner to observe the underlying conditions(Figure 7) (Tang et al., 2012; Bilton and Zaslawski, 2016; Matos et al., 2021).

Modes of Treatment of TCM

For the treatment of diseases and rejuvenation of health, TCM depends on distinctive theories and practices. These unique practices encompass Chinese herbal medicine, dietary therapy, acupuncture, cupping, and moxibustion, and some non-medication practices like 'Tuina', 'Qigong', and 'Taijiquan' (Newman, 2020; Matos et al., 2021).

Chinese Herbal Medicine

TCM includes the recuperation and healthcare on the basis of the theory of TCM and diseases are prevented, diagnosed, and cured by making use of TCM. Natural medicine and the products processed from the natural medicine comprising biological and chemical products, along with herbal, and mineral medicines are considered to be the fundamental sources of TCM (Wu, 2005; Matos et al., 2021; Ma et al., 2021). TCM are modernized with the passage of time. Modern TCM compounds comprise of four different types of compounds (Figure 8) and the traditional Chinese medicines developed by using modern techniques (Liu et al., 2009; Ma et al., 2021; Gu et al., 2022).

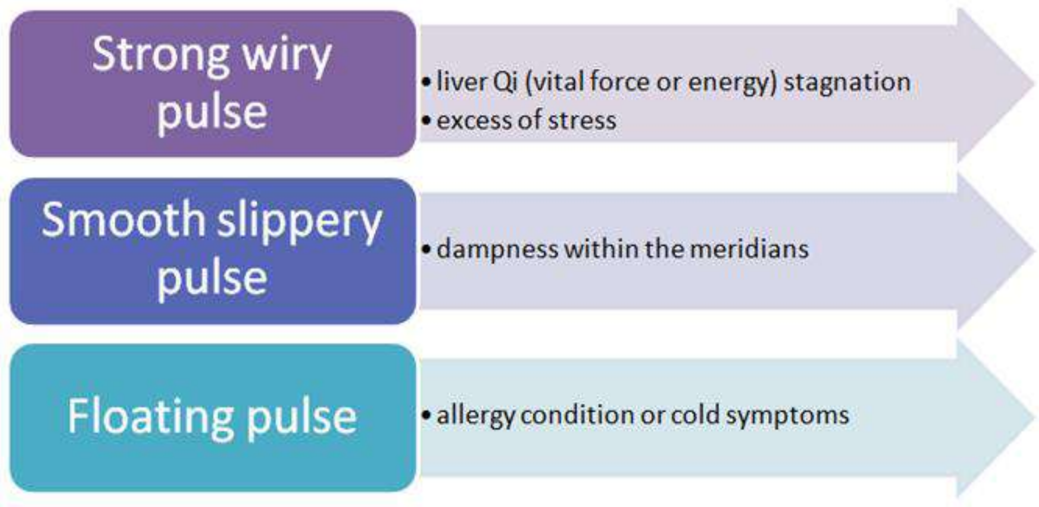

Fig. 7: Some pulse indicators indicating body conditions

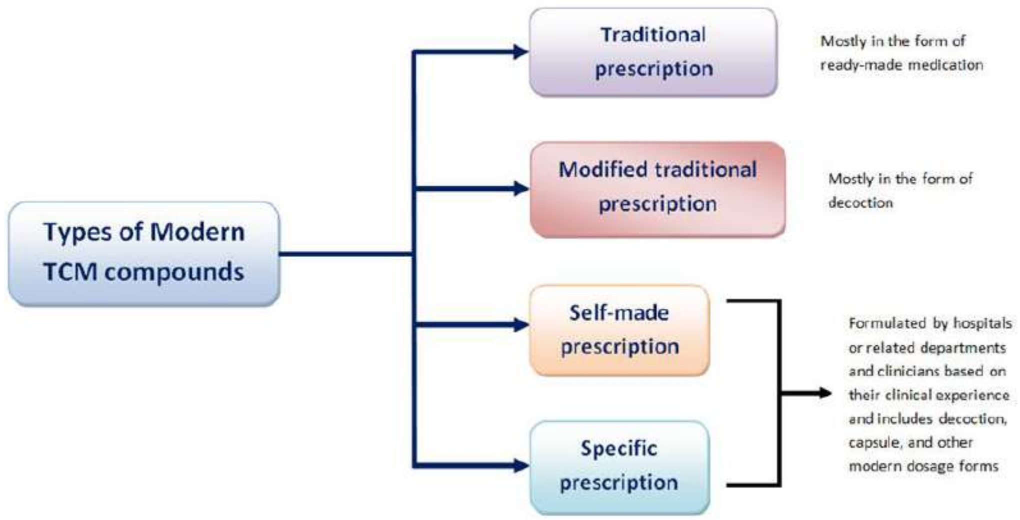

Fig. 8: Four major types of modern TCM compounds

Acupuncture

Acupuncture is a mode of treatment of TCM usually used for alleviating pain (Shah et al., 2022; Oh et al., 2022) that includes the penetration of needle(s), specifically filiform needle (Fernández-Jané et al., 2020), into body of patient at a fixed angle or point (Zhu et al., 2021; Zhang et al., 2022; Wang et al., 2023). The techniques or methods of acupuncture activate the certain body parts for treatment purpose (Lu et., 2022). These techniques include rotating and lifting (Ma et al., 2021).

Moxibustion

Moxibustion is a kind of therapy that uses burning and pressing moxibustion sticks or grass on specific points on the body to prevent or cure diseases. This is done for the thermal stimulation in body (Deng and Shen, 2013; Park et al., 2020; Han et al., 2021).

Tuina

Tuina therapy or Chinese Manual Therapy is one of the ancient and traditional methods used in curing several diseases in TCM (Al-Bedah et al., 2017). It involves holding, pressing, lifting, and rubbing the acu-points on body (Fang and Fang, 2013; Ma et al., 2021).

Qigong

Qigong is the combination of two words; "Qi" meaning vital force or energy and "gong" meaning capacity-building. So, "Qigong" is a way by which one can develop capacity to gather, flow and utilize the vital energy (Matos et al., 2021).

Fig. 9: Three primary schools of "Qigong"

Understanding genetic diseases from the perspective of Traditional Chinese Medicine (TCM)

Genetic diseases are caused by the mutation in a certain gene. These genetic diseases may adversely affect various body systems. According to TCM theory, many genetic diseases give rise to the changes in body of an individual affecting its normal functioning. These changes may include excessive phlegm, deficiency of Qi in different body organs, and unbalanced Yin or Yang in body organs (Zhai et al., 2020). Table 2 introduces TCM patterns some commonly found genetic diseases.

Table 2: Some commonly found genetic diseases and their TCM patterns

Genetic disease	Defect	Clinical manifestations	TCM pattern	References
Albinism	Mutation in genes responsible for the synthesis of melanin pigment	Skin hypopigmentation	Stagnation of blood, excessive heat production, lack of Qi in liver and spleen	Arveiler et al., 2020; Lasseaux et al., 2022; Li et al., 2023
Ankylosing spondylitis	Presence of HLA-B27 gene	Joint pain, inflammation, fatigue	Qi stagnation, increased dampness and heat in gallbladder	Voruganti and Bowness, 2020; Jia et al., 2022
Cystic Fibrosis	Defective CFTR (cystic fibrosis transmembrane regulator) gene leading to compromised chloride ion channel function	Pancreatic dysfunction because of lesions, congestion of lungs as a result of dense mucous, pulmonary infection	Lack of Qi in lung and spleen, phlegm obstruction	Chen et al., 2021; López-Valdez et al., 2021; Ong and Ramsey, 2023
Down's syndrome	Presence of extra chromosome 21 (Trisomy 21)	Reduced muscle tone, flat face and nose, small head, ears, and mouth, shorter neck with thicker skin on the back of neck, upward tilted eyes, and there is usually a fold of skin extending from the upper eyelid that covering the inner corner of eye, poor concentration and judgment, slow learning speed,	Phlegm-dampness pattern (pale and swollen face, watery nose, drooling, slow movements, and submissive disposition) Distinctive heat pattern (flushed face, yellowish nasal discharge, and red tongue, along with inquisitive, hyperactive, demanding, headstrong, and domineering nature)	Martin et al., 2009; Bull and Committee on Genetics, 2011; Mueller, 2016; Arumugam et al., 2016; Antonarakis et al., 2020
Hemochromatosis	Mutation in HFE gene	Lower body weight, fatigue, hair loss	Decreased Yin and Qi in spleen, increased internal heat, inactivity of blood and Qi in liver	Daniłowicz-Szymanowicz et al., 2021; Ulguim et al., 2022; Nojiri et al., 2023
Neurofibromatosis	Variation in the gene responsible for the synthesis of neurofibromin	Coloured patches on skin, blurred vision, lower intelligence level, high risk of cancer	Lack of Qi in kidney and spleen, inactivity of blood and increased phlegm in body	Osum et al., 2021;Tamura, 2021; Pillay-Smiley et al., 2023
Sickle-cell anemia	Defective hemoglobin S gene	Blood deficiency leading to fatigue and dyspnea	Lack of Qi in spleen, inactivity of blood in liver, accumulation of phlegm	Tsai et al., 2020;Wang et al., 2024
Usher syndrome	Mutation in MYO7A, USH2A, CLRN1 or CDH23 genes	Hearing loss, vision loss, loss of balance	Compromised blood flow in body, lack of Yin in liver and kidney, increased phlegm	Géléoc and El-Amraoui, 2020; Toms et al., 2020; Castiglione and Möller, 2022

Use of TCM for the Treatment of Genetic Diseases

Traditional Chinese medicine being a significant aspect of complementary and alternative medicinewhichhas formed its own unique theory, diagnosis and treatment system over years (Ling et al., 2014). It is known for its diverse roles in preventing and treating various diseases, as well as its application in other clinical practices in the present era.Although there are several methods of treatments have been introduced to treat genetic diseases, they may lead to long lasting adverse effects on the living body. So, traditional Chinese medicine is opted as an alternative way for treating genetic diseases for being less risky.

Acupuncture and Cupping

Acupuncture is considered to be the most common and most effective way of treatment. It has been evident that acupuncture is found effective for controlling and suppressing the clinical features of several genetic diseases. Such as neural acupuncture treatment and moxibustion is effective for dealing with a patient with Down's syndrome (Mueller, 2016; Hao et al., 2019). In cystic fibrosis, cupping is found effective for restoring Qi and improving fluid circulation in the body. Acupuncture reduces the pain associated with the cystic fibrosis(Lin et al., 2005; Nash et al., 2015) and sickle cell disease (Tsai et al., 2020).

Qigong and Taijiquan

Qigong and Taijiquan are the practices which can promote rehabilitation of Qi and smooth circulation of body fluids (Jahnke et al., 2010; Rodrigues et al., 2023).

Chinese Herbal Medicine

Chinese herbal medicine including *Folium eriobotryae*, *Radix stemonae*, root and leaf of *Prunus simonii*, *Eleocharis tuberosa*, root of *Ixora chinensis*, *Cornu bubali*, *Litsea cubeba*, *Pinellia ternate*, *Ardisia crenata*, *Procumbent gynura*, and *Gingko biloba* is found beneficial against cystic fibrosis with no adverse effects (Liang et al., 2023; Gómez-Ganda, 2023). Erzhi pills are found to have melanogenic effect and can be used against albinism (Li et al., 2023; Hong et al., 2024). *Astragalus membranaceus*, *Salvia miltiorrhiza*, and *Angelica sinensis* are the Chinese herbs that are considered to be effective against anemia due to sickle cell disease (Chen et al., 2018).

TCM and Gene Therapy

It has been found that TCM theory and gene therapy are consistent. Some drugs derived from traditional Chinese medicine can also be used as gene therapy carriers, therapeutic genes, synergistic treatments, and as combination drugs to reduce side effects (Ling et al., 2014).

Future Perspective

As genetic diseases result because of the changes in genes so they may influence various systems in one's body. Most of the genetic diseases cannot be treated; on the other hand, these diseases need to be managed frequently. Gene therapy is option for the patients to live their lives without the need to go through hassle of managing the disease on daily basis. Researches are being done to use TCM derived drugs in gene therapy and to find a better way to prevent and alleviate the symptoms associated with the genetic diseases.

Conclusion

Genetic diseases are the results of past mutational events. Their effects can only be reduced by treating or preventing these diseases. For the treatment of genetic diseases many techniques and therapies have been found and are being introduced in this era. But these have their complications. So, it is high time to switch to traditional Chinese medicine as an alternative method of treating genetic diseases as TCM is the safest way of treatment. Modes of treatment of TCM include acupuncture, cupping, moxibustion, Chinese herbal medicine, Qigong, Tuina Therapy, and Taijiquan. These techniques are found beneficial for treating and reducing the clinical features associated with different genetic diseases. Use of these therapies only has positive effects and no evidences of any toxic effects were found. Although use of traditional Chinese medicine has several advantages yet there is so much research has to be done in the aspect of finding novel medicines for preventing and treating various genetic diseases.

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Chapter 35

Camel Milk an Immune Modulating Agent and its Antidiabetic Effects

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ABSTRACT

Camel milk is magnificent natural healer with immunomodulatory and antidiabetic effects. This chapter brings out the specific aspect of camel milk which is immunoglobulins, lactoferrin and lysozymes that makes it to boost the immune system. These biomolecules act as an antibacterial, antiviral, and have anti-inflammatory effect; hence, camel milk could effectively assist in alleviating the diseases by modulating the immune system and its response towards various viral, bacterial, fungal and parasitic diseases. Moreover, other than the immunological consequences, camel milk has revealed early antidiabetic properties. With relatively high amounts of insulin-like proteins, camel milk helps in the normalizing of glucose tolerance and decreasing the need of external insulin in the case of diabetes. Various studies prove how camel milk may complement the treatment of diabetes and help regulate glucose concentrations.

KEYWORDS		
Camel Milk, Immune Modulating Agent, Antidiabetic Effects of Camel Milk	Received: 12-Jun-2024 Revised: 20-Jul-2024 Accepted: 21-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Camel Milk

An estimated 25.89 million camels are thought to exist worldwide, of which 89% are one-humped dromedary camels (*Camelus dromedarius*) and the remaining 11% are two-humped camels (*Camelus bactrianus*), which are typically found in Asia's cold deserts. More than 60% of dromedary camels are found in the arid regions of North East Africa, including Somalia, Sudan, Ethiopia, and Kenya (Jilo and Research, 2016).

Camel milk is a special type of milk and good for consumption with tremendous potential for value addition owing to its historical usage especially in the regions where the camel plays a social, cultural and economic role.

Compared to other types of milk, camel milk possesses a peculiar taste and remarkable nutritional values, and for a long-time it was in high demand among those populations, who are nomadic or have been involved in pastoral farming activities in arid and semi-arid regions of the world. In recent years, the health benefits of consuming it and its use as a dairy product just like cow's milk has made it to attract the international market.

In adverse circumstances like severe heat, a shortage of grass, and little water, camels can produce 4 to 30 liters of milk per day. Their lactation lasts for nine to eleven months, with a maximum lactation lasting two to three months. For this reason, camels are the main source of milk and meat in many arid and semi-arid regions of the world and referred as 'white desert gold' (Behrouz et al., 2022).

Nutritional Composition

Camel milk is a natural product which is a source of many nutrients hence considered as a healthy drink. It is rich in vitamins and minerals such as vitamin C, iron, calcium and B-group of vitamins. For instance, camel milk contains three times the amount of vitamin C than that of cows' milk, and plays roles in immunity and skin. It also contains proteins and is useful for circulation as it contains fats of the long chained and unsaturated types (Faye and Konuspayeva, 2012).

Overall, camel milk typically has the following components on average: 3.4% protein, 3.5% fat, 4.4% lactose, and 0.79% ash, with 87% being water. It has low sugar, low cholesterol, high levels of minerals (potassium, iron, copper, zinc, and magnesium), high levels of vitamin C, and protective proteins such lysozyme, immunoglobulins, lactoferrin, and lactoperoxidase (Jilo and Research, 2016).

Health Benefits

It is the health benefits of the camel milk which serves as a popular reputation of this product. Some scholars have gone further and proved that it can help in digestion especially for persons unable to digest milk or its products. This is attributed to the fact that it contains relatively lower lactose when compared to the milk of cow and other dairy animals, and has different protein structures, thus easy to digest for the persons unable to digest the milk from other dairy animals (Shabo, Barzel, Margoulis, and Yagil, 2005).

Other nutritional values include; camel milk being capable of enhancing the immune system. It has other biologically active substances such as immunoglobulins and lactoferrin that have antibacterial and anti-inflammatory effects. These components allow the body to be protected from infections and has anti-inflammatory activity, thus being beneficial for the human beings (Wernery and Research, 2006).

In addition, research has it that consumption of camel milk leads to enhanced managing of diabetes as it does wonders in increasing the level of insulin sensitivity and lowering down the blood sugar level. This makes it a worthy incorporation to the diet of people with diabetes or those with a propensity towards the disease (Agrawal et al., 2007).

Cultural and Traditional Importance

Camel milk has been not only a source of nutrition but also the identity of the various communities all around the world for several centuries. In the deserts where other food sources could be a bit hard to come by, camel milk is readily available and would come in handy. Camel milk can be taken fresh, fermented or incorporated in many traditional dishes and therefore is a very vital part of most local diets (Yagil, 2013).

Global Popularity and Market Growth

Over the years, Camel milk has gained acceptance in major markets other than the traditional markets. Due to these changes, it is becoming more common in specialty stores and online platforms across the globe as customers' demand healthier and tastier foods. This growth has been achieved based on its purported health benefits and the need for dairy products' substitutes for allergic and intolerance persons (Faye and Konuspayeva, 2012).

Among all the milk products, camel milk has been found to be highly nutritious and healthy with roots in cultural importance while experiencing a growing trend in the market. Because of these properties and further, possible health advantages, camel milk should be incorporated into the diet of many people especially to those who are in search of substitutes to normal animal milk. In light of emerging studies aimed at determining the diverse ways through which the product is useful, camel milk is expected to play an increasingly prominent role in feeding the world's population in the future.

General Benefits of Camel Milk

These acclimatization traits, thus the ability of camels to withstand high temperatures would be advantageous in eradicating thermosensitive disease-causing pathogens. This could be the reason why people have retained the notion that camel milk is an almost pathogen free commodity. However, irrespective of the fact that camel milk is commonly consumed without pasteurization, it rarely causes the spread of ailment (Dubey, Lal, Mittal, Kapur, and Agriculture, 2016).

Camel milk commonly called 'white gold of the desert' is product with nutritional and therapeutic value that can improve human health. Being a good source of nutrition and rich in bioactive compounds, camel milk has attracted interest in relation to therapeutic effects. It is expounded on the generalized qualities of camel milk accompanied by recent research findings.

Nutritional Profile

Scientifically, camel milk is found to be richer in a number of nutritional contents than that of cow milk. It is also rich in vitamins and minerals and vitamin C is found to be the concentration of three to five times greater than in cow milk. It also comes with a high vitamin C that is very essential for enhancing the immunity and fighting against infections (Konuspayeva, Faye, Loiseau, and analysis, 2009). This milk also has an appreciable level of Vitamin B1, calcium and iron hence is useful in body nourishment (Al Kanhal, 2010).

A liter of camel milk contains nutrients in a ratio that can suffice the human's requirement of potassium up to 100% while the sodium up to 57%. It also fulfills the 6% of calcium and phosphorus, iron, copper and zinc, and magnesium up to 40% and 24% of sodium (Dubey et al., 2016). None of the allergy proteins found in cow's milk such as β-lactoglobulin and low β-casein are present in camel milk (Mohammadabadi, 2020).

Digestibility and Lactose Intolerance

The digestibility of camel milk is one of its biggest benefits, particularly for those who are lactose intolerant. Compared to cow's milk, camel milk has a lower lactose concentration and a distinct protein structure, which can help certain people digest it more easily. Studies used when explaining why it may be good for camel milk to be used as a replacement for standard milk by those who are sensitive to lactose as it was established that it helped in reducing the discomfort that comes with taking milk that is rich in lactose (Ehlayel, Hazeima, Al-Mesaifri, and Bener, 2011).

Cardiovascular Health

Camel milk contains healthy fats, long chain polyunsaturated fatty acids which is good to the heart. These fats are desirable as they are associated with a reduced incidence of cardiovascular diseases and are healthy cholesterol fats. Camel milk consumption often can be beneficial to heart health by providing these essential fatty acids (Faye, 2013).

Hence, the inclusion of camel milk in nutrition is advised because it is good for overall health. Among its nutritional benefits, pharmacological properties, effectivity in digesting foods, fortifying the immune system, reducing inflammation, being an antioxidant, and a potential treatment for diabetes, as well as, boosting heart health is noteworthy. Its popularity as a functional food increases and is proved by the fact that research into its advantages discovers camel milk as a meal having significant health effects.

