Efficacy of Natural Products against Zoonotic Disorders

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ABSTRACT

A zoonosis, as described by many medical and health departments, is an infectious disease that is usually transmitted from animals to humans. The major cause of zoonoses are the microbial species, approximately 61% of which are known to be zoonotic in nature. However, the transmission of zoonotic diseases is also related with factors like climate change, environmental unstabilities, animal health and other activities of human such as urbanization, globalization and travelling. Few of the commonly known zoonoses include leptospirosis, echinococcosis, cysticercosis, rabies, anthrax, brucellosis, Chagas disease, Q fever, severe acute respiratory syndrome (SARS), Rift Valley fever, type A influenza, Ebola, haemorrhagic fever and HIV. Dealing with such deadly infections demands a great deal of advancement in the zone of therapeutics. Over the course of years, a large number of natural products are known to be a chief source of novel drug discoveries. Natural products derived from various medicinal plants have the efficacy to treat zoonotic diseases, given to their bioactive compounds and efficient classes of phytochemicals present in such medicinal plants including flavonoids, polyphenols and many others. Countless plant based classifications of vaccines (such as subunit, conjugate, recombinant, and polysaccharide vaccines) have also been derived to cure zoonotic infections like African swine fever virus (ASFV), SARS-CoV-2, HSV-1, HSV-2, DENV, hepatitis A and B, as well as several categories of notorious infections. Moreover, the recent trends in the medical field have also acknowledged the use of natural products as effective anti-zoonotic agents. One of these current trends is the practice of nanotechnology based applications of natural products. In consideration of the risk posed by threatening and wild zoonotic diseases, there is a tremendous need for such revolutionized plant based drugs and vaccines for the sake of a safer and sustainable environment for humans.

Key words: Zoonosis, transmitted diseases, microbial infections, natural products, plant based vaccines, rabies

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INTRODUCTION

A zoonosis (also called zoonoses -plural) is defined by WHO and multiple other medical and health departments as an infectious disease that is usually transmitted naturally amongst species, from animals to humans (Haider et al. 2020). About 61% of microbial species that have possibility to infect human beings are known to be zoonotic. Since 75% of the emerging pathogens have been originated from other animals and 33% of zoonotic diseases can extend from human to human after they have been introduced into human population (Yamada 2004;Jones et al. 2008). Activities like domestication of animals, hunting of wildlife in areas with new habitats as well as clearing of land for grazing farming have remarkably resulted in zoonotic infection in humans by means of microorganisms which are responsible to cause infections and diseases like echinococcosis, rabies, measles and smallpox (Wolfe et al. 2007;Karesh et al. 2012). Several other factors also contribute to the spread of zoonotic diseases which include landscape management, climatic changes, massive human, animal as well as commodity transportation (Jánová 2019). Climate change is reported to have a very complex impact over human health in addition to health of many animals as it alters the circumstances for pathogens in addition to vectors of numerous zoonotic diseases (Leal Filho et al. 2022).
Some of the major zoonotic diseases include leptospirosis, echinococcosis as well as cysticercosis, anthrax, toxoplasmosis, rabies, brucellosis, Chagas disease, severe acute respiratory syndrome (SARS), Q fever, Rift Valley fever, type A influenza,Ebola, haemorrhagic fever as well as the original emergence of HIV (Grace et al. 2012;Karesh et al. 2012). Bovine vaccinia (abbreviared as BV), which is caused by a virus known as Vaccinia virus(VACV), is also a zoonotic disease that is characterized by formation of exanthematous lesions which are present in the mammilla of dairy cows as well as on the hands of milkers and is considered as significant public health problem in recent studies (Matos et al. 2018). The recent Coronavirus disease pandemic occurred in 2019 (COVID-19), which was caused as a result of SARS-CoV-2 has also been designated as a novel zoonosis (Gollakner and Capua 2020).In order to prioritize immediate attention on zoonosis, it is proposed that an ongoing investigation should be launched into the food systems that are animal-based (such as wildlife) for the purpose to identify: (a) Zoonosis risks; (b) Investigation of potential amplifying hosts from acknowledged viral reservoirs; (c) Implementation of IUCN and also OIE methodologies for risk analysis for the sake of emergence of pathogen, plus zoonosis arising due to wildlife trade industries which include much broader investigation of anthropogenic drivers in order to identify crucial factors that can be eventually addressed practically; (d) Encouragement of social distancing among humans and wildlife; (e) Application of international domesticated animal food as well as zoosanitary canons on almost all species that are used for food purposes worldwide (Haider et al. 2020).