Antidiabetic Effects of Camel Milk

Camel milk might assist in managing diabetes as pointing out by one of the current studies. It is known to regulate blood sugar levels and improve the utilization of insulin by the body tissues. Such property of camel milk may be due to insulin like peptides, which are very useful to diabetic people or those who are most likely to develop the disease (Agrawal et al., 2007). Camel milk is a very effective therapeutic substitute that ensures fewer insulin injections in diabetic patients. This statement means that from the epidemiological surveys of the various population groups, diabetes was seen to be less frequent in those that took camel milk (Dubey et al., 2016).

According to data from the International Diabetes Federation, there were 415 million cases of diabetes globally in 2015, and by 2040, there are predicted to be over 640 million cases. Furthermore, as per the National Diabetes Survey of Pakistan, 27.4 million individuals (≥20) or 26.3% of the population has diabetes in 2016–2017 (Hussain et al., 2021).

Of all the health benefits associated with camel milk, its antidiabetic qualities have received the greatest research attention. Camel milk's antidiabetic qualities have been investigated in a variety of in vitro and in vivo models, and in the near future, research on its possible uses for the treatment of diabetes will be a major area of concentration (Muthukumaran, Mudgil, Baba, Ayoub, and Maqsood, 2023).

Abdalla reports that a study conducted in India compared juvenile diabetes patients receiving standard treatment with those who additionally drank camel milk. The results indicated that the camel milk group had considerably lower HbA1C and blood sugar levels. Due to its special qualities, camel milk insulin has the ability to regulate and modulate immune responses in cells. A significant concentration 150 U/ml of insulin is present in camel milk (Jilo and Research, 2016).

Immune Modulating Agents

Immune modulating drugs are compounds that alter how the immune system reacts to certain dangers, including infections, cancers, and autoimmune illnesses. These substances have the ability to either stimulate or inhibit the immune system, which makes them useful therapeutic agents for a variety of illnesses. Since immune modulators aid in achieving a balanced immune function, their usage can be critical in both clinical and therapeutic contexts.

Immunostimulants with the ability to raise immune responses above baseline can be employed as immunomodulators. Clinical diseases such as cancer, infections, and chronic inflammation can be effectively treated using immunostimulants. Adjuvants such as immunomodulators can improve antigen uptake and increase vaccination efficacy. They may serve as the immunosuppressants required to treat organ transplant rejection and autoimmune illnesses (Munang'andu, Mudronova, and Popelka, 2024)

Types and Mechanisms

Immunostimulants

These substances enhance the activity of the immune system which in turn make the system more effective in combating infections and cancer cells. Immunostimulants include vaccines, substances that prepare the immune system to identify sure infections and fight against it, and cytokines, substances that enhance the action of the immune cells, such as interferons and interleukins (Kuby, Kindt, Osborne, and Goldsby, 1994).

Immunosuppressants

These medications reduce the activity of the immune system and thus has the advantage of being applied where the immune system is over-active such as in organ transplants and auto-immune diseases. Some of the immunosuppressive drugs include corticosteroids, calcineurin inhibitors including cyclosporine, and those monoclonal antibodies that inhibit specific immunological pathways (Strober, Fuss, and Blumberg, 2002).

Biologics

Biologics are a form of immune-modulating agents which are taken from life forms. Some examples of these agents are cell-based therapies that are obtained from the patient's body such as stem cells, fusion proteins that consist of two or more proteins bonded together, and monoclonal antibodies which are produced artificially. These substances are quite special because they can address and alter the different parts of the immune system with the needed precision and rates in order to administer correct and effective treatments for various diseases like cancer, autoimmune diseases, and chronic inflammation sicknesses (Weiner, 2015).

Applications

Autoimmune Diseases

Immunomodulating drugs help decrease the abnormal immune response against the individual's own tissues in diseases like lupus, multiple sclerosis, and rheumatoid arthritis. This is evident as these disorders have shown changes in treatment due to development of Human Biologics such as B cell depleting drugs such as rituximab and TNF inhibitors such as infliximab among others (Smolen, 2016).

Cancer Therapy

Given specific tumor types, new hope has been provided by drugs including immune checkpoint inhibitors (such as pembrolizumab) as well as some CAR-T cell therapy giving patients new approach to cancer treatment option hence immunotherapy can be considered as one of the promising approaches to cancer treatment. These treatments increase the ability of the body to recognize cancerous cell and destroy them (Sharma and Allison, 2015).

Infectious Diseases

Moreover, immune modulators can be utilized to improve the body's defense against infections. For instance, it is generally known that interferons can be used to treat viral illnesses such as hepatitis B and C (Pawlotsky, 2014).

Immune modifying drugs are essential to contemporary medicine because they offer focused and efficient approaches to treating a wide range of illnesses. These medications support immunological balance and enhance or decrease the immune response, respectively, thus improving patient outcomes. The creation of fresh and enhanced immune modulators will increase their therapeutic potential as research progresses.

Camel Milk as an Immune Modulating Agent

Numerous health advantages of camel milk have been discovered, including its antiviral, antibacterial, antitumor, antifungal, antioxidant, hypoglycemic, and anti-cancer properties. Furthermore, camel milk can prevent ageing symptoms and could be an effective naturopathic treatment for autoimmune disorders (Behrouz et al., 2022).

Apart from its use as a food supplement, camel milk has anti-inflammatory and anti-microbial properties. Because camel milk is normally consumed raw, it retains many of the biochemical and immunological properties that are often lost in the milk preservation process (Dubey et al., 2016).

Compared to cow's milk, camel milk has higher concentrations of protective proteins such lysozyme, IgG, and secretory IgA. Additionally, it has been shown to exhibit insulin-like activity, which controls and modifies ß cell activities. Therefore, in numerous immune-mediated diseases, the modulation of the immune response by camel milk has been substantiated (Behrouz et al., 2022).

Immunoglobulins and Immune Proteins

Immunoglobulins and lactoferrin, which have strong antibacterial and anti-inflammatory qualities, are abundant in camel milk. These bioactive proteins reduce inflammation and help the body fight off infections, strengthening the immune response. A variety of bacteria and viruses have been demonstrated to be inhibited in growth by lactoferrin in particular, which adds to the protective properties of milk against infections (Khan and Iqbal, 2001).

Essential for enhancing the immunological capacity of the body, Immunoglobulins especially IgG are present in higher concentrations in camel milk. Still, camel milk holds immunoglobulins which provide passive immunity and the ability to inactivate infections. Besides, camel milk contains a peculiar set of tiny antibodies, or VHH, nanobodies that have more stability than typical antibodies and can bind selectively to antigens. They have also shown their effectiveness in countering viruses and poisonous substances, thus increasing the immunity (Hamers-Casterman et al., 1993) (Muyldermans, 2013).

Lactoferrin and Antimicrobial Peptides

Lactoferrin which is a glycoprotein that has the capacity to bind with iron in the camel milk possess immense antibacterial, antiviral and anti-inflammatory properties. It is vital to the innate immune response due to the meager fact it binds iron, and this fines a bacterium's growth. Besides, the concentration of lactoferrin elevates the activity of the neutrophils, macrophages, and natural killer cells which forms a part of immune system (Redwan et al., 2014).

Some of the AMPs present in camel milk are lactoperoxidase and lysozyme which supplemented the milk's antibacterial properties. These peptides kill the bacteria by disrupting the cell walls and membranes of the bacterial infected organism (Al-Saleh et al., 2011).

It is commonly recognized that camel milk offers protection from harmful germs. It is said to have an inhibitory impact on a variety of fungus, bacteria, and Gram-positive and Gram-negative bacteria. The presence of several naturally occurring inhibitory components, including lactoferrin, lysozyme, lactoperoxidase system, and different immunoglobulins, is frequently credited with camel milk's antibacterial activity (Muthukumaran et al., 2023).

Anti-inflammatory and Antioxidant Properties

Many diseases are related to each other and most of them have chronic inflammation as one of the major signs; persons of metabolic syndromes have many autoimmune diseases. The bioactive composition in camel milk such as unsaturated fatty acid along with vitamin C and E have found to possess strong anti-inflammatory capability. These chemicals help in the elimination of free radicals and the lowered expression of inflammatory cytokines which are beneficial in decreasing oxidative stress and inflammation (Mudgil et al., 2018).

Consuming camel milk, vitamins E and C vitamins present in it help the body fight oxidative stress. Presence of oxidative stress is observed in ageing as well as development of chronic diseases. It also explained that the antioxidants in the camel milk protect the cells and tissues from oxidative stress and free radical damage by maintaining the structural integrity of the cells (Alavi, Salami, Emam-Djomeh, and Mohammadian, 2017).

There is a scientific evidence proving that camel milk can control the level of cytokines and inflammation factors. It has been reported to reduce interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) which are potent pro-inflammatory cytokines (El-Agamy, 2007).

Modulation of Autoimmune Responses

Autoimmune diseases occur when the immunity system triggers an immune response against the tissues of the body. The findings on the biomolecules found to modulate autoimmune reactions in camel milk have been presented. Different scientific researches show that camel milk can be very helpful in autoimmune diseases like rheumatoid arthritis, and especially type 1 diabetic patients. The compounds present in the milk might reduce the impact that autoimmune processes may have and thus help facilitate immunotolerance (Agrawal et al., 2007).

Antiviral Activities

Antiviral potentials against many viruses have been reported of camel milk. It also consists of Immunoglobulins and Lactoferrin through which it shows the power to inhibit the exact replication process of viruses and to reinforce the body's protection from diseases. For instance, lactoferrin has been pulled out to deter viruses including hepatitis B and C, HIV and the flu from getting into the cell and multiplying (Redwan et al., 2014).

In a study conducted by El Fakharany et al. it was proved that IgGs and lactoferrin of camel milk were effective in inhibiting Hepatitis C Virus (HCV). It is noteworthy that camel IgGs outperformed human IgGs in identifying HCV peptides. The beneficial action of camel lactoferrin against HCV was demonstrated by its ability to inhibit HCV replication by 0.25–1.25 mg/mL. The results of a related investigation on the antiviral activities of human, bovine, and camel lactoperoxidases against the herpes simplex virus type 1 showed that all lactoperoxidases could inhibit the HSV-1 in a vero cell line model (Muthukumaran et al., 2023).

Clinical Implications and Future Directions

Therefore, it is proposed that camel milk's immunomodulatory properties offer the potential to be utilized in a variety of therapeutic applications. It is a valuable supplement in the treatment of inflammatory conditions, autoimmune and infectious diseases because it enhances immune reactions, has anti-inflammatory properties, and provides protection against infections.

Future researches should focus on undertaking clinical trials in order to determine the prospect therapeutic applications of camel milk in various populations. Besides, to understand the ability of the extract as immunomodulatory agent in detail, one needs to look deeper into the molecular level of how it interacts with the immunological system, which would explain more about its prospect as a natural drug.

It can be specially noted that camel milk is rich in immunoglobulins and antimicrobial peptides, anti-inflammatory chemicals, and antioxidants, which makes it an immunomodulator of power. The effectiveness of the substance for medical application see in their ability to increase activity of the immune system, to combat infections and manage inflammation. This paper identified that with more research camel milk can be an important nutritional and therapeutic aid in the management of several disease conditions attributed to the immune system.

Conclusion

Camel milk is a food that is high in macro- and micronutrients and rich in nutraceuticals. The breed, the stage of lactation, and seasonal fluctuations all affect the chemical makeup of camel milk. Because camel milk contains a variety of helpful microbes, including Lactobacillus, as well as the chemical components lysozyme and lactoferrin, it has the potential to have antimicrobial properties. Due mostly to the bioactive peptides that are produced from it, camel milk is also linked to antidiabetic effects. Investigations conducted in vitro revealed the suppression of different enzymatic markers, but investigations conducted in vivo revealed the involvement of additional pathways in the antidiabetic effects of camel milk.

Consumption of camel milk is on the rise due to the numerous health benefits that are associated with it setting special emphasis in regulating immunity. Camel milk is in contrast to cow's milk is nutritious because it contains special proteins, antibodies and enzymes which strengthen body immunity. Some of these components are; immunoglobulins, lactoferrin and lysozymes which have antibacterial, antiviral and anti-inflammatory properties.

Some of the studies show that camel milk reduces autoimmune diseases and allergies by regulating the chemical messengers in the system. It has comparatively low allergenicity, and thus can be recommended to persons with cow's milk allergy or lactose intolerance. Further, the milk has been proved to have a positive impact on gut health which is in some way associated with immune system.

Altogether, it can be concluded that camel milk can be used in the diet to boost the immune system and to prevent different infections and diseases. Consequently, the further advancement of science in the utilization of camel milk could then be considered as a considerable aspect of nutritious and therapeutic interventions for immunity.

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Chapter 36

Nature's Defence: Harnessing Botanicals to Combat Mastitis

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ABSTRACT

The dairy industry is heavily damaged by the disease known as bovine mastitis. Bovine mastitis occurs when pathogenic microbes infiltrate into the mammary gland and cause the destruction of tissues. Due to that, there will be a reduction in milk production and quality and also financial losses to the dairy department by culling the animals and expanding on the treatment. The etiology of mastitis includes various microorganisms like bacteria, viruses, algae, and yeasts. Notorious organisms such as *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococci*, and coagulase-negative *staphylococci* (CNS). For the treatment and control of mastitis, various antimicrobials are used but unfortunately, these arise a scenario of Antimicrobial Resistance (AMR) which does not cure the disease as well as forming residues in milk which contributes to environmental damage and indirectly food safety. To combat with these challenges various protocols and measures were adopted like biosecurity protocols, vaccination protocols, nano therapy, and new generation antimicrobials. These play a crucial role in control but do not stop it from spreading. Promising antibacterial properties against mastitis pathogens have been demonstrated by phytotherapy, specifically using essential oils derived from plants such as *Nigella sativa*, *Aloe vera*, *Azadirachta indica*, *Curcuma longa*, and *Cinnamon cassia*. Furthermore, several additional plants, including *Syzygium aromaticum*, *Cymbopogon citratus*, *Punica granatum*, *Centratherum anthelminticum* and *Allium sativum*, have shown a strong antibacterial effectiveness against microbes that cause mastitis. These botanical extracts have considerable antibacterial activity and contain bioactive substances including flavonoids, alkaloids, and essential oils that could be used in addition to or instead of traditional mastitis therapies.

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INTRODUCTION

Bovine mastitis is a notorious and deadly disease that is the cause of culling animals as well as treatment costs from this disease worldwide. Mammary gland inflammation in dairy cattle is caused by the entrance of pathogenic microorganisms which destroy the tissues (Zigo et al., 2021). According to a recent report, mastitis is caused by about 137 species of microorganisms which include bacteria, algae, and yeasts (Prusa, 2020). Mastitis, as a result, yields reduced milk production, bad quality milk, and financial losses to the dairy industry by culling the animals as well as treatment costs and extra labor (Hogeveen et al., 2019). According to recent statistics, India is among the largest milk producers globally, with production is about 16% (Dervillé et al., 2023). Mastitis annual financial losses in India, the United States, the United Kingdom, and globally are estimated at 1.1 billion dollars, 2 billion dollars, 371 million dollars, and 35 billion dollars respectively (Tarazona-Manrique et al., 2019). Notorious bacteria from gram-positive and gram-negative that cause mastitis are *staphylococci*, *Escherichia coli*, *streptococci*, and *Klebsiella pneumonia* (Otenga, 2023). An opportunistic pathogen that emerged to cause bovine mastitis is coagulase-negative staphylococci (CNS) (Vidlund et al., 2024). For the treatment of mastitis, a lot of antibiotics are used from different families which results in antibiotic resistance. Antibiotic resistance is examined by many researchers around the world. According to the report by Estonia and Ethiopia, a high resistance comes from penicillin against s. aureus and CNS (Rusenova et al., 2022). In West Bengal India, resistance has been shown to tetracyclines and β lactams by some gram-negative bacteria (Saha et al., 2014). Clindamycin, cefotaxime, and penicillin resistance is shown in Mexico by some Gram-positive as well as negative pathogens (González et al., 2023). Antimicrobial resistance reports from Canada show *Streptococcus uberis* and *Streptococcus dysgalactiae* produce some resistance genes to antibiotics (Vélez et al., 2017). Fluoroquinolones and spectrum β lactams showed resistance to *E. coli* in southern Taiwan when they found residues in mastitis milk (Mahdavi et al., 2022). Therefore, changes in the treatment should be followed in those protocols which have no residues as well as not affecting other milk properties and milk yields. So, use of the ethnomedical plants will help in reducing mastitis to dairy herds and have no milk residues as well, so this milk will be beneficial for the well-being (Qureshi et al., 2023).

Standard Strategies and Control of Bovine Mastitis

Biosecurity

Mastitis is a common disease so for that there should be proper checks and balance of the disease so for measures there should be good biosecurity so that the infectious agent cannot approach the animal so for that there should be proper hygiene, and effective therapeutic protocols. For that purpose, "5 point plans" developed by the National Mastitis Council which contains control program for mastitis, and that plan tell us the approaches for the prevention of mastitis (Ruegg, 2017). In European countries, researchers suggest the protocol named BIOCHECK CATTLE® which is used for the checking of Biosecurity across the farms (Rissala, 2022).

Antimicrobial Therapy

In the field and dairy farms, there is a lot of usage of antimicrobials. These antimicrobials are given through different routes but most commonly through parenteral and intramammary routes, which stops the progression of the disease further as well as locally reduce the inflammation of the udder. So, for that purpose, it is a common and standard strategy to control mastitis. Fluoroquinolones, penicillin, sulfonamides, tetracyclines, and β lactams are from different families used for the treatment of mastitis but usage of these has some residual effects on the health of the consumers (Vidović et al., 2022). So the usage of antibiotics leads to antibiotic resistance and as well as disturbing the food chain and ecosystem (Kabelitz et al., 2021).

Vaccination

To combat antimicrobial resistance (AMR) the development of a vaccine against mastitis took place. Vaccine results come when there is proper administration and formulation of the vaccine has been approved. Most mastitis vaccines used are polyvalent Startvac® containing inactivated J5 strain of E. coli and SP 140 strain of S. aureus because they are the major pathogen involved in mastitis. Startvac® and Mastivac® are the commercially available vaccines but according to studies, no significant result is shown by these products in clinical mastitis nowadays (Tashakkori et al., 2020).

Alternative Treatments: Potential Solutions

Nano-therapy

Nanotechnology is a new technique used now-a-days in many diseases and it has successful results. Nano-therapy is used in the fields of reproduction, genetics, and medicine. There are a lot of nano-formulations in the form of gel as well as in coated form. Along with types like silver, gold, zinc, copper, and chitosan nanoparticles which are used for the control of bovine mastitis (Orellano et al., 2021).

Therapy of Bacteriophage

These are the viruses that propagate and proliferate inside the bacteria, and, in this way, they reduce and suppress bacterial proliferation. They are specific to specific bacteria. Bacteriophages for the mastitis pathogen are present in *E. coli*, *S. aureus*, *S. uberis*, and *S. dysglactiae* and these bacteriophages are ready to produce vaccines (Guo et al., 2021; Titze et al., 2020).

Phytotherapy

One of the most popular and promising non-traditional methods for treating and preventing various illnesses in cattle is phytotherapy (Groot et al., 2021). The biological diversity of plants provides a never-ending source of novel possibilities for potential use as medicinal substances. Besides that, these plants can play a role of synergism with antibiotics and increase their efficacy (Cheesman et al., 2017). Numerous plant-derived substances are useful in treating mastitis, according to scientific data. Aromatic oily liquids, or Essential Oils, are formed from plant ingredients and are used in phytotherapy for a prolonged period (Ebani and Mancianti, 2020). Tomanić et al. (2023) recommended that *Thymus serpyllum*, *Origanum vulgare, Thymus vulgaris*, and *Satureja montana* be included in Essential Oil-based pharmaceutical formulations (Phyto-Bomat®) as a part for mastitis control regime because they resolve symptoms after treatment and prevent the progression of clinical mastitis in situations where sub-clinical mastitis exists.

Animal Derived Antimicrobials

Saliva, tears, bronchial mucus, colostrum, and milk all include the multifunctional glycoprotein lactoferrin, which has a wide range of biological activities, such as antimicrobial, anti-inflammatory, immunomodulatory, anti-catabolic, and antioxidative properties (Cheng and Han, 2020). Beyond lactoferrin, antibacterial proteins found in milk include lysozyme, immunoglobulins, lactoperoxidase, and β-defensin. These proteins work by inactivating bacteria, preventing bacterial adhesion to mammary tissue, and neutralizing poisons. It has been effectively demonstrated that lysozyme, which hydrolyzes the peptidoglycan, a key component of bacterial cells, can increase the efficacy of antibiotics against *S. uberis* and *S. dysgalactiae*, which are linked to bovine mastitis (Kabelitz et al., 2021).

Most Prevalent Bacteria in Mastitis

The mastitis was associated with 13 distinct bacteria species. Of all the isolates, 49.53% were *S. aureus*, which often recovered bacterial species. *Streptococcus agalactiae* (23.85%), *S. hyicus* (8.89%), *S. epidermidis* (6.53%), and *Bacillus* spp. (3.76%), *S. hominis* (1.42%), *E. coli* (1.40%) *S. xylosus* (0.94%), *Streptococcus dysgalactiae* (0.93%), *Corynebacterial* spp. (0.91%). Prototheca and yeast reported for 0.49% of isolates, respectively. Two (0.95%) isolates tested positive for coagulase-negative *staphylococci*. It is recommended that mastitis control in the research area focus on practices for managing contagious mastitis, due to the high prevalence of contagious pathogens. (*S. aureus*, *Str. agalactiae*) (Ali et al., 2008).

Therapy of Mastitis by using Essential oils

Essential oils are volatile compounds extracted from plants through distillation, retaining the characteristic fragrance of their botanical source. Traditional medical systems worldwide prescribe essential oils extensively, citing their numerous biological and pharmaceutical properties, including antifungal, antibacterial, antimutagenic, anti-inflammatory, anticancer, antidiabetic, antiviral, and antiprotozoal effects (Raut and Karuppayil, 2014).

Dalchini (*Cinnamon cassia* oil)

Due to its miscibility in milk, potential antibacterial mechanisms, and antimicrobial effectiveness against key pathogens causing bacterial bovine mastitis, *cinnamon cassia* oil is a valuable addition to dairy products. All pathogen isolates from bovine mastitis that have been investigated have been inhibited by *C. cassia* oil. Discs containing 20µL of 2.5% (v/v), *C. cassia* oil solution produced inhibition zones of 29.7, 19.4, 26.0, 33.5, and 30.8 mm for *S. epidermidis*, *S. aureus, S. xylosus*, *S. hycius,* and *E. coli* respectively, in the disc diffusion assay. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of *C. cassia oil* were 0.00625 and 0.025% (v/v), 0.025 percent and 0.10% (v/v), and 0.0125 and 0.05%, respectively (Zhu et al., 2016). The antibacterial activity of plant-derived antimicrobials, such as thymol, carvacrol, eugenol, and transcinnamaldehyde (TC), against the main pathogens responsible for bacterial mastitis, was studied in milk. The four compounds generated from plants showed antibacterial efficacy against several microorganisms, including *Streptococcus uberis, Staphylococcus aureus*, *Streptococcus dysgalactiae* and *Escherichia coli* (Faleiro and Miguel, 2013).

Neem (*Azadiracta indica*)

Neem oil works well to prevent udder infections. *Azadiracta indica* is utilized as an insect repellent in its bark, seeds, leaves, and roots. In the past, *Azadiracta indica* was used to manage livestock insects like horn flies, flow flies, and biting flies. Mastitis and *E. Coli* are successfully combated by *Azadiracta indica* oil. *Azadiracta indica* is an alternative treatment for bovine mastitis and a useful anti-inflammatory and antibacterial medication (Uchegbu et al., 2011).

Haldi (*Curcuma longa*)

Different Curcuma longa rhizome fractions' in vitro antibacterial activity was examined against clinical isolates of *S. aureus* as well as standard strains. Compared to the reference strain of *S. aureus*, the clinical isolates were found to be more sensitive for 148 distinct fractions (Kali, 2015).

Kalajira (*Nigella sativa*)

It may help dairy cows recover from subclinical mastitis caused by Staphylococcus aureus infections by acting as a treatment agent for the extract from kalajira leaves. According to reports, when *Nigella sativa* extract was injected into Holstein cows, the number of milk somatic cells in the quarters infected with *Staphylococcus aureus* dropped (Mushtaq et al., 2018).

Tulsi (*Ocimum sanctum*)

Aqueous extract of *O. sanctum* leaf was found to have immunotherapeutic effects in treating sub-clinical mastitis (SCM) in cows. After administering an intramammary infusion of an aqueous leaf extract of *O. sanctum*, various parameters were measured, including somatic cell count (SCC), total bacterial count (TBC), milk differential leukocyte count (DLC), phagocytic activity and index, and concentrations of leukocyte lysosomal enzymes like myeloperoxidase and acid phosphatase. According to the findings, the *O. sanctum* aqueous extract therapy decreased the TBC and increased the numbers of neutrophils and lymphocytes along with improving the phagocytic activity and phagocytic index. Analogously, mice treated with the extract also exhibited a considerable increase in the lysosomal enzyme findings of the milk polymorphonuclear cells (PMNs). The results indicated the presence of several biologically active components with antibacterial and immunomodulatory properties in the raw aqueous extract of *O. sanctum* (leaf). Thus, this study supports the therapeutic use of medicinal herbs and highlights how readily available, non-toxic compounds might improve breast immunity (Sharun[1] et al., 2021).

Gheegwar (*Aloe vera*)

The findings indicate that 76% of *S. aureus*, 88% of *E. coli*, 97% of *Streptococcus uberis*, and 88% of methicillin resistance *staphylococcus aureus* cells experienced lysis because of treatment with *aloe vera* gel extract that damaged their cell membrane. Anthraquinones are thought to be responsible for cell membrane breakdown.7

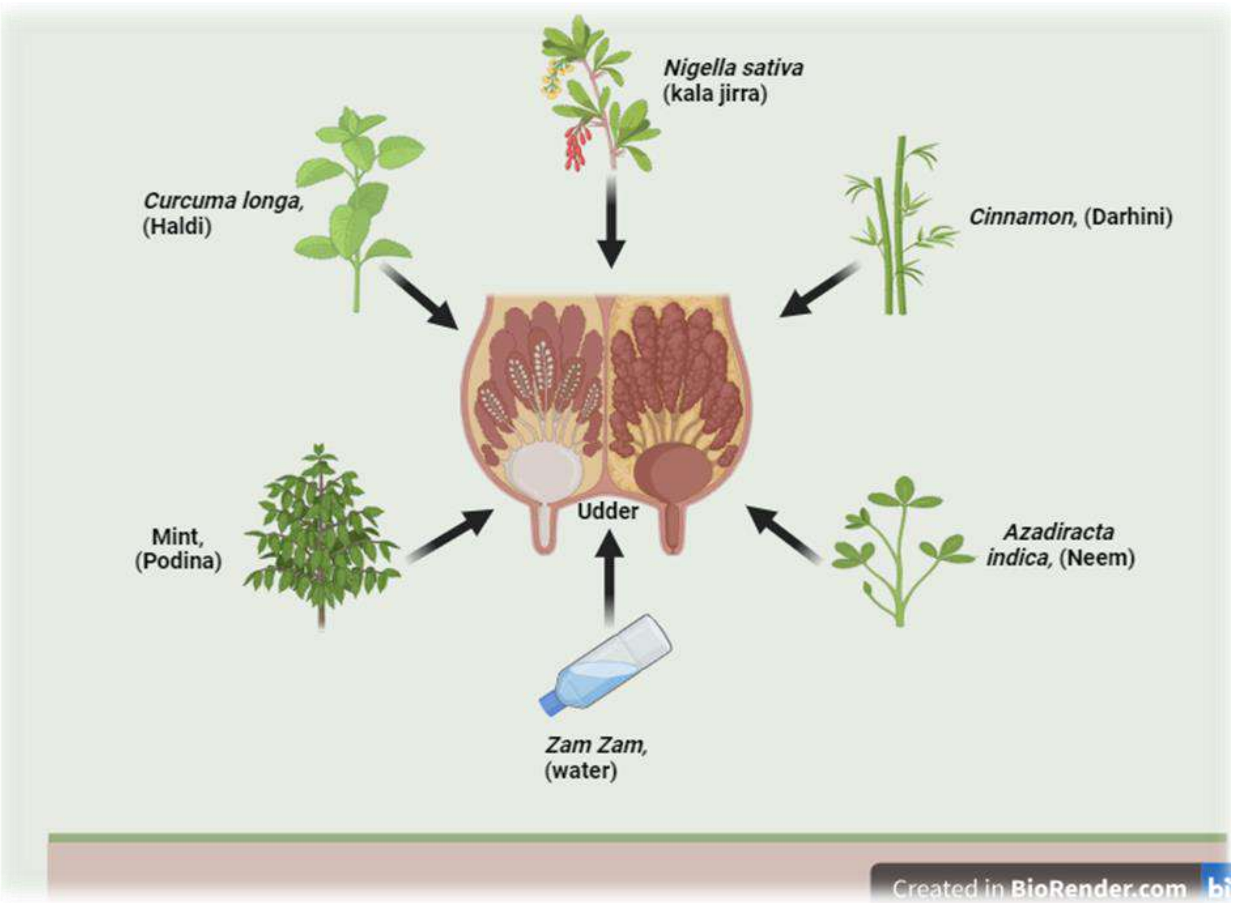

Fig. 1: Use of different botanicals for the control of mastitis

***Zam-Zam* Water**

The Prophet Mohammad of Islam (peace and blessings of Allah be upon him) said: " The water of *Zam-zam* is the finest water on Earth; it serves as nourishment and a source of healing from diseases" (El-desoukey, 2020). *Zam-Zam* water has antioxidant properties as most diseases of animals and humans are due to oxidative stress. It is alkaline in nature that it reduces cytotoxic and clastogenic effects (Yazdi et al., 2017). *Zam-Zam* water has antimicrobial properties against pathogenic microbes like *E. coli* and *salmonella* (El-desoukey, 2020) which are commonly found in the milk and udder of mastitis cow. *Zam-Zam* water also contains calcium and magnesium as well as fluorides which have germicidal properties as well as it does not allow the growth of algae (Boshra et al., 2021). Fig.1 shows the use of botanical compounds for the control of mastitis.

Conclusion

The chapter underscores the severe impact of bovine mastitis on dairy operations worldwide, leading to diminished milk production, compromised quality, and substantial economic losses. This disease, caused by various microorganisms, including antibiotic-resistant strains like *S. aureus* and *E. coli*, poses challenges due to traditional antibiotic treatments that contribute to resistance and leave harmful residues in milk. Alternative approaches such as biosecurity measures, vaccination, nano-therapy, and phytotherapy using plant-derived compounds like essential oils offer promising avenues for combatting mastitis. These natural extracts contain potent antibacterial agents that could serve as effective and sustainable alternatives to conventional treatments, potentially reducing reliance on antibiotics while safeguarding food safety and environmental health. Continued research and implementation of these alternative therapies are essential to managing and mitigating the pervasive impact of mastitis on dairy herds globally.

Table 1: Other Botanicals and their efficacy against mastitis pathogens

Botanical	Microorganisms	Material	Action	References
Triticum aestivum *Oryza sativa* *Bunium persicum* *Allium sativum*	*Klebsiella pneumoniae* *E. coli* *S. aureus*	Methanolic extracts, flavonoids, saponins and alkaloids	Showed a strong zone of inhibition methanolic extracts and alkaloids showed the best results	(Amber et al., 2018)
Alpinia zerumbet	*S. aureus*	Ethanolic extract and essential oil	At the concentration of 100 mg/mL$^{-1,}$ the strains were extremely sensitive as well also when we used ethanolic extract	(Castro et al., 2016)
Cinnamomum zeylanicum *Syzygium aromaticum*	*S. aureus*	Compounds isolated include eugenol and cinnamaldehyde	Lower MIC, higher antibacterial activity, affected biofilm formation	(Budri et al., 2015)
Punica granatum	*S. aureus, S. saprophyticus* and non-aureus staphylococci	Hydroalcoholic extract	At a concentration of 0.125 mg/mL^{-1} , strong antibacterial activity	(Moreira et al., 2014)
Cymbopogon citratus	*Streptococcus uberis, P. aeruginosa, E. coli, S. aureus, and Staphylococcus positive and negative coagulases*	Hydroalcoholic extracts and essential oils	Satisfactory results from essential oils and high antibacterial activity	(Goncalves et al., 2013)
Cymbopogon nardus *Symphytum officinale* *S. Officinalis* *Calendula officinalis*	*S. aureus*	Extract of n-hexane, dichloromethane, ethanol/water, and ethanol.	Strong activity even affects biofilm formation	(Diaz et al., 2010)
Zingiber officinale *Ocimum basilicum*	*Staphylococcus* spp.	Isolated compounds (carvacrol, thymol, and cineole) and essential oils	Equally active, but less than carvacrol and thymol essential oils of *Z. Officinale*	(Dal Pozzo et al., 2011)

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Chapter 37

Use of Traditional Chinese Medicine in Cancer Treatment

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ABSTRACT

Traditional Chinese medicine is among the alternate approaches in the treatment of numerous forms of cancer may not be overemphasized because more than 400 herbs have therapeutically important effects. Herbs help in various ways such as stimulating the immune system, inducing cellular suicide, and inhibiting cancer proliferation. TCM also incorporates the acupuncture procedure, to reduce the symptoms of cancer and reduce the treatment complications. Moreover, in cancer patients, the acceptance of acupuncture increases due to the minimal safety profile and low side effects. To improve TCM related to cancer and get a desirable outcome, traditional therapies can be applied concurrently, such as acupuncture, herbal medicine, etc. Herbs of TCM can be effective in the course of treatment, which, being their multiple natural ingredients, enable to correct the pathologies. Although TCM is likely to affect the body as a whole and have multi-dimensional effects on cancer treatment, we need to know the molecular targets and combine TCM with traditional cancer treatment. TCM provides patients with tailor-made comprehensive care, so it can be considered a good complementary technique in the process of cancer treatment. It will need more research and effort in integration to utilize TCM capabilities to their full potential.

KEYWORDS		
Traditional Chinese medicine, Cancer, Acupuncture, Herbals	Received: 15-June-2024 Revised: 20-July-2024 Accepted: 21-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

The greatest cause of mortality globally is cancer, which also poses a significant obstacle to raising life expectancy. According to data released by the World Health Organization (WHO) in 2019, cancer is the primary reason for death accounting for nearly 10 million deaths in 2020 (WHO, 2022). Based on statistics from different locations, there is a significant variation in the most predominant cancer types globally, mainly in terms of male incidence (eight different cancer types) and male and female death (seven and eight types, respectively). In 112 countries, men are diagnosed with prostate cancer more often than any other cancer (Alonso et al., 2018). Lung cancer is diagnosed in men 36 times more often than colorectal and liver cancer 11 times. Prostate cancer and lung cancer rank first and second, respectively, in 48 and 23 countries, while liver cancer is the 3rd most prevalent source of death for males worldwide (Mattiuzzi et al., 2019).

The two most common cancers diagnosed in women are breast cancer (reported in 159 countries) and cervical cancer (in 23 of the remaining 26 countries) (Alonso et al., 2018). The death rates for women are more varied, with breast and cervical malignancies ranking 1st and 2nd in 110 and 36 countries, respectively, while lung cancer is third in 25 countries (Bray et al., 2004). In 202, men had a 22% higher global incidence rate of all cancers than women, with 186 incidents per 100,000 people. However, due to changes in cancer forms and risk factors, there are substantial regional variations. For example, Australia and New Zealand have higher incidence rates of skin cancer, especially non-melanoma types, attributed to intense sun exposure among their predominantly fair-skinned populations, as well as improved disease detection. These geographic disparities highlight diverse risk factor exposure, types of cancer prevalent, and challenges in early detection and prevention (Tran and Collaboration, 2019). Globally, the mortality rate from cancer is 43% greater for men than for women, with the difference in mortality between the sexes being twice as large as the difference in incidence. This mortality disparity is influenced by different cancer-type distributions (Jemal et al., 2011).

Rapid advancements in cancer immunotherapy (CIT) in recent years have highlighted the critical interaction between the human immune system and cancer. Even while CIT has proven to be remarkably effective in treating a variety of tumors, only a small percentage of patients with terminal illnesses benefit in a long-term, profound way from these treatments (Kumar et al., 2021). This intricacy most likely results from the immune systems sophisticated and finely tuned structure. Like any well-designed system, the immune system's ability to effectively abolish cancer cells depends on a sequence of biological processes. Additionally, the immune system has several fail-safes, checkpoints, and negative feedback loops that enable precise control and the termination of an immune response (Hegde and Chen, 2020).

Furthermore, cancer is a complex and adaptive illness that arises from several genetic mutations that impair normal cell activity and function (WHO, 2022). However, these genetic alterations can make cancer cells more identifiable to the immune system as alien, which presents a chance for CIT. Patients with cancer present with different symptoms, and tumors can differ even within the same person because of differences in the surrounding microenvironment and clonality of cancer cells (Marusyk et al., 2012). Moreover, some cancers develop from long-term inflammation, and some take advantage of or avoid immune reactions as they spread.

There are several possible consequences from this dynamic interaction between the developing immune system and emergent cancer, including total cancer elimination, continued equilibrium between the two, or unchecked tumor growth that eludes the immune surveillance (Greten and Grivennikov, 2019). By pursuing long-lasting effects and increased survival rates for cancer patients in both the terminal and early stages, CIT seeks to change these results in the direction of cancer eradication. Although CIT has great potential for specific patients, the more general objective of "curing cancer" poses substantial obstacles to CIT research (Bai et al., 2021).

The practice of TCM holds significant promise in treating a wide spectrum of illnesses, with cardiovascular disease, and autoimmune disorders, making it a valuable source for modern pharmaceutical development. Many medications developed from TCM have shown notable efficacy in treating various disorders (Fung et al., 2015). Examples of these drugs include celastrol, quinine, digitoxin, and artemisinin. The use of artemisinin-based medicines to treat malaria is one of the most well-known examples; in 2015, it was awarded the Nobel Prize in Physiology and Medicine. This recognition has sparked a greater interest in TCM and a commensurate demand for data resources of TCM (Wang and Chen, 2023).

The main ingredients of TCM are herbs; more than 11,000 plant species are listed in TCM-related pharmacopeias, of which about 700 species are used often. Many herbs are often used in TCM formulations to treat various diseases, leading to the development of thousands of herbal formulas that are often used in clinical settings (Lee, 2000). Theoretically, several active substances in TCM herbal formulae can simultaneously regulate different cellular targets, returning patients' physiological regulatory networks to balance and treat various disorders (Man et al., 2022). Nevertheless, despite these advantages, the majority of TCM formulae and components' molecular targets are still poorly understood, which presents a major obstacle to the use of TCM and TCM-based medication discovery (Li et al., 2022).

How Traditional Chinese Medicine Works

The foundation of TCM is a cohesive Chinese cosmology that situates human health in the larger scheme of the cosmos. This cosmology is the result of generations' worth of collective knowledge that was developed via observation, meditation, and introspection on the human body and natural phenomena. It was first developed through intellectual discussion (Xutian et al., 2009). TCM medicine focuses on reestablishing equilibrium between the complexly interwoven elements to liberate the universe's life force, which manifests as vigor and vitality in the human body. Harmony Among systemic therapies, pair therapy (CCT) is unique due to its empirically supported efficacy in treating mental health and addiction disorders (Pinquart et al., 2016). Psychotherapy in the style of systemic therapy sees psychological illnesses as impacted by social interactions rather than as discrete issues (von Sydow et al., 2010). The social environment often involves a person’s spouse and family members as a significant element. A systemic approach highlights the interactive character of issues and their contributing causes by identifying recurrent patterns of causality between relationships and symptoms (Lee, 2014). Systemic therapies can be used with individuals, couples, or groups because they are characterized by their conceptual framework of understanding the interactive dynamics of problems and their components rather than by the number of participants. Empirical research in CCT has clarified the interactions between couple relationships, adverse childhood experiences, and the emergence and progression of addictive behaviors, such as gambling disorders (Lee, 2014). Virginia Satir (1916–1988), a pioneer in family therapy, laid the groundwork for congruence couple therapy (CCT), a manual-based systemic therapy (Lee et al., 2017). Four integrative and iterative dimensions make up the theoretical framework provided by CCT for interventions. Research has indicated that CCT can effectively manage symptoms and enhance mental well-being, emotional control, and interpersonal bonds, especially when treating alcohol, drug, and gambling addiction (Lee and Addiction, 2009). A basic tenet of CCT and TCM is the interconnection of illness and addiction, respectively. Whereas the family system perspective of CCT sees people as complex systems interacting with their environment on four levels intrapsychic, interpersonal, intergenerational, and universal spiritual TCM sees the body as a system of organs interacting with one another and the environment (Lee et al., 2019; Lee and Awosoga, 2015). According to this theory, addiction cannot be effectively addressed in a vacuum; rather, all four dimensions and their interconnections must be taken into account (Lee and Culture, 2020). Relationships with spouses and families are both a person's natural environment and an essential resource, having a big impact on their physical and emotional well-being. One's perception of powerlessness or frustration can be impacted by the quality of exchanges in these relationships, which can vary from conflict-ridden or avoidant to supportive and reassuring. According to TCM, emotions have a direct impact on how important organs work, and bad emotions can cause physical problems (Liao, 2006). TCM concentrates on physiological processes to preserve health, whereas CCT modifies physiological and mental functioning by focusing on human connections, communication, and behaviors (Lee and Culture, 2020).

Herbal Medicine in Cancer Treatment

The discovery of "Ma Huang" (Ephedrae herba) in around 3000 BC marks the beginning of Chinese understanding of botanical medicine even further. China's materia medica history began during the Eastern Han period (AD 25–220) with the publication of the "Shen Nong Ben Cao Jing" (Divine Husbandman's Classic of Materia Medica), often referred to as The Canon of Materia Medica or Shennong's Herbal Classic (Audette and Bailey, 2008).

Chinese medicines have been used for millennia, and their effectiveness in treating and preventing cancer has been established (Perkins, 2004). Their benefit as natural medicines is that they have fewer side effects and are less toxic. Of the almost two thousand herbs listed in the Chinese Herbal Register, roughly four hundred have been demonstrated to have therapeutic advantages for various cancer kinds, including brain, stomach, liver, lung, prostate, and breast cancer (Matos et al., 2021). Their processes could include boosting immunity, encouraging cancer cell death, decreasing metastasis, and impeding the progression of cancer. Chinese herbal medicine is being cast off more often as an alternative to traditional cancer treatments. Herbal combinations have been shown to produce more potent and long-lasting healing effects (Zulfiker et al., 2017). Herbs can also protect normal tissues, make the body more sensitive to radiation and chemotherapy, and stop tumors from metastasizing and returning. Chinese herbal treatment fights tumors without harming healthy cells since, unlike Western medicines; it balances the body as a whole in addition to focusing on particular lesions (Zulfiker et al., 2017). It also lessens the negative effects of chemotherapy and radiation, sleeplessness, and exhaustion, all of which considerably improve patients' quality of life and lengthen their survival times. In China and other parts of South and East Asia, a wide variety of medicines and therapies have been used in cancer treatment over the past two millennia (Zulfiker et al., 2016).

Acupuncture in Cancer Care

Recently, there has been a noticeable increase in the demand for complementary therapies among cancer patients. According to a survey done throughout Europe, more than one-third of cancer patients use complementary therapies to reduce side effects from their treatment or to alleviate their symptoms (Molassiotis et al., 2005). Some patients may be seeking potentially dangerous and unproven alternative medicines due to this trend, which shows an unmet need within traditional medicine (Filshie and Rubens, 2006). Since symptoms are frequently caused by medication side effects and the location of the disease rather than the underlying diagnosis itself, many complementary medicines are not specifically designed to cure cancer. As a result, symptoms across individuals with different cancer diagnoses are frequently comparable (Black et al., 2015).

Based on Traditional Chinese Medicine, acupuncture stimulates certain body spots with needles or pressure (known as acupressure) to control the flow of "Qi," or life force. According to recent scientific research, the neurological system is responsible for the effects of acupuncture. This is supported by studies (Zhao et al., 2014) that demonstrate changes in brain functional MRI signals and the release of neurotransmitters during treatment. Furthermore, it has been demonstrated that acupuncture affects gene expression, which raises the synthesis of opioids. Western Medical Acupuncture has emerged as a result of clinicians with Western training accepting acupuncture more widely due to its strong scientific backing (White et al., 2018).

Still, a lot of medical professionals with Western training are dubious about the effectiveness of acupuncture, frequently attributing its benefits to the placebo effect or the practitioner's interpersonal abilities. Because of this mistrust, randomized controlled studies (RCTs) involving acupuncture now have to include sham acupuncture control arms (Sagar, 2008). However, because of the ongoing debate about the usage of penetrating and non-penetrating sham controls, many "control treatments" are not genuinely inactive (White et al., 2018). Certain fake needles are like stage daggers in that when applied to the flesh, the blunt needle retracts into the handle sheath.

Genuine acupuncture deactivates some areas of the amygdala, hippocampus, and anterior cingulate cortex while activating brain regions such as the nucleus accumbent and hypothalamus. Sham stimulation, on the other hand, mostly impacts the sensory cortex. According to (Wu et al., 2002) these results imply that acupuncture may have an impact on the affective-cognitive component of pain perception. Moreover, correlations between signal intensities and analgesic outcomes have been observed (Zhang et al., 2003).

Further studies employing PET scanning showed that, in comparison to sham needles, acupuncture produces extra effects in the ipsilateral insula with larger activation patterns (Pariente et al., 2005). When using acupuncture for cancer treatment, a licensed professional who can communicate effectively with the patient's oncology team should provide the

Table 1: Use of different herbal medicines in cancer treatment

Sr.	Scientific name	Chinese name	Bioactive compounds	Uses	Effects	Effects on genes and proteins	Effects on Pathway	Reference
1.	*Oldenlandia diffusa*	Bai Hua She She Cao	1-formaldehyde-4-hydroxyl, 2-hydroxy-3-methyl-anthraquinone, 2-hydroxy-7-methyl-3methoxyanthraquinone, and vanillic acid	Antioxidant, anticancer, immune regulation	Promote apoptosis in prostate cancer, clorectal cancer, cervical cancer, gastric cancer and other types of tumor cells.	Inhibit the expression of CXCR1, CXCR2, and CXCR4, suppress the production of MMP.9. In mouse model of kidney malignancy, the proteins caspase 7 were suppressed and caspase 3 and Fas were increased.	Stop bladder cancer T24 cell growth by blocking the JAK2/STAT3 pathway.	(Che et al., 2019; Guo et al., 2019; Liu et al., 2019; Zulfiker et al., 2016)
2.	*Curcuma longa*	CL, Jiang Huang	Curcumin	Therapeutic agent against chronic diseases and Anti-cancerous, spice and pigment.	prevent cervical cancer cells from proliferating and migrating and suppression of thyroid cancer growth and encouragement of apoptosis	Lessen the PI3K/AKT/mTOR signaling pathway's activity in oral squamous cell cancers. suppress glioma cell migration and proliferation while encouraging apoptosis. Its mode of action is intimately linked to the suppression of NEDD4 synthesis, an oncogenic protein. reduce the expression of the apoptosis-related protein Bcl-xl and stop the synthesis of Cyclin B1.	In hepatocellular cancer, lower Snail expression to prevent TGF-induced epithelial-mesenchymal transition (EMT).	(Feng et al., 2019; Liu et al., 2019; Yan and Cen, 2015)
3.	*Astragalus membranaceus*	Huang Qi	astragalus polysaccharide and astragaloside	Anti-viral, anticancer, immune regulation	inhibition of invasion and migration of cervical cancer cells. control the proliferation and metastasis of ovarian cancer. inhibits the proliferation of breast cancer cells. induce apoptosis of non-small cell lung cancer.	The downregulation of immune checkpoint proteins PD-1 and PD-L1 and the suppression of migration-related protein expression. MMP-2 and MMP-9, as well as reducing the production of these proteins and inhibiting ERK phosphorylation	Prevents breast cancer cells from growing by obstructing the PI3K/AKT/mTOR pathway. increases the expression of the apoptosis-related proteins caspase 3 and caspase 9, which controls the death of cancer cells, as well as raising the fraction of Bax/Bcl-2. cause macrophages to polarise into the M1 subtype and activate their anticancer potential.	(Liu et al., 2019; Park and Park, 2018)
4.	*Panax ginseng*	Ren Shen	Ginsenoside	cardiovascular protection, antitumor, and antiaging, Immune modulation	Promote endometrial cancer cells apoptosis,	Ginsenoside Rg5 can also increase the expression of the protein Bax and reduce the Bcl-2 protein in gastric cancer cells., which lowers the activity of the cancer cells. overexpression of the apoptotic protein and ROS generation BAX and caspase 3/9	Elevated levels of caspase 3 protein and cleaved poly ADPribose polymerase (PARP), indicators of apoptosis. Ginseng may inhibit the invasive migration and dissemination of stomach cancer cells by modulating the miR125b/STARD13/NEU1 signaling pathway.	(Chen et al., 2019; Liu et al., 2019)

5.	*Ganoderma lucidum*	Ling Zhi	proteins, amino acids, sterols, polysaccharides, triterpenoids, and alkaloids	Anti-diabetes, improve cardiovascular, anti-aging, anti-cancerous,	prevent breast cancer, endometrial cancer, and lung cancer cells from proliferating and dying	reduce the expression of the metalloproteinase tissue inhibitors MMP-2, MMP-9, TIMP-1, and MMP-2. The expression of TIMP-2 has to be raised. In addition, angelica polysaccharide downregulates cyclins and Bcl-2, cleaves caspase 3 and E-cadherin, raises Bax, and inhibits the TGF-signaling pathway.	Regulation of cell cycle and the increase of Bax/Bcl ratio. downregulate MMPs to inhibit metastasis of prostate cancer cells	(Martínez-Montemayor et al., 2019; Su et al., 2018; Zhang et al., 2019)
6.	*Angelica sinensis*	Dang Gui	polysaccharides, organic acid, and volatile oil	Analgestic, Anti-cancerous, anti-inflammatory,	Has immune-boosting and anticancer properties. therapy for anaemia associated with tumours. The death of cancerous cells	enhanced the expression of the cAMP-responsive elementbinding protein (CREB) in breast cancer cells, cleaved PARP, and upregulated caspase 3/9.	Inhibits PI3K/AKT/mTOR signaling pathway of cancer cells	(Chen et al., 2017; Chen XiaoPeng et al., 2013; Chiu et al., 2017)
7.	*Panax notoginseng*	San Qi	Panax notoginseng saponins (PNS)	enhancing immunity, anti-oxidant, anti-tumor/cancer, and anti-aging,	cancer treatment, which includes boosting immunity and stopping cancer cells from functioning. minimises the capacity of cancer cells to adhere; prevents colorectal and breast cancer cells from invasively spreading;	lowers the expression of MMP3, MMP-9, and vimentin and enhances the expression of E-cadherin and the cancer suppressor genes Brms1, Mtss1, and Timp2. reduces the protein levels of intercellular adhesion molecule-1 (ICAM-1) and E-selectin in endothelial cells EA.hy926 and integrin-1 in HCT-116.	lowering MMP-9 and raising E-cadherin expression	(Kim et al., 2018; Yang et al., 2016; Yu et al., 2012)
8.	*Scutellaria barbata D. Don*	Ban Zhi Lian	flavonoids, diterpenoids, and polysaccharides	antitumor, antivirus, and antioxidation	Inhibits migration ability of cancer cells. promote apoptosis of cancer cells.	The caspase 3/9 protein was increased and the Bcl-2 protein was downregulated to induce apoptosis. There should be an increase in Bax, Bak protein, and E-cadherin; a decrease in Bcl-2 protein, N-cadherin, and vimentin; and an inhibition of proliferation.	reduces MMP-2/9 production, which lowers VEGF and HIF-1 expression to prevent the development of a cancer microenvironment.	(Jiang et al., 2015; Pan et al., 2016; Sun et al., 2017)
9.	*Licorice*	Gan Cao	glycyrrhizic acid	antibacterial, antiviral, anti-inflammatory and anti-tumor	controls the process of cancer cells going through autophagy and apoptosis, which leads to their demise. cause oral cancer cells to undergo apoptosis. prevent stomach cancer cells from invasive and metastasizing	overexpression of the autophagy protein LC-3 and the apoptosis-inducing factor (AIF).	raising the cleavage of caspase 3/9 and PARP and raising the Bax/Bcl-2 ratio. expression of vimentin and MMP-2/9, and upregulate E-cadherin expression. suppress the ROS/pkc-/ERK signalling pathway to prevent cancer cells from undergoing EMT.	(Jiang et al., 2017; Lin et al., 2018; Liu et al., 2019)
10.	*Radix Salvia miltiorrhiza*	Dan Shen	tanshinone	Anticancerous,	suppresses the growth of lung adenocarcinoma, colorectal cancer, breast, prostate, and stomach adenocarcinoma.	preventing the MAPK/ap1 signal transduction pathway from driving the production of MMP-9.	elevated cytoplasmic level of cytochrome c and the activation of caspase 3/9, which causes PARP lysing	(Lee et al., 2017; Liu et al., 2015; Wu et al., 2018)

treatment. Patients favor it since it is a safe therapeutic option with a low profile of side effects (Sagar, 2008). Less than 0.55 out of every 10,000 individuals get significant side effects from acupuncture (White, 2004). A wide variety of acupuncture methods are accessible and efficient. Acupressure, auricular acupuncture, electroacupuncture, and patient-administered acupuncture are only a few of the methods that have been studied in randomized controlled trials (RCTs). A common treatment plan for acupuncture is weekly appointments for six weeks or twice-weekly treatments for three weeks, though the frequency and length of sessions vary greatly among practitioners. Patients with advanced cancer require modifications to their treatment plans based on their time constraints. Acupuncture is frequently more sensitive to cancer patients; those who are "strong reactors"—those who require fewer, milder treatments—need just shorter sessions (Mann, 2000).

Acupuncture needle points differ greatly as well; segmental, trigger, and conventional points customized for certain ailments are used by Western physicians (White et al., 2018). Meta-analyses of acupuncture trials are difficult to evaluate since there is disagreement about the best dosage, where to place needles, and how long to treat patients.

Recent developments in clinical research on acupuncture suggest that acupuncture may be useful in helping cancer patients manage their symptoms and receive supportive treatment. Anxiety, sadness, insomnia, hot flashes, discomfort, and gastrointestinal side effects are among the symptoms that have responded well to acupuncture treatment. As 45% of cancer patients globally are expected to survive for five years or longer after treatment (Coleman et al., 2008), Supportive treatments that can lessen symptoms without requiring long-term medication are becoming more and more necessary. Acupuncture can also be used as an adjuvant therapy in settings for palliative and end-of-life care (Standish et al., 2008).

Conclusion

Cancer is a major global health concern. It comes in a variety of forms and takes numerous lives. People are looking for better medical care. Even with advancements in standard therapies, there is always a need to find ways to extend patients' lives and increase their chances of survival. There is some hope in Traditional Chinese Medicine (TCM). It employs both conventional wisdom and natural remedies. TCM treats patients via acupuncture, herbs, and other techniques. Herbal remedies comprise a variety of herbs and mixtures that help strengthen the body's defenses, destroy harmful cells, and prevent cancer from spreading. TCM uses a variety of medicines that target different body areas to prevent cancer. TCM offers individualized care to patients wherever they may be, which makes it an excellent tool in the battle against cancer. TCM may help usher in a new era of cancer therapy that is healthier for patients and doesn't make them sicker with more study and development of its medicines.

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Chapter 38

Therapeutic Potential of Sterculia Seeds in Metabolic Syndrome

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ABSTRACT

Metabolic syndrome (MetS) represents a significant health concern globally, necessitating diverse strategies for its management. Non-pharmacological approaches, including lifestyle modifications, dietary adjustments, and the incorporation of nutraceutical and functional foods, play a crucial role in addressing MetS. Among the plant genera showing promise in alleviating MetS is *Sterculia*, a member of the Malvaceae family encompassing over 200 species with documented ethnopharmacological uses. The seeds composition of certain *Sterculia* species has been studied, revealing compounds with therapeutic potential. This chapter focuses on the promising effects of antioxidant compounds and cyclic fatty acids found in *Sterculia* seeds. These bioactive constituents hold the potential for preventing or treating the metabolic abnormalities of MetS.

KEYWORDS
Malvaceous, *Sterculia*, Seed´s oil, Cyclic fatty acids, Inflammation, Oxidative stress

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INTRODUCTION

Metabolic syndrome (MetS) is currently one of the most important public health problems in the world. It is considered one of the most persistent epidemics globally, silently spreading with a high annual morbidity rate and a steady increase leading to the appearance of metabolic diseases early in life (Saklayen, 2018). The prevalence of MetS varies according to geographical region, place of residence, population composition, and the type of definition used. However, it is estimated globally to range from 10 to 84%, with an average of 20-25% in the adult population (Sherling et al., 2017).

MetS is characterized by the combination of three or more metabolic abnormalities that are interconnected and associated with a two-fold higher risk of developing cardiovascular diseases and a five times higher risk of developing type 2 diabetes mellitus, two of the principal metabolic diseases nowadays (Grundy et al., 2004; Aguilar-Salinas and Viveros-Ruiz, 2019). The main manifestations of MetS include insulin resistance, abdominal obesity, hypertension, atherogenic dyslipidemia (elevated blood levels of triglycerides and LDL-cholesterol, and low levels of HDL-cholesterol), high fasting serum glucose concentrations, endothelial dysfunction, oxidative stress, chronic low-grade inflammation and pro-thrombotic state (Kaur, 2014; Grundy, 2016; Harrison et al., 2020).

The pathogenesis of MetS may involve a genetic or epigenetic origin or can be the result of environmental and lifestyle factors, such as diet (quantity and quality), gut microbiota, or physical activity, considered as the main etiological factors. Among the mechanisms suggested explaining the pathophysiology of MetS, the most important is related to the presence of insulin resistance (IR), which is strongly interconnected with visceral obesity, inflammation, and oxidative stress. Adipose tissue plays a predominant role in the development of MetS. Besides functioning as an energy depot, it is a physiologically active tissue that secretes hormones like leptin and adiponectin, which control appetite and satiety, and regulate energy metabolism (Saklayen, 2018). Additionally, visceral fat promotes IR and the release of fatty acids that accumulate in organs such as the liver and muscle, further predisposing to IR, dyslipidemia, and oxidative stress. Adipose tissue also produces pro-inflammatory adipokines such as interleukins IL-1β and IL-6, and tumor necrosis factor-alpha (TNF-α), generating a state of low-grade chronic inflammation in tissues (Zand et al., 2017; Mastrocola et al., 2018). Inflammation also affects vasodilation, causing arterial hypertension, leading to serious cardiovascular problems (Kaur, 2014). In recent years, various studies have documented the important role of the increased activity of the enzyme stearoyl-CoA desaturase (SCD) in diseases such as cancer, Alzheimer's disease, skin disorders, and particularly in those associated with MetS. In consequence, it has become a new therapeutic target for the treatment of these pathologies (Peláez et al., 2020).

An effective strategy for managing MetS should include prevention, early diagnosis, and a multifactorial medical approach. Both pharmacological and non-pharmacological strategies have been applied, with combined treatments being the preferred option. Pharmacological treatments mainly focus on the individual components of the syndrome, with medications such as statins for treating dyslipidemia, or aspirin, diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers for treating hypertension, as well as drugs to reduce insulin resistance, such as metformin and thiazolidinediones (Kuete, 2017).

On the other hand, non-pharmacological strategies have a greater impact than pharmacological ones, as they address the problem comprehensively. They involve lifestyle changes, such as dietary modifications for weight reduction and maintenance, and the inclusion of bioactive compounds and nutraceuticals, such as polyphenols, vitamins, omega-3 polyunsaturated fatty acids, with activities as antioxidants, vasodilators, anti-atherogenic, antithrombotic, and anti-inflammatory (De la Iglesia et al., 2016; Rochlani et al., 2017). Dietary antioxidants can exert preventive and/or therapeutic effects on some metabolic alterations. These compounds are found in foods, such as vegetables, legumes, fruits, and seeds, or might be administered in supplements. Their mechanisms of action is related to the maintenance or restoration of the redox homeostasis by its interaction with the endogenous antioxidant defense system (Durazzo et al., 2021). In addition to MetS, this homeostasis unbalance can be provoked by the overproduction of free radicals caused by pollution, ultraviolet radiation, smoking, and infections, which together may cause cancer, diabetes, cardiovascular and neurodegenerative diseases (Masenga et al., 2023).

Dietary lipids have received a lot of attention in dietary recommendations that usually include replacing dietary saturated fatty acids with unsaturated fats or with carbohydrates from whole grains foods. However, the diverse effects of specific fatty acids and the interindividual variability of responses make it challenging to establish specific recommendations (Harrison et al., 2020). In recent years, special interest has been given to cyclopropenoic fatty acids contained in the seeds' oil of plants from the genus *Sterculia*, due to their activity as inhibitors of the enzyme SCD (Peláez et al., 2020).

Sterculia **Genus**

The Malvaceae family comprises tropical flowering trees and shrubs, and some climbing and herbaceous species; contains over 240 genera and nearly 2300 species (Thabet et al., 2018). These plants possess secondary metabolites, including flavonoids and other compounds with diverse bioactivities. Flowers and seeds from *Hibiscus* and *Theobroma* have applications in the food industry, while fibers from *Gossypium*, such as cotton, are used in the textile industry (Robles-Valdivia and Sánchez-Otero, 2022). Among the key genera, *Sterculia* stands out for its commercial and medicinal significance (El-Sherei et al., 2016).

The genus *Sterculia* belongs to the subfamily Sterculioideae, and includes 200 species approximately, mainly distributed in tropical and subtropical regions (pantropical genus) (Rodríguez and Santamaría-Aguilar, 2020). Species within the *Sterculia* genus are notably prevalent in the Asian tropics, while in the Americas, approximately 38 species are reported (Fig. 1). These species thrive in diverse habitats, including tropical rainforests, humid and very humid forests, and altitudes of up to 1600 meters above sea level (Rodríguez and Santamaría-Aguilar, 2020).

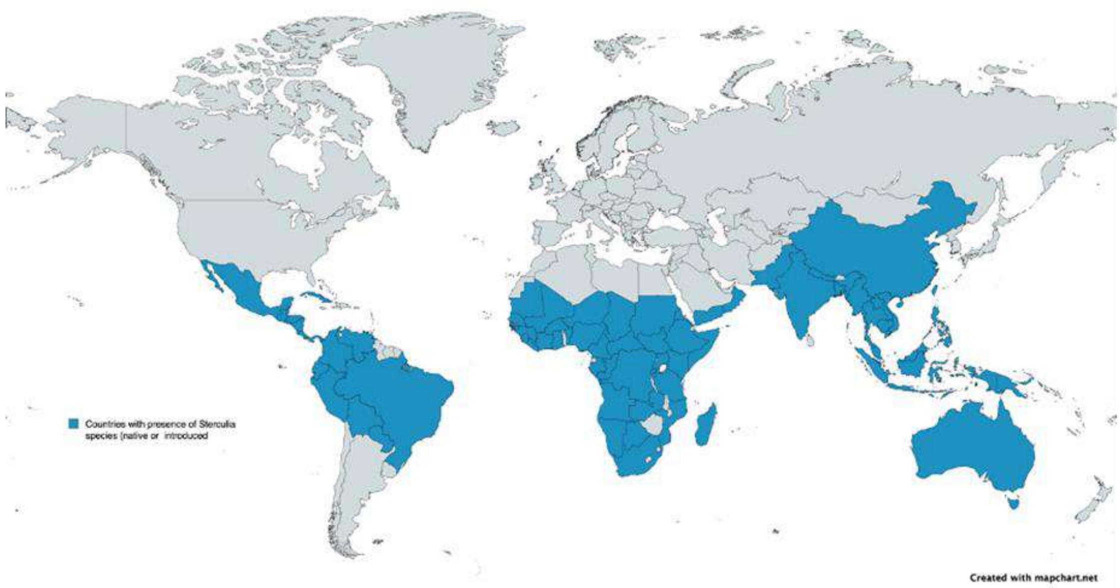

Fig. 1: Distribution of *Sterculia* genus in the world. (Own elaboration in www.mapchart.net adapted from POWO, 2024. http://www.plantsoftheworldonline.org/).

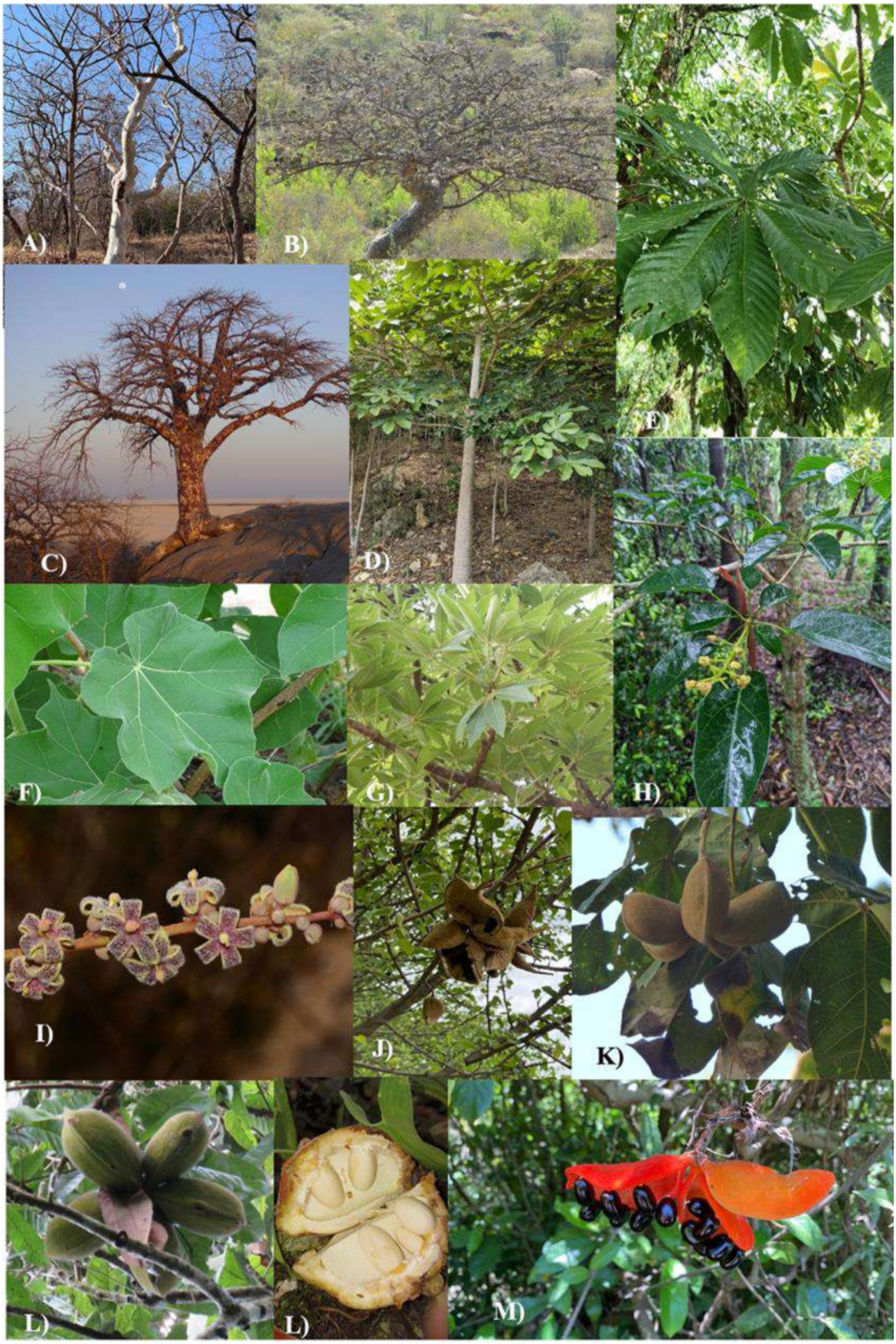

Fig. 2: Trees, leaves, flowers, fruits, and seeds of *Sterculia* species. A) *S. urens*, B) *S. rogersii*, C) *S. africana*, D) *S. apetala*, E) *S. mexicana*, F) *S stigera*, G) *S. murex*, H) *S. quadrifida*, I) *S. gutata*, J) *S. africana*, K) *S. apetala*, L) *S. mexicana*, M) *S. lanceolata*. From https://mexico.inaturalist.org/observations (All images licensed CC-BY).

General Description

Sterculia species are bushes or trees, reaching heights of up to 45-50m. They feature large leaves, arranged alternately or spirally along the stems. Leaves can be simple and entire or exhibit 3 to 5 lobes or digitately compound structures. The inflorescences are typically axillary or terminal, forming panicles or occasionally racemes, and are multifloral, often adorned with trichomes. The flowers are actinomorphic, either staminate or possessing pistils. The fruits are generally pendulous and comprise up to 5 follicles. They are ovoid in shape, with surfaces that can be smooth or rough, usually brown, yellow, or green, which may turn red upon maturation and open upon ripening. The pericarp is woody, with villi on the outside and rigid trichomes, often urticant, on the inside. The seeds may range from 1 to 22 per follicle, depending on the species (Rodríguez and Santamaría-Aguilar, 2020) (Fig. 2).

Sterculia species have diverse applications in pharmacology and traditional medicine, as substitutes for tobacco in cigarettes or as flavoring agents in tobacco products, for paper manufacturing, for construction, and in biodiesel production (Bindhu et al., 2012; El-Sherei et al., 2016).

Seeds

The seeds are typically encased within a black hard shell. They are ovoidal or oblong in shape and commonly possess fleshy cotyledons and abundant endosperm (Fig. 3). They are consumed by people raw, boiled, or roasted and also serve as animal forage (De Britto Policarpi et al., 2018; Rodríguez and Santamaría-Aguilar, 2020).

Fig. 3: Seeds of different species of *Sterculia*. A*) S. cordata, B) S. foetida, C) S. africana, D) S. monosperma, E) S. quadrifida, F) S. apetala.* From: https://mexico.inaturalist.org/observations (All images licensed CC-BY).

Phytochemistry and Bioactivities Associated with *Sterculia* Seeds

Seeds from *Sterculia* are composed of various proportions of lipids, proteins, carbohydrates, water, fiber, and ashes. For instance, *S. foetida* seeds are rich in lipids, constituting up to 52% of their cotyledons, with 21% protein, 22% carbohydrates, and 4% ashes (Ong et al., 2013). Phytochemical studies have identified a diverse array of compounds within *Sterculia* seeds, including fatty acids, saponins, alkaloids, phenylpropanoids, flavonoids, tannins, and terpenoids (Table 1) (De Britto Policarpi et al., 2018; Jafri et al., 2019).

Table 1: Compounds present in seeds from *Sterculia* species.

Compound type and name	Specie	Reference
(Flavonols)	*S. lychnophora*	Wang et al., 2003
Kaempferol-3-*O*-b-D-glucoside		
Isorhamnentin-3-*O*-b-D-rutinoside		
(Phytosterols)		
b-sitosterol		
(Alkaloids)		
Sterculinine I and II		
(Glycosphingolipids)		Wang et al., 2013
Cerebroside I and II		
Water-soluble polysaccharide fraction		Wu et al., 2008
(Phytosterols)	*S. striata*	De Britto Policarpi et al., 2018
β-Sitosterol		
Campesterol		
Stigmasterol		
(Tocopherols)		
α-Tocopherol		
β-Tocopherol		
γ-Tocopherol		
δ-Tocopherol		
(Phenolic compounds)		
Vainillic acid		
Ferulic acid		
Ellagic acid		
Catechin		
Rosmarinic acid		
(Alkaloids)	*S. foetida*	Jafri et al., 2019
Capsaicin		
(Phytosterols)		
g-Sitosterol		
(Esters)		
Butyl-citrate		
(Esssential aminoacids)	*S. urens*	Galla et al., 2012
Histidine		
Isoleucine		
Leucine		
Lysine		
Methionine		
Phenylalanine		
Threonine		
Valine		
(Esssential aminoacids)	*S. murex*	Regnier et al., 2017
Histidine		
Isoleucine		
Leucine		
Glutamic acid		
Cyclopropenoic fatty acids	*S. foetida*	Rani et al., 2010
Sterculic acid	*S. foetida*	Ong et al., 2013
	S foetida	Kavitha and Murugavelh, 2019
	S. foetida	Alam et al., 2021
	S. apetala	Herrera-Meza et al., 2014
	S. mexicana	Herrera-Meza et al., 2013
	S. striata	Chaves et al., 2004
Cyclopropenoic fatty acids	*S. apetala*	Herrera-Meza et al., 2014
Malvalic acid	*S. mexicana*	Herrera-Meza et al., 2013
	S. foetida	Ong et al., 2013
	S. foetida	Kavitha and Murugavelh, 2019
	S. striata	Chaves et al., 2004
Cyclic fatty acids	*S. apetala*	Herrera Meza et al., 2014
Dihydrosterculic acid	*S. tavia*	El-Sherei et al., 2016

The ethnobotanical knowledge surrounding *Sterculia* plants is well-documented, particularly in Chinese and African traditional medicine. The leaves of *S. africana*, *S. striata*, and *S. setigera* are utilized to combat various microbial and fungal infections; the leaves of *S. foetida* are used as insect repellents and as laxative and diuretic; *S. setigera* bark is used for infertility treatments (Thabet et al., 2018); the seeds of *S. lychnophora* are applied in treating pharyngitis, coughs, and constipation (Wang et al., 2003); the leaves of *S. quadrifida* are utilized by Australian aboriginal communities to treat wounds, stings, and eye pain (Darojati et al., 2022); the leaves and bark of *S. apetala* are employed to alleviate respiratory illnesses, arthritis, and malaria (Rodríguez and Santamaría-Aguilar, 2020). The extracts and compounds of *Sterculia* species have also demonstrated antibacterial, insecticidal, cytotoxic, and antioxidant properties (Table 2).

Table 2: Bioactivities nonrelated to MetS associated with seeds of *Sterculia* species.

Specie	Extract/Compound	Bioactivity	Reference
S. apetala	Hexanic/Sterculic oil	Cytotoxic Prostate cancer treatment	Contreras-López et al., 2022
S striata	Aqueous	Antitumor	Alshambaty et al., 2021
S. villosa	Methanolic	Anxiolytic,sedative, cytotoxic	Barua et al., 2019
S. foetida	Aqueous/Lectin	Antibacterial, hemolytic	Braga et al., 2015
S. foetida	Methanolic	Antimicrobial, antiosteosarcome	Jafri et al., 2019
S. foetida	Methanolic	Cytotoxic, thrombolytic, antiarthritic, analgesic, antipyretic	Alam et al., 2021
S. guttata	Ethanolic	Anti-parkinsonism	Dhaliya-Salam et al., 2022
S. javanica	Extract (polarity not indicated)	Increase in spermatogenesis, sexual behavior	Widianti et al., 2018
S. lychnophora	Polysaccharides	Probiotic bacteria proliferation	Huang et al., 2024
S. lychnophora	Ethanolic	Antibacterial	Yang et al., 2016
S. nobilis	Methanolic	Gastroprotective	Song et al., 2015

Pharmacological studies focusing on *Sterculia* seeds metabolites applied to MetS and its manifestations are scarce. One of the most studied groups of compounds are the cyclic fatty acids (CFAs) present in their oil. CFAs are rare in nature, exhibit intriguing bioactivities, and constitute a significant percentage of the triacylglycerides found in *Sterculia* seeds (Dąbrowski and Konopka, 2022).

Cyclopropenoic Fatty Acids

The seeds of *Sterculia* species represent an interesting source of fats. These lipids commonly include the most prevalent fatty acids, such as palmitic, stearic, oleic, and linoleic acids, together with cyclic fatty acids (CFAs). CFAs are produced by certain bacteria, as well as plant species within the Malvales, Sapindales, and others, including *Litchi chinensis* (Dąbrowski and Konopka, 2022). Moreover, in some species of *Sterculia*, various fatty alcohols have been identified, such as docosanol, hexacosanol, and n-triacontanol (Thabet et al., 2018).

CFAs are characterized by the presence of a cyclopropane ring in their acyl chain. The CFA found in seeds of Malvaceous plant species is dihydrosterculic acid (cis-9,10-methylene octadecanoic acid). Additionally, cyclic acids containing a cyclopropene ring are referred to as cyclopropenoid fatty acids (CPFA). The two primary CPFA found in *Sterculia* seeds are sterculic acid (8-(2- octylcyclopropen-1-yl) octanoic acid) and malvalic acid (7-(2-octylcyclopropen-1-yl) heptanoic acid) (Dąbrowski and Konopka, 2022). Their structures are depicted in Fig. 4.

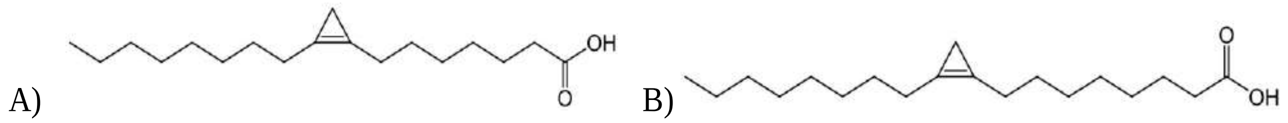

Fig. 4: Structures of cyclopropenoid fatty acids present in *Sterculi*a seeds. A) Malvalic acid (https://www.wikidata.org/wiki/Q412814) B) Sterculic acid (https://www.wikidata.org/wiki/Q2345401). From: https://creativecommons.org/publicdomain/zero/1.0/ (Licensed CC-0).

Sterculic acid is recognized for its ability to inhibit the enzyme stearoyl-CoA desaturase (SCD) in both insects and animals; in insects, the inhibition of SCD can significantly impact maturation and reproduction, suggesting its potential as biocide agents (Yu et al., 2011). In mammals, SCD plays a crucial role in lipid metabolism, making the inhibition of this enzyme a therapeutic target (Wang et al., 2015). Several investigations have analyzed the mechanisms underlying the effects of consuming sterculic oils as treatments for MetS and its manifestations.

Cyclopropenoic Fatty Acids in Metabolic Syndrome

Stearoyl-CoA desaturase (SCD) plays a key role in lipid metabolism since it catalyzes the synthesis of monounsaturated fatty acids, particularly oleic acid (18:1) and palmitic acid (16:1), which are the main fatty acids in adipose tissue (Gómez et al., 2003). Its inhibition has emerged as a promising therapeutic target since an increased SCD activity has been observed in animal models and humans with obesity, metabolic syndrome, diabetes, arteriosclerosis, cancer, Alzheimer's disease, skin disorders and viral infections (Ntambi et al., 2002; Warensjo et al., 2006; Hodson et al., 2013; Manni et al., 2017; Alsharari et al., 2017; Pelaez et al., 2020).

Genetic deletion or pharmacological inhibition of SCD has shown promising effects in improving various aspects of MetS in animal models. For example, transgenic mice lacking SCD do not develop obesity or insulin resistance when exposed to high-calorie diets. They exhibit lower body adiposity, enhanced insulin sensitivity in the liver, adipose tissue, and skeletal muscle, decreased hepatic triglycerides and cholesterol esters, elevated metabolic rates, and resistance to the development of non-alcoholic fatty liver disease (Rahman et al., 2005; Gutiérrez-Juárez et al., 2006; Miyazaki et al., 2009; Liu et al., 2010; Lounis et al., 2016). Recently, pharmaceutical companies have been developing synthetic SCD inhibitors as potential therapies for various liver diseases, dermatological conditions, Alzheimer's disease, and cancer (Uto, 2016).

Studies examining the impact of sterculic oil (SO) on metabolic syndrome have reported positive therapeutic effects (Table 3). Major et al. (2008) investigated the effects of SO supplementation in hamsters fed a high-fat and cholesterol diet, observing reductions in body weight and body adiposity. Ortinau et al. (2012) reported that SO administration in leptin-deficient *ob/ob* mice has beneficial effects on glucose tolerance, insulin resistance, and reduces liver inflammation. In another study, Ortinau et al. (2013) observed that the supplementation of obese OLETF rats with SO led to reductions in serum glucose concentrations, abdominal fat and adipocyte size, along with the increase in the glucose transporter GLUT1 expression.

Table 3: Bioactivities related to metabolic syndrome associated with seeds of *Sterculia* species.

Specie	Model	Treatment %	Results	Reference
S. foetida	Hamsters fed a high-fat and 0.2% cholesterol diet	0.5 SO	Reduced: Body weight Adiposity	Major et al., 2008
S. foetida	Leptin deficient ob/ob mice	0.5 SO	Increased: Glucose and insulin tolerance Reduced: Liver inflammation	Ortinau et al., 2012
S. foetida	Obese OLEFT rats	0.5 SO	Reduced: Glucose Intra-abdominal fat Dyslipidemia Increased: GLUT1	Ortinau et al., 2013
S. mexicana	Spontaneously hypertensive rats (SHR)	0.8 SO	Reduced: Body weight Blood pressure Adiposity Triglycerides Cholesterol Increased: Adiponectin	Herrera Meza et al., 2013
S. apetala	Obese Zucker rats	1.3 SO	Reduced: Triglycerides PPARg Leptin	Reyes-Saldaña, 2015
S. apetala	Wistar rats fed 30% sucrose	1.15 SO	Reduced: Cholesterol Triglycerides Adiposity Hepatic steatosis	Morales-Cano, 2018
S. apetala	Wistar rats fed 30% fructose	1 SO Simultaneous	Prevented: Hypertension Insulin resistance Hepatic steatosis Adiposity Hypertriglyceridemia	Ramírez-Higuera et al., 2019

SO: sterculic oil

The preventive and corrective effects of SO from *S. apetala* and *S. mexicana* seeds have been investigated in rat models of MetS, including obese Zucker rats, spontaneously hypertensive rats (SHR), and rats induced to MetS through the ingestion of 30% sucrose or fructose in drinking water. Studies conducted by Herrera-Meza et al. (2013), Reyes-Saldaña (2015), Morales-Cano (2018), demonstrated that SO administration after MetS induction, leads to reductions in body weight, blood pressure, abdominal adipose tissue, adipocytes size, serum levels of triglycerides, cholesterol, insulin, and adiponectin, and an improvement in insulin sensitivity and hepatic steatosis.

In the preventive treatment, where the oil was administered together with MetS induction, rats did not exhibit the alterations observed in those receiving fructose only, including changes in blood pressure, insulin resistance, serum levels of glucose and triglycerides, hepatic steatosis, and body adiposity (Ramírez-Higuera et al., 2019).

Other studies evaluating the effects of SO have shown positive impacts on protein oxidation in the liver and adipose tissue inflammation (unpublished results). Altogether, these findings suggest that SO administration is a promising therapeutic intervention for mitigating the various components of MetS. Further research is needed to fully elucidate the underlying mechanisms and to assess its potential clinical applications.

Antioxidant Activity

There exists a close relationship between oxidative stress and chronic inflammatory conditions, both involved in the development of MetS alterations. The endogenous antioxidant system plays a crucial role in preventing degenerative diseases by enhancing the immune response and shielding the body from the detrimental effects of free radicals. In addition, antioxidant compounds help mitigate oxidative stress and alleviate inflammation by neutralizing free radicals and reactive oxygen species, thereby reducing the risk of developing metabolic disorders and related complications (Masenga et al., 2023). In that respect, extracts obtained from *Sterculia* seeds containing bioactive phytoconstituents such as flavonoids, tannins, and phenolic acids, have demonstrated beneficial effects as free radical scavengers, anti-inflammatory agents, and adjuncts in the treatment of conditions including type II diabetes mellitus, obesity, and dyslipidemia (Thabet et al., 2017; Jafri et al., 2019) (Table 4).

Table 4: Antioxidant activities of *Sterculia*´s seeds.

Specie	Extract	Compounds/Activity	Reference
S. striata	Methanolic	Phenols and RSA	De Britto Policarpi et al., 2018
S. striata	Methanolic (raw and roasted seeds)	Phenols	Gomes de Moura et al., 2011
S. apetala	Continuous solid-liquid extraction water/ethanol	Phenolic compounds and RSA	Mosca et al., 2018.
S. foetida	Oil from seeds	RSA	Bose et al., 2021
S. foetida	Ethanolic	RSA	Jafri et al., 2019
S. setigera	Ethanolic and petroleum ether	RAS	Nahla et al., 2018
S. quadrifida	Ethanolic	Flavonoids, phenols and tannins	Dillak et al., 2019
S. murex	Methanolic (roasted seeds)	Phenolic compounds and RSA	Regnier et al., 2017
S. lychnophora	Ethyl-acetate, methanolic and aqueous	Flavonoids and phenols	Tyagi et al., 2024
S. lychnophora	Aqueous (Polysaccharides)	Ferric reducing antioxidant power and RSA	Huang et al., 2024
S. scaphigera	Ethanolic	*In vivo* assays Increase in superoxide dismutase and catalase activities Reduction of glutathione levels	Dhage et al., 2013
S. scaphigera	Methanolic	RSA	Ogale et al., 2014

RSA: Radical Scavenging Activity

Conclusion

The genus *Sterculia* possesses over 200 species, but only a fraction has been studied to date. Notable among these are *S. foetida*, *S. apetala*, *S. mexicana*, *S. lychnofora*, *S. scaphigera*, *S. africana*, *S. urens*, and *S. striata*. While the seeds of this genus have historically been utilized primarily as food or a source of oil, their nutraceutical and pharmacological potential remains largely unexplored. Cyclic fatty acids found in the seed oil have demonstrated efficacy in preventing and treating metabolic alterations associated with MetS in animal models. However, further investigation is needed to describe their mechanisms of action and explore their use in humans. Other compounds present in the seeds, such as phenolic compounds, flavonols, and sterols, exhibit free radical scavenging activity, which could help alleviate the oxidative stress inherent to the chronic inflammation state associated with metabolic syndrome. Furthermore, compounds like alkaloids, polysaccharides, and essential amino acids present in these seeds deserve exploration to assess their potential therapeutic effects.

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Chapter 39

Traditional Methods and Alternative Strategies for the Control of Neglected Helminthic Zoonoses

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ABSTRACT

Neglected diseases are those absent from the global health agenda, although they could be a source of health damage that is associated with economical losses and suffering. They are mainly prevalent in poor hygienic conditions that are located in different areas, and some have a larger geographical distribution. Many exhibits different life cycles, require a vector for transmission or need animal reservoirs, which makes them difficult to control. Most parasitic diseases are somehow neglected, especially in low-income countries. Zoonoses are defined as diseases transmitted by animals to humans or vice versa. Here, the generalities of zoonoses are presented with emphasis on their epidemiology, aspects of basic biology including morphology and physiology, and a critical and reflective analysis of traditional control methods is continued. This chapter focuses on the importance of three zoonotic diseases: Dipylidiasis, Ancylostomiasis, and Taeniasis. Drug resistance is exposed as an important problem in the treatment of infectious diseases, which gives rise to the need for a constant search for therapeutic alternatives. Alternative control strategies are based mainly on the use of natural products, and we present proposals for the use of *Bacillus thuringiensis* applied on different life stages of the parasites as an alternative strategy in the control of parasitosis, based on scientific evidence.

KEYWORDS Zoonotic diseases, Biocontrol, Drug resistance, Alternative control	Received: 05-June-2024 Revised: 12-July-2024 Accepted: 17-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Zoonotic Diseases

Zoonotic diseases are naturally acquired by humans, comprising a large percentage of long existing and new diseases. Even though some of them are 100% preventable through vaccination or other methods, several of these diseases are considered public health problems worldwide, to some extent due to the close coexistence that animals have with humans in various domestic, agricultural and wildlife settings. Zoonoses have an impact on the marketing and production of products intended for consumption, which together represent a threat to food security and a burden on government health systems (Rahman et al., 2020). The most important zoonoses caused by parasites have a variable distribution in the world, since parasitosis depends on various factors that are highly variable in different areas of the globe. The methods of spread can be variable and will depend on animals, climate, human migration, water cleanliness, etc. to determine these diseases is through diagnostic and control methods (Pisarski, 2019). Also, many diseases tend to be endemic mainly in regions where the infrastructure, economy, social environment and health conditions are characterized by poverty.

Human-animal interaction has increased with domestication, and over the past 70 years, several diseases totaling 250 have been classified as both re-emerging and emerging zoonoses, and their distribution patterns, frequency and geographic location have spread throughout the world. A wide range of factors have been identified as essential, including climate, greater human-animal interaction, degree of adaptation of pathogens, animal production systems, vectors, urbanization, and climate change, among others. In this regard, zoonoses account for 61% of the total number of pathogens affecting humans and the potential of zoonoses to contribute to the appearance of new emerging or re-emerging diseases in humans has also been pointed out (Salyer et al., 2017). The amplification of pathogens occurs when domestic animals that are closer to people interact with wild animals, thus establishing a circle in which different animals participate such as cats, ruminants, dogs, horses, among others that can be carriers or reservoirs of the pathogen. Thus, habits such as allowing pets to sleep with their owners, a situation that occurs between 14-62% worldwide, are potential triggers in the development and emergence of zoonotic diseases (Chomel and Sun, 2011). Both pet and stray dogs may act as reservoirs of zoonotic parasites that cause significant veterinary, medical, and economic problems. The point at which human, animal and environmental health come together is where the concept of "one health" is applied and restricted to mainly zoonotic diseases (Torres-Velez et al., 2019). The occurrence of signs such as diarrhea in humans is associated with the consumption of food containing pathogens, thus the group of pathologies known as foodborne diseases arises and some of them are classified as zoonoses.

Taeniasis-cysticercosis

Taenia solium taeniasis-cysticercosis transmitted between pigs and humans, is between the most important foodborne transboundary parasitic infections. Taeniasis are cyclozoonoses diseases, as their transmission requires more than one vertebrate. According to worldwide estimates, 2.6 to 8.3 million people have neurocysticercosis and its mortality rate is 28,000, which is considered one of the most important food-borne zoonotic diseases. (Havelaar et al., 2015; Hallal-Calleros et al., 2016). For cysticercosis, both free-roaming pigs with access to human feces form an essential binomial for its transmission dynamics that influence the increase in frequency and are a reason for the existing variability in its frequency. The definitive host of the adult phase (*Taenia*) is the human, (figure 1) and the pig hosts the larval phase in the muscles (cysticercus or metacestode). Pigs become infected by ingesting the microscopic eggs excreted in human feces by *Taenias*. In addition, if a human ingests eggs, he can also develop cysticercosis which can lodge in the muscles, but also in the brain causing neurocysticercosis.

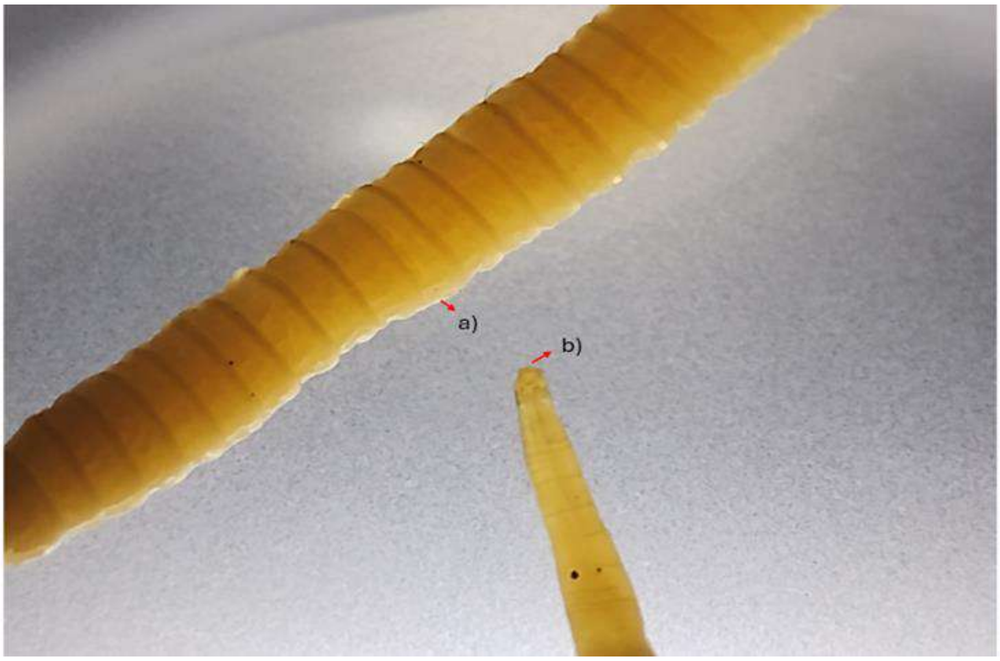

Fig. 1: *Taenia* spp. a) Mature proglottids, b) Scolex.

Once the eggs reach the stomach, hatch originating the oncosphere, which can be transported by the bloodstream and the metacestodes can develop in the brain, staying mainly in the interior or parenchyma, although they can also be lodged in the subarachnoid space. In some cases, they can lodge in the ventricles, and they are found grouped with a racemose pattern in the extra parenchymatous presentation, which occludes the circulation of cerebrospinal fluid and causes hydrocephalus and other complications. When lodged in the choroid plexus, colloidal metacestodes can be observed, which are characterized by a collagen capsule and by mononuclear inflammatory cells that may be surrounding the parasite in the granular and calcified stages (Del Brutto et al., 2014). The possibility that the metacestode lodges in different parts of the brain causes a wide variety of heterogeneous and non-specific signs and symptoms ranging from headache, increased intracranial pressure, epileptic seizures, among others, making its diagnosis difficult; Furthermore, the number of metacestodes, their state of degeneration, the degree of the inflammatory response, and the difference in susceptibility or resistance of the host, are determining factors in the severity of the disease (Garcia y Del Brutto, 2005; Verma et al., 2010). In the case of taeniasis, humans are the host of the adult parasite. Taenias are cestodes with a structure called scolex with 4 suckers and a crown of hooks, which helps with morphological diagnosis; next, the neck is followed by strobile measuring up to 4 m in length and contains the proglottids, which can have around $50\text{-}60x10^3$ fertile eggs that they release into the environment, being ingested by pigs which will develop cysticercosis (Gilman et al., 2000). The symptoms reported by carriers are very general and non-specific, such as stomach pain, diarrhea and nausea, and patients may even be asymptomatic. Traditional tools for detecting gastrointestinal parasitosis, such as coproparasitoscopic tests, commonly fail in the diagnosis, being immunological and molecular tests more accurate and reliable for diagnosis.

Dipylidiasis

Dipylidium caninum (figure 2) commonly known as dog tapeworm, can accidentally lodge in the intestines of humans with a cosmopolitan distribution; It has been found in countries such as Germany, USA, Mexico, among others. It has an obligate indirect life cycle, involving arthropods like fleas (*Ctenocephalides felis*, *Xenopsylla cheopis*, *Trichodectes canis*, *Pulex irritans* and *Felicola subrostratus*) and lice (*Trichodectes canis*), in which the phase named metacestoid or cysticercoid is harbored. The adult phase of the parasite is the tapeworm or Taenia, that can be found in dogs, cats and humans, who get infected by accidentally ingesting infected fleas or lice. Flea larvae will feed on eggs found in the environment that were shed in the feces by proglottids of animals infected with *D. caninum*. Taenia can have a variable length between 22 and 48 cm and proglottids are shaped like cucumber or rice seeds, allowing their macroscopic identification in feces. The scolex has an approximate diameter of 0.5mm, with four suckers and a rostellum containing three or four pairs of hooks, whose function is to fix the parasite to the intestinal mucosa. Mature gravid proglottids have two sets of sexual organs, therefore it is a hermaphroditic parasite; within these proglottids there are ovigerous capsules with packages containing 7 to 30 eggs, with a diameter between 34 and 40µm. Although *D. caninum* infections are generally not serious in humans or animals, a high parasite load can cause abdominal pain, flatulence, weight loss, enteritis, diarrhea or constipation, and anal pruritus, guiding the clinical diagnosis in companion animals, since dogs exhibit a behavior known as scooter behavior that consists of rubbing the anus on the floor making traction with the thoracic extremities (Nerissa Ramnath et al. 2009). Clinical manifestations include growth retardation growth retardation, reduced work capacity and general health impairment. These infections occur in humans, mainly in children, as they are at risk of ingesting infected fleas. Diagnosis is mainly based on the observation of proglottids, and eggs found in feces (Narasimham et al., 2013; Saini et al., 2016).

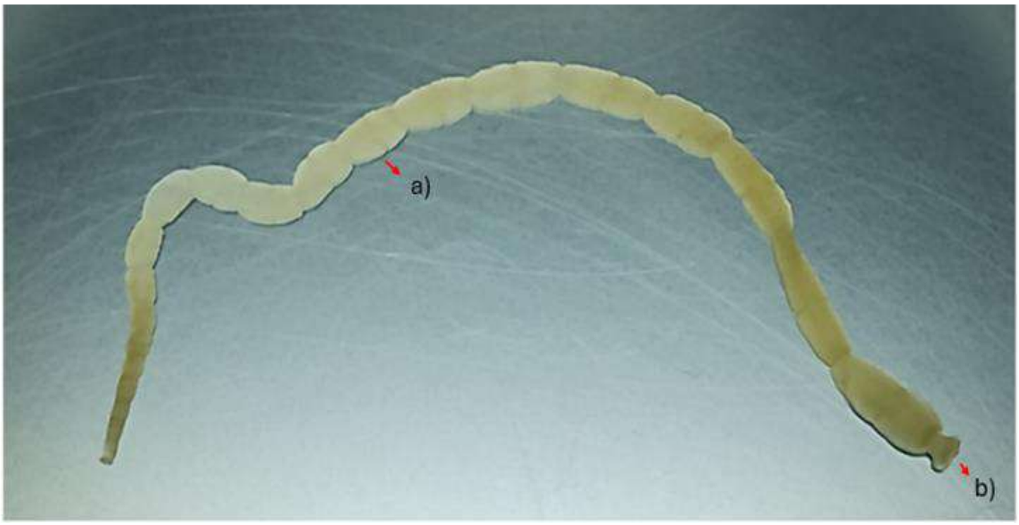

Fig. 2: *Dipylidium caninum*, a) Proglottids, b) Scolex.

Ancylostomiasis

Is a common gastrointestinal helminthic zoonoses (figure 3); The development of cutaneous infections requires contact with the infective stages of *Ancylostoma caninum*, which will lead to eosinophilic enteritis (Landmann and Prociv, 2003). *Ancylostoma* spp. infections have been reported to be 37.19%, followed by *Toxocara* spp. (24.79%), *Taenid* spp. (20.66%), *Diphyllobothrium latum* (1.65%), and lastly *Dipylidium caninum* (1.65%) to name a few. Male dogs have been shown to have a higher prevalence (27.3%) than female dogs (18.91%) of zoonotic parasites (Suganya et al., 2019).

Control Methods against Zoonoses

For disease control, the general principles must be applied, as well as the application of vaccines for sick people, in the case of animals that are healthy they must be placed in restriction, as well as avoiding any movement of healthy animals to control the population, carry out diagnostic methods, disinfection, eliminate vectors and carry out adequate surveillance methods. If the corresponding preventive methods were implemented, zoonotic diseases would be preventable, however, failure to do so would become a threat to public health. The principles of the "One Health" policy should be put into practice. This concept is based on the collaboration of multiple disciplines working together locally, nationally and globally to maintain the health of animals, people and the environment (AMVA, 2008).

Effective control of zoonoses must bring together different areas such as research, economics, sociology, government and citizens, especially those related to animal and public health (Murphy et al., 2019); also, other activities that must be carried out to control zoonoses are strict isolation and quarantine, public awareness, health education and training, as well as the implementation of biosecurity on farms, mass vaccinations, testing and if necessary the culling of animals. Training and education must also be provided for those groups of people who are at risk of zoonotic diseases, and methods of prevention and control of emerging and re-emerging diseases must be established in order to improve health, prevent morbidity and avoid the death of people and animals.

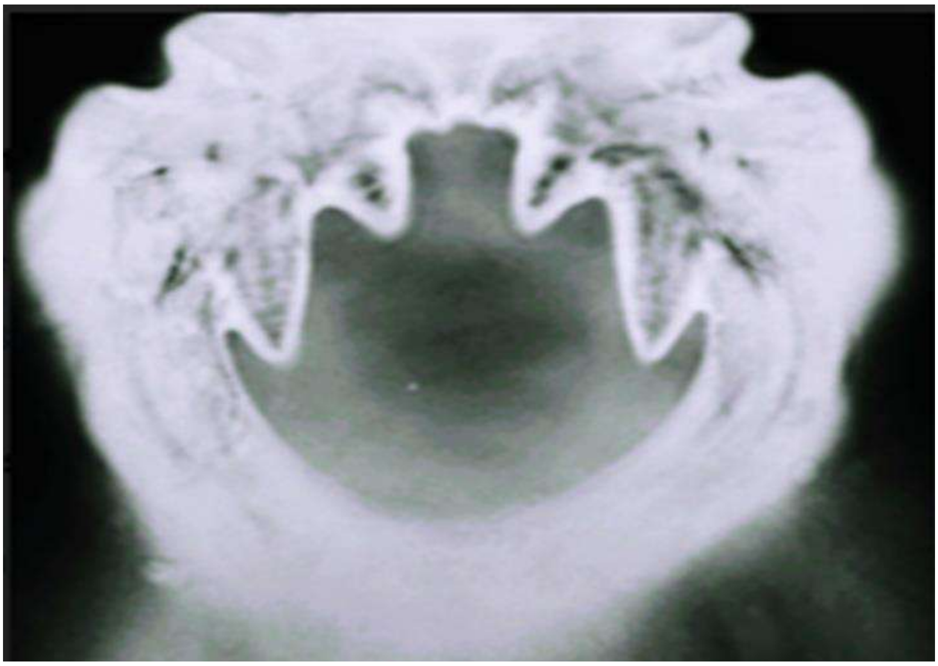

Fig. 3: *Ancylostoma caninum,* a) The buccal capsule of the helminth, b) dorsal teeth are observed 40x (Dunstan-Guzmán, 2020).

When proper nutrition is carried out, the immune system of humans and animals is prevented from fighting off serious parasitic infections. It is important to control animals such as dogs and cats from hunting wild animals such as birds, reptiles and some mammals as they play an important role as intermediate hosts for many parasites that end up causing zoonoses.

The high prevalence of vector-borne diseases (mainly ticks) has developed the use of products with repellent effects, as well as those that completely eliminate these parasites (Otranto and Dantas-Torres, 2013).

It is also important to control other vectors such as lice and fleas as they also have a great impact on human health. It is important to avoid these diseases by applying certain cleaning routines such as collecting and eliminating pet excrement, cleaning children's areas, avoiding contact between people and faeces, washing hands before and after playing, eating and when in direct contact with animals; hygiene is fundamental for the control of zoonotic diseases. However, when infections are identified, appropriate treatment should be given with certified medicines that guarantee the safety, efficacy and quality control of the manufacturing laboratory.

Anthelmintic Drugs

Most countries that have high incidence rates of tropical diseases have insufficient financial resources to invest in the development and production of drugs to control these diseases. However, there is, albeit in smaller quantities, a repertoire of drugs that are used in research that has previously been carried out in animals and are subsequently used in veterinary and human use. In addition, most anthelmintics have limited action among trematodes, cestodes and nematodes. The treatment commonly used to control trematodes or cestodes in humans is praziquantel, although it lacks activity against nematodes, the benzimidazoles have activity between phyla and are more active against nematodes than against cestodes or trematodes. Moreover, for more than thirty years, ivermectin has been used and this has been a disincentive for the discovery of new anthelmintic drugs. The classification of anthelmintics is based on their chemical structure and mode of action. For some of the world's major zoonoses, the main registered drugs are used: blood parasites (schistosomiasis) are treated mainly with oxamniquine or praziquantel; cestodiasis (taeniasis), with benzimidazoles, albendazole, niclosamide and praziquantel; parasites such as fascioliasis with triclabendazole; intestinal roundworms (nematodes) mainly with avermectins, benzimidazoles, pyrantel, levamisole, milbemycins, tribendimidine, to mention a few; tissue roundworms (filariasis)are treated with diethylcarbamazine, albendazole, ivermectin (Holden-Dye and Walker, 2018).

To treat mixed infections such as nematode and trematode infections, drug combinations have been used to achieve a broad-spectrum effect with activity against parasites of the same phylum.

Resistance to Anthelmintic Drugs

Pharmacoresistance or drug resistance is the development of the ability to withstand the effect of a drug designed to cure a disease or to mitigate symptoms, by the cells against which the drug acts, be it microorganisms, parasites, or tumor cells; therefore, drugs that were usually effective against certain organisms are no longer capable of eliminating or inhibiting them. Drug resistance is generally the result of evolution and develops in response to selective pressures exerted on living organisms. Resistance is produced by various mechanisms, among which the four best known are: inactivation or modification of the drug rendering it ineffective; the alteration of the target element preventing the action of the drug; the alteration of the metabolic pathway in which the drug interferes, using alternative pathways; reduction in the bioavailability of the drug, either by decreasing its absorption or by increasing efflux. Resistance to anthelmintics has presented itself in various forms even with different formulations. That is, when a parasite population shows a change where the susceptibility to a compound across population generations decreases, this can be defined as resistance (Geary et al., 2012). Due to the difficulty to monitor the anthelmintic resistance, the use of molecular markers for anthelmintic resistance is convenient.

Alternative Approaches to Drugs based on Botanical Medicine

Proposals for the use of plant products of natural origin as an alternative to conventional anthelmintics have gained momentum, however, they have been used previously in developing countries with problems of parasitic diseases in humans and animals. Research has shown that these natural alternatives have activity against parasites and are mostly readily available and accessible. It is important to identify the active components present in the extracts as this information is important to be able to develop and design new synthetic actives that have the same properties, as well as to consider using phytochemicals that are present for a combined strategy with commercial anthelmintics (Lanusse et al., 2018). It is also important and necessary to rigorously identify the active components, which must then be evaluated and tested before their true effect on parasite control can be adequately determined in the future. For example, one treatment used against malaria and against human schistosomiasis are artemisinins, which are originally extracted from the wormwood plant (*Artemisia absinthium*), another example is the myrrh preparation (Mirazid), which is obtained from the *Commiphora molmol* plant that is commonly used as a fasciolicidal treatment and is for human as well as animal use, also reported to have properties against protozoa and helminths (Abdelaal et al., 2017).

Alternative Approaches to Medicines based on the use of Nematophagous Fungi

A number of micro-organisms have been studied that may be useful for the biological control of zoonotic parasites and parasites of human medical importance. In 1888 it was described for the first time that the fungus *Arthrobotrys oligospora* was capable of capturing nematodes (Zopf, 1888); From there, different studies were performed on fungi where they were identified and classified according to their capacity as nematode traps, endoparasites, egg or adult parasites or toxin producers. Likewise, the nematophagous fungus *Trichoderma virens* has been evaluated against embryonated eggs of *Toxocara canis* (De Souza, 2017), causing a decrease in the number of larvae found in mice; *Paecilomyces lilacinus*, *T. harzianum* have also been tested in the hatching of *Ancylostoma* eggs; against *T. canis* eggs, *Pochonia chlamydosporia* and *P. lilacinus* have shown strong activity (Carvalho et al., 2011); *Purpureocillium lilacinum* has also been reported to be most effective in reducing the number of *T. canis* larvae (Maia et al., 2019); *P. chlamydosporia* is effective *in vitro* against *T. saginata* eggs (Araujo et al., 2009; Araujo et al., 2012); For the capture of *Ancylostoma* spp. *in vitro*, *Arthrobotrys cladodes, A. oviformis, A. oligospora, A. conoides, Duddingtonia flagrans, Monacrosporium appendiculatum, A. robusta, M. thaumasium, A. bronchophaga, and Nematoctonus robustus* have been reported to be successful (Carvalho et al., 2009), *Pleurotus eryngii in vitro* reduced the number of *A. caninum* larvae, *P. chlamydosporia and Paecilomyces lilacinus* showed ovicidal activity against *Dipylidium caninum* (Araujo et al., 2009). Thus, nematophagous fungi can be considered a promising tool for parasites of zoonotic importance when used as a biological control.

Alternative Approaches to Drugs based on the use of Bacteria

The use of beneficial and harmless microorganisms has been used as biological control of animal parasites, they have an effect depending on the stage of the parasites' life cycle and are capable of inducing death and non-viability or decreased movement. It has been reported that the use of the bacterium *Bacillus thuringiensis* has been effective for the control of pests affecting crops and even the mechanism of action that the bacterium has on some pests has been proposed and determined. There is a diverse group of *B. thuringiensis* proteins (Cry and Cyt) that have activity against invertebrates (nematodes), as well as insects (Diptera, Lepidoptera and Coleoptera). The main target site is with midgut epithelial cells as it smoothes them to insert itself into the membrane to form pores (Bravo et al., 2007). However, its use in the control of parasites that are considered zoonotic and affect both animals and humans is more recent. These bacteria have shown activity against ectoparasites such as *P. cuniculi* mite, which mainly affects rabbits. In this parasite, the histological damage caused by BT has been studied and its effects has been tested in naturally infected rabbits (Dunstand-Guzmán et al., 2015; Dunstand-Guzmán et al., 2017).

In the search for new alternatives, strains of the bacteria *B. thuringiensis* have been evaluated against some parasites; Cappello et al. (2006) reported a 90% reduction in egg excretion of *Ancylostoma ceylanicum* in mice; Dunstand-Guzman et al. (2023) evaluated *in vitro B. thuringiensis* GP526 strain on *T. pisiformis* eggs, showing macroscopic damage and loss of integrity in the eggshell; Also, *B. thuringiensis* confronted with *Dipylidium caninum* inhibited motility, demonstrating the antiparasitic effect that this bacteria has against public health diseases (Table 1).

Biological Alternatives for the Control of *Taenia* spp.

The use of nematophagous fungi has been reported to control viability in *Taenia* spp. eggs. Ovicidal activity has been described for fungi *Pochonia chlamydosporia* and *Duddingtonia flagrans*, considered lethal on eggs of *T. saginata* and the fungus *Monacrosporium thaumasium* on *Taenia taeniaeformis* eggs. The mechanism of penetration of the fungus into tapeworm eggs is not yet fully known, but it is postulated that enzymatic activity is the main route of attack for the penetration of the fungus into the eggs (Araújo et al, 2012). Also, to control the adult cestode, the use of botanical extracts has been reported. An example is the hydroalcoholic extract of the *Tamarindus indica* seed at 25, 50 and 100 mg/ml. The treatments induce paralysis and death of the cestode *T. solium* in less than one hour (Bhadoriya et al., 2011). The drupe extract of *Melia azedarach* in *T. solium* cestode at doses of 0.1% y 0.2% induces a lethality with a LT_{50} of 52 y 32 minutes respectively (Szewczuk et al., 2006). For the control of cysticercosis due to *Taenia* spp., the use of recombinant vaccines based on parasite antigens has been referred, with the most effective vaccines being those using antigens obtained from oncospheres, demonstrating high effectiveness in various animal models such as rodents, pigs, sheep and cattle (Flisser et al., 1979; Lightowlers, 2003).

Table 1: Antiparasitic effect of *Bacillus thuringiensis* on different species of parasites

Parasite	Host	*B. thuringiensis* strain or protein	Dose/mortality (Ref.)
Rhipicephalus microplus	Bovine	GP123, GP138, GP130, GP140	1.25 mg/ml 79-96% (Fernández -Ruvalcaba et al., 2010)
Dipylidium caninum eggs	Dogs	GP526	10 mg/ml 100% 600 µg/ml 75%. (Peña et al., 2013)
Ancylostoma ceylanicum larvae	Human, Hamsters	Cry 5B protein	200 µg/ml 100% (Cappello et al., 2006)
Haemonchus contortus	Ruminants	Cry5B protein	60mg/kg 91% (Sanders, 2020)
Trichostrongylus colubriformis eggs and larvae	Ruminants	*Bt* subspecies *Kurstaki*	0.38 ng/ml 50% 1.1µg/ml 50% (Bottjer et al., 1985)

To reduce the parasite load of *T. solium* in community-reared pigs, synthetic peptides have been used to make vaccines based on protein sequences of *T. crassiceps* (Huerta et al., 2001). Information on the anthelmintic activity of bacteria to break the biological cycle of *Taenia* spp. is limited to date; however, there are studies that suggest that proteins produced by bacteria may be a potential alternative for the control of this parasitosis. Cry 5B was administered *in vivo* in mice as an anthelmintic against *Heligmosomoides bakeri* (Hu et al., 2010) and against *Haemonchus contortus* in its adult and larval stages (O`Grady et al., 2007).

***Bacillus thuringiensis* against Zoonotic Parasitosis**

B. thuringiensis is one of the few safe bacterial alternatives with therapeutic potential against cestodiasis; GP526 strain demonstrated efficacy against *Dypilidium caninum in vitro*, where a concentration of 1,000 µm/ml of the crystal-spore extract was lethal in 82.75% of the ovigerous capsules in 3.5 hours (Figure 4).

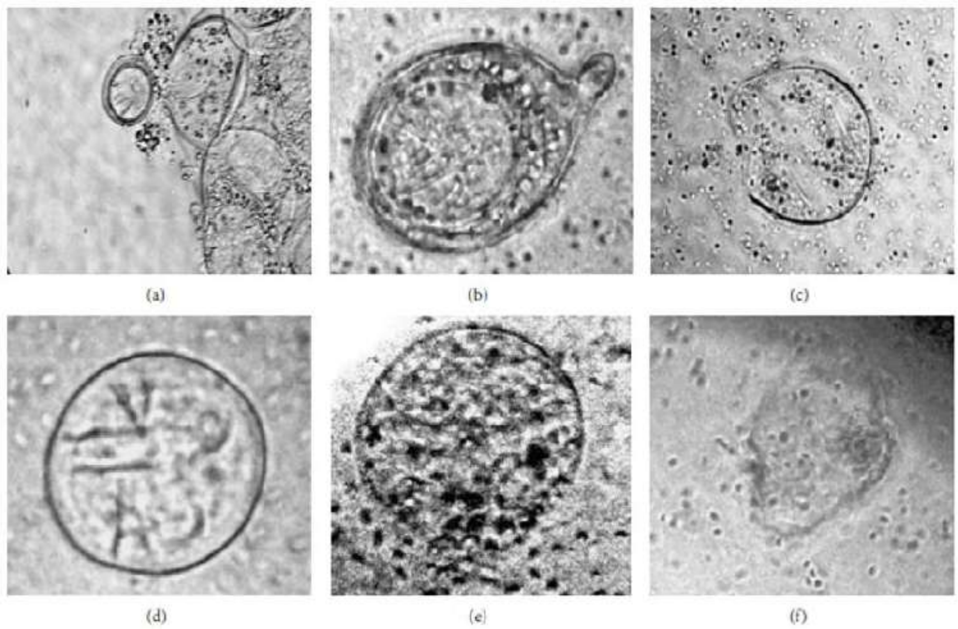

Fig. 4: Lethal effect on *Dipylidium caninum* eggs caused by the GP526 protein of *Bacillus thuringiensis,* (a) Lysis of the ovigerous capsule, (b)Eggshell with fracture, (d) Exit of the embryo, (e-f) destruction of hexacanth embryo (initial and final stages) (Peña et al., 2013).

Bacillus thuringiensis* against *Taenia

Several species of the genus *Taenia* are susceptible to death by *B. thuringiensis*. In *in vitro* studies with *Taenia pisiformis*, the spore-crystal complex of GP526 strain alters the structure of the integument surrounding the genital pore of mature gravid proglottids, which is reflected in a decrease in its size, and a decrease by 60% in the number of eggs released 3 hours after incubation (Dunstand-Guzmán et al., 2021). The effect that *B. thuringiensis* has on the structure and size of the genital pore of *Taenia pisiformis* could be attributed to apoptotic cell death, since has been reported that PS2Aa1 toxin of *B. thuringiensis* was able to induce the expression of caspases on tumor cells (Brasseur et al., 2015).

Bacillus thuringiensis* against *Ancylostoma caninum

The nematicidal effect of various *B. thuringiensis* strains was evaluated in the adult stage of *A. caninum* males and females, as well as its ovicidal and nematicidal effect. The GP526 strain was capable of inducing lethality in 81.47% of *A. caninum* eggs with 135 µg/mL after 72 h. It also killed 65% of adult *Ancylostoma caninum* nematodes at 60 µg/mL of spore-crystal complex. Also, DG03 strain was effective against the adult nematode by inducing a mortality of 71.66%, while the ovicidal effect was 36.7% with 60 µg/mL. GP526 strain caused tissue damage in the adult and egg phases of the nematode, and the crystal spore complex of the same strain induced uterine prolapse, altering the cuticle and intestine 24 h post incubation; It also caused the paralysis and death of the adult parasite. In gravid females it causes the loss of continuity of the cuticle and exteriorization of the uterine tubes accompanied by uterine detachment; this finding was not observed in non-gravid females; In the case of eggs, vacuolization and an alteration of internal cell division were observed (Dunstan-Guzmán, 2020).

Biological Alternatives for the Control of *A. caninum*

Among the alternative control methods for *A. caninum*, there is a history of the use of botanical extracts, some recombinant vaccines, the use of nematophagous fungi and bacteria that produce powerful toxins against nematodes (Carvalho et al., 2009; Shaziya and Goyal, 2012). Considering the feasibility history of the use of biological agents for parasite control, the bacterium *B. thuringiensis* is an excellent candidate due to its safety and *in vitro* and *in vivo* effect on nematode larvae and eggs (Meadows et al., 1989).

Conclusion

Zoonoses are caused by a strongly interrelatedness among animals, humans and the environment. epidemiological control shows that there are currently endemic areas and free areas that have been controlled with a unique approach. Currently, the best way to control any disease is to use strategies that combine the vectors, the pathogen and the reservoir as an integrated approach, with hygiene and education being essential factors. Early and accurate detection of zoonotic pathogens are convenient to apply effective control measures. For a unified approach, adequate surveillance is important, prevention or control, as well as one health focused research for intervention steps in the transmission of zoonotic pathogens. It is important to have knowledge of the region or zone, but also about the animal population, the local ecology and the parasites that affect local animals in order to be able to correctly manage parasitic infections in the tropics and thus be adapted for better management. Also, there is an urgent need for alternative strategies for parasitic control in view of the growing threat that anthelmintic resistance poses to animals and humans when using pharmaceuticals, it is important to consider toxicity and tolerance to the host as the presence of residual chemicals in tissues that are used for commercial supply, as well as the wastes that are disposed of and cause toxicity to the environment that have effects on non-target organisms that are important for the ecosystem. Based on its effectiveness and safety, *B. thuringiensis* is proposed as a potential broad-spectrum anthelmintic treatment in animals, allowing the interruption of the biological cycle of several zoonotic parasites.

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Chapter 40

Traditional Pakistani Medicines in Modern World

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ABSTRACT

As documented by WHO, traditional medicines include all the knowledge passed down through generations of indigenous peoples' beliefs, practices, and experiences about how to stay healthy, avoid getting sick, identify problems, and treat them, regardless of whether or not this knowledge can be rationally explained. In many areas of the modern world, peoples considered traditional medicines as an initial line of defense. "Complementary and alternative medicine" is another term for traditional medicine when it is used outside of its primary cultural setting. This chapter delves into the two primary traditional medicinal systems in Pakistan, namely Unani Tibb and Herbalism. Primary system is the treatment of disease through temperament of body while later focuses on the cure of disorders through different herbs and plants which have medical importance. Among the many conventional medical systems that are still in use today (developed countries), the Pakistani system ranks high.

KEYWORDS Traditional Medicine Systems, Unani Tibb, Herbalism, Modern Medicine system	Received: 15-June-2024 Revised: 02-July-2024 Accepted: 27-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Traditional medicine (TM) and other complementary and alternative medical systems have been used for centuries. Irrespective of the availability of western biomedical healthcare, they are offered globally. Complementary and alternative medicine (CAM) is used by up to 80% of people in non-Western nations, and it is believed that half of the population in the Western world uses CAM. Dissatisfaction with Western biomedicine, worries about medication side effects, and personal beliefs supporting a holistic approach to health are thought to be the main causes of the use of complementary and alternative medicine (Sara et al., 2017).

Whole body systems (Ayurveda, homoeopathy, Unani, and Traditional Chinese Medicine); mind-body medicine (prayer, meditation, mental healing); biologically based therapies (use of natural substances, such as herbs, foods, vitamins, dietary supplements, herbal products); manipulative and body-based practices (massage); and energy medicine (Reiki) are the main categories of Traditional/Complementary and Alternative Medicines (TCAM) in vogue in both developing and developed countries. Traditional medicines have long been a vital component of Pakistani culture and have helped a sizable portion of the populace get healthcare (Uzma et al., 2023; Sara et al., 2017).

The widespread use of traditional medicines (TMs) has deep roots in aboriginal culture and continues to play a significant role today (Rahman et al., 2019). Fossil evidence suggests that people have been using plants for medicinal purposes for at least 60,000 years. The indigenous people of Pakistan have relied on traditional treatments for a variety of ailments since ancient times. Many different ailments, including headaches, stomachaches, cuts, and wounds, have been treated using this wealth of knowledge and medicinal flora from generation to generation (Bhardwaj and Gakhar, 2005).

There have been medicinal uses for about 50,000 flowering species worldwide, according to the literature (Ahmad et al., 2021). About 600 plant species in Pakistan have been found to have therapeutic properties, while the country's rich flora includes approximately 6,000 kinds of flowering plants (Nakagawa, 2001; Shinwari, 2010). 80 percent of Pakistanis living in rural regions still rely on traditional medication made from plants (Bodeker and Fredi, 2002). Traditional medicinal herbs continue to serve as the backbone of healthcare systems in rural and outlying locations (Qureshi, 2005).

Traditional Medicine Systems

According to Anon (2001), the Unani medicine system is dominant traditional healing method in Pakistan. It is utilized for the treatment of numerous disorders using medicinal flora found in the local area (Ali et al., 2019). In Pakistan, herbalism, alternatively known as herbal medicine, constitutes another system of traditional medicine. It encompasses the utilization of vegetative plants or byproducts derived from them for therapeutic or medicinal purposes. According to group of researchers, although any portion of a plant can be utilized for medicinal purposes, the most prevalent components include foliage, bark, seeds, roots, fruits, and flowers (Acharya and Shrivastava, 2008).

Traditional Medicines in Pakistan

More over two-thirds of Pakistanis call rural areas home (Population Reference Bureau, 2003). Health indicators have been profoundly affected by poverty, which is exacerbated by illiteracy, women's low status, and insufficient sanitation and water supply (World Bank, 2002). Pakistan is home to 45,000 people who practice traditional medicine and majority of traditional healers are located in rural areas. The fact that they are present in rural areas indicates that the majority of their customers are people living in rural Pakistan (Adeniyi et al., 2018).

About 52,600 licensed Unani doctors work in both the public and private sectors across the country. Nearly 360 tibb clinics and dispensaries are providing free medication to the public through provincial health agencies (Rahman, 2019). Pakistan is now the eighth biggest exporter of medicinal flora for herbal medicines (Hussain et al., 2006).

Traditional Medicines in Modern World

There is a rapidly expanding market for traditional herbal treatment all across the globe. More than 10% of 3, 80,000 species of higher plants are utilized in various therapeutic formulations (Prance, 2001). By 2050, the worldwide market for medicinal plants would be worth $5 trillion, according to some estimation (Shinwari, 2010). As a result, many people around the world choose herbal remedies, and Pakistan's indigenous and tribal communities hold the traditional knowledge and information about these plants in high regard (Khan et al., 2019; Gul et al., 2012; Arooj, 2023; Nadeem et al., 2013).

Traditional Medicines in Developed Countries

The drug Atropine codeine, dioxin, morphine, and quinine are only a few of the significant pharmaceuticals derived from vegetation and their metabolites that have a lengthy history of usage in contemporary "western" medicine. The 2nd half of 20th century has seen a meteoric rise in the use of herbal remedies in industrialized nations (Qaseem et al., 2019). Herbal medicines have seen a revival in popularity in recent years, thanks to a desire to tap into traditional healing wisdom. Herbal products are becoming a part of so-called "integrative" or "complementary" medical systems, particularly in North America and Europe.

A multitude of sites, such as WHO (WHO, 1999), Commission E of German (Blumenthal *et al.*, 2000) and Scientific Cooperation of Europe on Plant-based medicine (ESCOP, 1999), provide graphs on particular herbaceous plants. Particularly in United States, traditional therapies and techniques, like use of herbal medicines, experienced a meteoric rise in popularity towards the end of the twentieth century, driven by rising interest in self-care (Hussain et al., 2022; Tyler, 2000). Numerous plant-based products with various biologically proven effects, such as antioxidants, antiseptic, diuretic, CNS stimulant, sedative, expectorant, digestive, etc., can be found in the European market.

Response of people towards TM's

Many people have a favorable impression of these products over worldwide because they are "natural" rather than "synthetic," these are sparkle of a safe and sound lifestyle, which can facilitate people to wipe off other conventional "allopathic" medicine, and they believe these products are safer than drugs (Tyler, 2000).

Unani Tibb System (Ancient and 1st Medicine System)

When it comes to treating illness, the Unani medical system takes a comprehensive approach, including not only the physical but also the psychological, spiritual, and ecological factors. For optimal health, Unani recommends a combination of medications, beverages, and dietary adjustments. A key component of unani medicine is the recognition of the interconnected nature of the body's systems and organs. Because of this, practitioners often look at the full body (Ali and Alam et al., 2007).

Temperament of Human Body

In their descriptions of the human body's "humor," Unani tibbs and scholars distinguish four different fluids: Dam is hot and wet, balgham is cold and wet (phlegm), safra is hot and dry (yellow bile), and sawda is cold and dry (black bile) (Rahman et al., 2014). A heated temperament is a sign that one's dam humour has been more prominent than their other humours. A chilly temperament indicates sawda dominance, dry temperament safra dominance, and moist temperament phlegm dominance, in the same manner.

According to Majusi (2010), health is achieved when the humours are blended in appropriate dimensions, both in terms of quantity and quality. A natural bodily force known as Tabiat maintains this balance. When it comes to the makings of a person's temperament (humour), Tibb identifies six crucial elements, sometimes known as lifestyle influences. The first is the surrounding air; the second is food and drink; the third is moving around and relaxing; the fourth is thinking about and feeling things; the fifth is sleeping and being awake; and the sixth is eliminating waste and fluids. When these things are in harmony with one another, the body functions normally; when they are out of whack, illness ensues (Siddiqui, 2009b).

Maintenance of One's Health According to Unani Tibb

Follow these steps and follow these guidelines from Unani tibb to take care of your health and cure diseases according to your temperament. People with Sanguine type temperament (moist and cold) should limit their intake of sugar and fatty foods while increasing their consumption of fiber and water. Consistent heart-healthy activity and five to six hours of sleep per night is essential. People with choleric type temperament (moist and hot) need to stay away from warmer climates and hotter temperatures (Jabin, 2011). People with Phlegmatic type temperament (moistand cold should avoid foods and drinks that are heavy in milk, cheese, refined sugar, carbohydrates, and gluten, as well as foods and drinks that are cold or ice-cold and glutinous. People with melancholic type temperament (dry and cold) should eat vegetables, nuts, beans, peanuts, eggplant (brinjal), and tomatoes are off-limits to them. Coffee and tea are bad. Try to incorporate breathing exercises into their routine if you're struggling with insomnia, feelings of loneliness, or sadness. (Jabin, 2011).

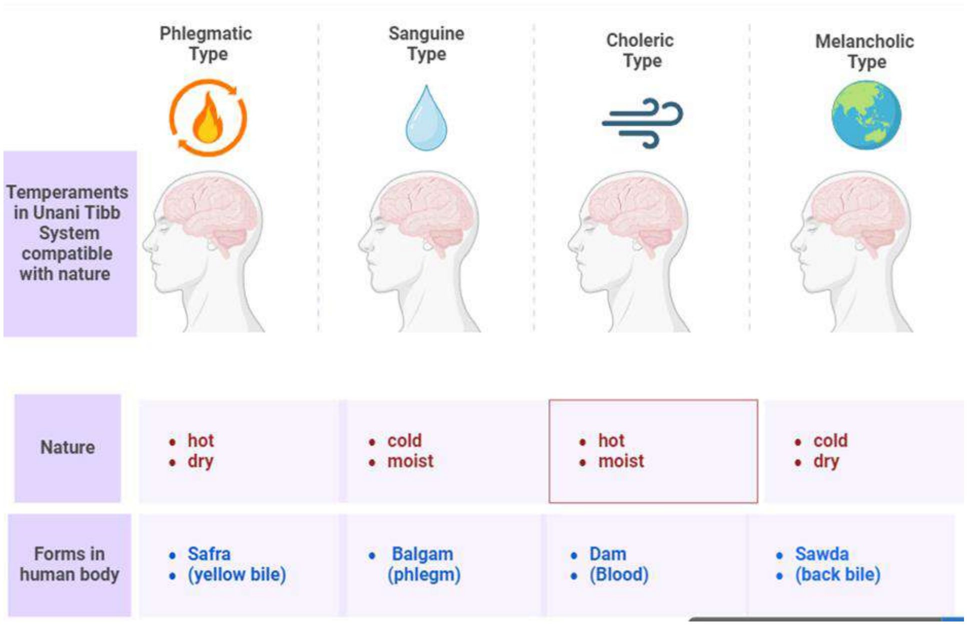

Fig. 1: Unani Tibb temperaments present in human body according to nature.

Place of Unani Tibb in Pakistan

According to the WHO (2001), the Unani system is overseen by a government organization in Pakistan, which was established by an Act signed in 1965. The Pakistani government recognizes both "modern" and "traditional" medical practices, including Unani Tibb (traditional medicine). The practice of Unani medicine spread from its Greek roots to Asia and Arabia. 36,000 practitioners, including 2,000 women, serve the whole rural population and a large number of urbanites in Pakistan; they are all graduates of Tibbi colleges.

According to a 2006 study by Hamayun and colleagues there are currently around 40,000 Unani doctors registered with the government. Karachi is home to one of nine medical institutions in the nation, Hamdard Tibbia College, also known as the College of Eastern Medicine. Approximately 350 hakims, who practice traditional medicine, graduate from these schools annually.

Herbalism/ Herbal system (2nd traditional medicine system)

Herbalism is a diagnostic practice in which herbalists assess diseases by examining the pulse, tongue, feces, sight, voice, shape, and touch of the patient. They then prescribe treatments based on their expertise. These herbs enhance the body's ability to function and boost immunity due to the minerals they contain. The practice of taking medical plants for healing goes back to the earliest days of human civilization (Uzma et al., 2023). Based on data drawn from the Bible and the Talmud, it is known that aromatic plants like myrtle and incense were used in several ceremonies that were part of a healing process. Hippocrates' books, written between 459 and 370 BC, provide a classification of 300 therapeutic plants based on their physiological effects (Kelly, 2009). Wormwood was used to treat fever, garlic was used to combat opium, intestinal parasites, deadly nightshade and henbane and mandrake were applied as fragrant hellebore, haselwort and narcotic were used as sea onion, emetics, asparagus and parsley and garlic were utilized as hypotensive, and pomegranateand oak were employed as acidic (Hammad et al., 2020).

Herbalism in Pakistan

Traditional herbal therapies and remedies have been widely used in this region for a significant period of time (Shaikh and Hatcher, 2005). Aromatic herbs are mostly utilized for culinary, aromatic, and medicinal purposes. These plants include chemicals that possess many biologically significant properties, such as antibacterial and antioxidant capabilities. Herbalism and folk medicine practitioners have utilized them as natural remedies for millennia, including in ancient practices such as Ayurvedic medicine. The herbal sector is experiencing a steady rise in value due to the growing demand for traditional medicine (Shinwari et al., 2006).

Herbal Medicines in Developed Countries

The Supplemental Health and Education Act of 1994, passed towards the end of the 1990s, greatly boosted sales of dietary supplement goods in the United States, including botanical and herbal supplements (Tyler, 2000). Herbal remedies that boast medicinal properties are often classified as pharmaceuticals in the European Union whilst those that don't fall more into the food or cosmetics category. The scientific and legislative requirements that control the advertising of herbal remedies are now being worked on to bring them into harmony (Hussain et al., 2023).

List of Pakistani Traditional Herbal Medicines

Several prominent herbal medicines have a significant role in treating various diseases and ailments mentioned in literature and Fig 2.

Echinacea is used to enhance the defenses and assist the body in combatting infections. Utilized for the treatment of conditions such as fever, boils and herpes. Dong quai, is utilized to address gynae issues such as premenstrual stress, menopause and period discomfort. Several researches suggest that quai has the potential to reduce blood pressure. Garlic is employed to mitigate the danger of coronary artery disease by diminishing the amount of circulating fats and cholesterol, which is a sort of blood fat. Garlic's antibacterial and antiviral characteristics make it effective in combating colds, sinusitis, and other respiratory diseases. Ginger has been demonstrated in numerous trials to be effective in reducing nausea, particularly nausea caused by motion and morning sickness. Hypericum, also referred to as St John's Wort, is a well-recognized name for this plant. Research indicates that St John's Wort is as efficacious to certain pharmacological antidepressants in managing light to moderate depression. (Arring et al., 2018).

Cumin

Cumin, scientifically known as *Cuminum cyminum*, is a type of herbaceous plant that blooms annually and belongs to the Apiaceae family. It is referred to as 'zeera' in Pakistan (Nadeem et al., 2003). Cumin seeds bear resemblance to fennel seeds in terms of their appearance, albeit being smaller and having a darker hue (Jazani et al., 2008). Cumin seeds are nutritionally dense, including significant quantities of fat, protein, and dietary fiber. Cumin seeds contain significant amounts of vitamins B and E, as well as many nutritional elements, particularly iron (Bettaieb et al., 2011).

Benefits of Cumin

Anti-oxidative and Anti-diabetic Effects

Cumin possesses strong antioxidant properties, allowing it to effectively neutralize hydroxy, peroxy, and DPPH free radicals. As a result, it can prevent the oxidation of lipids caused by these radicals (Thippeswamy and Naidu, 2005. Cumin seeds have been found to have an antidiabetic impact in people with diabetes. Patients with diabetes showed a marked improvement after taking C. cyminum orally (Minf and Aifa, 2015).

Digestive Stimulant Action

The enzyme activity of lipase from the pancreas reduced when 1.25% cumin was consumed. Nevertheless, it amplified the actions of amylase, pancreatic trypsin, and chymotrypsin. The quantity of bile acids produced and released within a given period of time was dramatically changed by the ingestion of cumin in one's diet. Platel and Srinivasan (2000a) found that bile acid secretion increased by up to 70% in the experimental group in comparison with the control group.

Anti-inflammatory Effects

Anti-inflammatory effects and underlying mechanisms of cumin essential oil were studied in lipopolysaccharide stimulated cells (Wei et al., 2015). Cumin oil has the ability to suppress NF-κB and mitogen stimulated protein kinases, which means it can reduce inflammation in RAW cells that have been primed by LPS (Srinivasan et al., 2018).

Mint

A broad variety of medical uses have been associated with plants belonging to the mint family, which includes fragrant mint herbs. Theriaca, a poem by the Greek poet and physician Nicander of Colophon (197–170 BC), makes an interesting allusion to mints in their oldest known written form, describing them as "delighting in gleaming rivers". King Hammurabi of ancient Babylon (1800 BC) is believed to have penned the earliest records of mint plants; he prescribed them for therapeutic uses, namely gastrointestinal (Audenaert, 2013).

Unique History of Mint Use for Gastro-intestinal Disorders

Several medical literatures cite mints as a treatment for cholera; the first of these is also credited to Pliny (Hajar, 2012). Paulus Aegineta recommended consuming "juice of pomegranate sprinkled with mint" as a treatment for cholera (Raj et al., 2021) nutritious drink for cholera patients was created by Sydenham using mint A number of studies have demonstrated that essential oils of various mints have demonstrated in lab activity against many parasites, including roundworms, Echinococcus, and Trichostrongylidae (Maggiore et al., 2012; Katiki et al., 2011).

For Reproductive Purposes

Because of their abortifacient qualities, mints have found extensive use in reproductive medicine, particularly in the areas of feminine hygiene and contraception. Contraception was mostly confined to the "barrier methods" in ancient Greece, when the earliest documents on female health were made. Pessaries, particularly wool balls put into the female reproductive system, were flavored with mints for the cooling and calming effect they produced (Zareef et al., 2003).

Act as Animal Repellent

It is well-documented that Mint herbs, particularly pennyroyal, possess insect repellent and larvicidal growth/reproduction regulating properties against numerous insects. These include mosquitoes, which are known to spread diseases like malaria, yellow fever, dengue, and zika (Ansari et al., 2000; Rocha et al., 2015; Kumar et al., 2011).

For Urinary and Cardiovascular Disorders

A small number of sources discuss the potential benefits of mint for the urinary and cardiovascular systems. Like Pliny, Aulus Cornelius Celsus justified the use of pennyroyal and spearmint as diuretics and stones removers (Hajar, 2012). According to recent studies, the Mentha x villosa species can lower blood pressure by causing bradycardia and vasodilation (Lahlou, 2001). Several mint compounds may exhibit this vasoactive effect, but menthol is the only one that has been proven to do so (Silva, 2020).

For Pain and Inflammation

So, from classical antiquity onward, mints were applied topically or taken internally to alleviate the inflammatory symptoms of various ailments, such as pain, redness, and fever. Pliny used mints in his formulae for irritation of the mouth and eyes (Hajar, 2012). Leg atrophy, likely caused by poliomyelitis, demyelinating disorders, or trauma, was treated with one of these preparations as a rubefacient (Pinto, 2017).

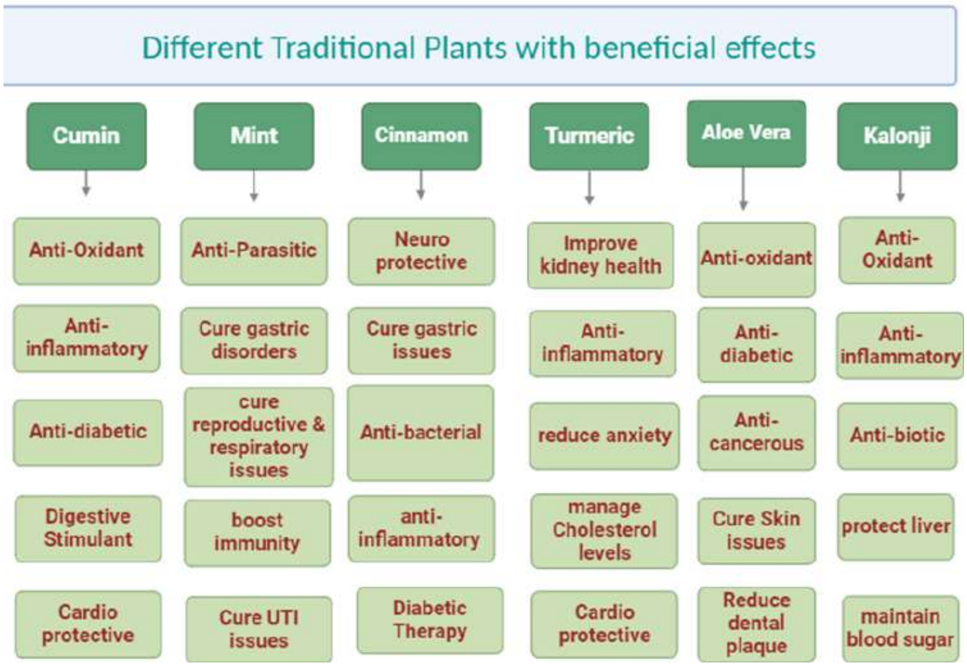

Fig. 2: Different examples of beneficial plants/herbs used in Pakistan

Cinnamon

For example, diabetes, formerly known as the "thirsty disease" in China before the term diabetes mellitus was coined in modern medicine, has been treated with a variety of traditional Chinese medicines for hundreds of years (Lahlou et al., 2001). Cinnamon trees can be found on every continent, and the genus has been home to about 250 different species (Spiriling, 2001). There are procyanidin A-type and B-type linkages in the procyanidin components (DerMarderosian and

Beutler, 2011). Cinnamon and berries are the sources of these procyanidins. Additionally, they possess antioxidant properties. Similarly, cinnamaldehyde or trans-cinnamaldehyde, the primary component of cinnamon, is present in the essential oil and contributes to both the aroma and the various physiological consequences related to cinnamon (Lawrence, 2007).

Cinnamon has a history of usage as a diabetic therapy and neuroprotective agent in traditional Chinese medicine, which dates back about four thousand years (Beck, 2005). Additionally, inflammation, gastrointestinal issues, and urinary infections can all be alleviated using cinnamon's health-promoting properties (Babylonian, 2018). After demonstrating that cinnamon essential oil was effective against Streptococcus mutans, Chaudhari et al. (2012) drew the conclusion that cinnamon essential oils could serve as a viable substitute for other antibacterial substances in combating the bacteria that cause mouth infections.

Ginger

Zingiber officinale is the scientific name, and it is a member of the ginger family (Zingiberaceae). The rhizome, or subterranean stem, of the ginger plant is utilized both medicinally and as a seasoning. Use it as juice, oil, or in any of its dried, powdered, or fresh forms (Shahrajabian, 2019). Many different kinds of "stomach problems" can be alleviated by ginger. These include nausea associated with motion sickness, morning sickness, colic, upset stomach, gas, diarrhea, nausea after cancer therapy, vomiting and nausea after surgery, and lack of appetite. Additional applications include alleviating aches and pains associated with rheumatism, muscular tension, menstruation, coughing, and bronchitis. Pain in the stomach, low back, or chest can also be alleviated by ginger. Ginger is a common ingredient in many culinary and drinks recipes (Shahrajabian, 2019).

Possible Risks and Benefits

There are several advantages and disadvantages to every medical treatment option. Becoming an educated medical consumer is crucial for protecting and improving our health. Traditional and herbal medicines, in all their forms, have extensive medicinal and preventative uses. There is no system in place to ensure the safety and efficacy of herbal remedies. Therefore, it is possible that contaminants or batch-to-batch variations are to blame for some of the documented harmful effects. Herbal remedies may be more likely to cause side effects due to their high length (Hudaib, 2011). In order to make conventional therapies safer and more successful, this paper discusses the various benefits and hazards of consuming herbal products. Worldwide, more and more people are turning to herbal remedies as an alternative to conventional medication for the relief of a wide range of medical conditions, including cardiovascular disease, diabetes, hypertension, and even some forms of cancer. Herbal remedies are more commonly used in India due to their accessibility (Ernst, 2007).

Future Prospects of Pakistani traditional medicines system in world

There is a burgeoning market for herbal remedies, sometimes known as "Unani" or the Greco-Arab medical system. Astonishingly, the annual revenues of herbal products already surpass US$40 billion. Among the countries bordering the eastern Mediterranean, Pakistan is unique in having officially sanctioned Unani educational institutes. It is critical to have a national strategy plan that will lead to improved sector cooperation in Pakistan, and the government has established a variety of institutions and efforts to achieve just that (Shaikh and hatcher, 2005).

Conclusion

Pakistanis have used traditional medicine for decades, rooted in their rich culture. The healing methods include herbal treatment, ancient spiritual therapy, and Unani Tibb. Pakistani traditional medicine uses medicinal plants and herbs for rehabilitation, and medicinal use is one of the most frequent forms. Traditional healers like hakims and herbalists use their understanding of plant therapy to treat a wide range of ailments and problems, from minor to chronic. Unani Tibb, another ancient Greek medicinal practice with Muslim roots, is also popular in Pakistan. Unani Tibb's comprehensive approach to treatment includes diet, lifestyle adjustments, herbal remedies, and physical therapy to restore equilibrium. Even though modern medicine is growing more popular in Pakistan, traditional healing methods are still significant in remote regions lacking easy availability of modern healthcare. Pakistanis still use traditional medicines due to their cultural relevance, low cost, and perceived efficacy. While there are many positive aspects to traditional medicine, there are also some negative aspects, including issues with safety, standardization, and quality control. Traditional and modern medical methods are being combined to give safe and effective treatment to Pakistanis.

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