2. EFFICACY OF NATURAL PRODUCTS

For many novel drug discoveries, numerous natural products have remarkably been a chief source (Beutler 2009). Though, in the past two decades their use has been reduced as result of technical barriers in order to screen natural products in high-throughput assays against multiple molecular targets (Harvey et al. 2015). Recently, the biological effects of natural products are of great interest for pharmaceutical industries, cosmetics industries, health and food industries and number of scientific studies (Ekiert and Szopa 2020). Several phytochemicals from natural plants have showed anti-cancer

(Khan and Uddin 2021), anti-inflammatory (Azab et al. 2016), anti-microbial (Zida et al. 2017), anti-viral (Shahzad et al. 2020), and anti-parasitic activities (Shabnam et al. 2013). As zoonosis are defined as infectious diseases which spread due to natural cause from animals to humans and or humans to animals, all types of pathogenic agents like bacteria, viruses, parasites, fungi, and prions cause them (Wang et al. 2014).

Transmission of zoonotic disease is related with climate change, environmental factor, animal health and other activities of human like urbanization, globalization as well as travel (Shaheen 2022). Around 75% of incipient infections occurring in humans have been stated to initiate from different zoonotic pathogens (Shahid and Daniell 2016a).Since the mid-20th century, the golden age of natural products and antibiotics have served as influential therapeutics against several pathogenic bacteria (Rossiter et al. 2017). The natural products, mainly the ones that have been derived from microbes, have widely been observed as a copious source of many lead compounds crucial for the drug discovery. Fungal, bacterial, parasitic as well as many viral infections have been treated by these compounds (Frediansyah et al. 2022). Recently the most threatening zoonotic disease is covid-19. Many vaccines derived from plant source have been developed recently against viral diseases (Hager et al. 2022). Natural products have been used widely for their therapeutic effect to many illnesses, several chemical drugs have been isolated from natural products. Though, natural products are byproduct they don’t have scientific validation that’s why numerous scientific trials are being conducted in order to evaluate the efficacy of a broad range of natural products (Kim et al. 2016).

3. NATURAL PRODUCTS AGAINST ZOONOTIC DISEASE

Natural products have the efficacy to work against many zoonotic diseases. Some of the natural products are discussed here that have beneficial effects against the diseases. These are as follow;

3.1. MEDICINAL PLANTS

Traditional Chinese and Ayurvedic medical systems have both utilized plants as a form of treatment (Jaiswal et al. 2016). Because secondary metabolites are produce by medicinal plants, they have served as a source for medications to treat cancer as well as viral, bacterial, and protozoal infections (Harvey 2007). By bonding with viral proteins and enzymes, secondary metabolites found in the medicinal herbs can stop viral penetration and reproduction (Li and Peng 2013).

3.1.1.*GLYCYRRHIZA GLABRA*

The plant *Glycyrrhizaglabra*, is known as licorice, a member of Fabaceae family. The plant's dried roots have a distinctive smell and flavor that is pleasant. The primary element that can be separated from roots is glycyrrhizin. The hepatitis C virus (HCV) was 50% suppressed by glycyrrhizin. Additionally, offering defense against the influenza A virus, glycyrrhizin reduced the number of lung cells that infected by influenza. It has demonstrated its impact on the SARS Co virus in addition to being power full against the viruses ofhepatitis and influenza (Ali et al. 2021). Early on, glycyrrhizin successfully slowed the replication of the SARS-Co virus. Additionally, glycyrrhizin altered transcription factors like protein 1 and nuclear factor B as well as cellular signaling pathways including protein kinase C, casein kinase II, and others. Additionally, it has been concluded that the virus is inhibited by the overexpression of nitrous oxide (Cinatl et al. 2003).

Further research revealed that the two licorice constituents (glyasperin A and glycyrrhizic acid) had an effect on the SARS-Co virus replication process. It has been concluded that glycyrrhizic acid interfered with the virus's ACE-2 receptor and that glyasperin A prevented the virus from replicating (Sinha et al. 2021).

3.1.2. *ALNUS JAPONICA*

The East Asian alder tree, also known as *Alnus japonica*, may reach heights of up to 22 meters. It has a rapid growth rate and is deciduous. It is a member of the *Betulaceae* family, usually referred to as birch family, which has six genera of woody trees and shrubs that grow nuts. *A. japonica* leaves and bark extract are used as a meal to increase immunity to influenza. According to studies, the *A. japonica* bark's methanolic extract has potent antiviral properties against the H9N2 subtype of the avian influenza virus (Tung et al. 2010).

Diarylheptanoids from *A. japonica* were extracted and demonstrated inhibitory action against papain-like protease, which is necessary for SARS-CoV replication. Platyphllenone, hirsutanonol, hirsutenone, rubranol, oregonin, rubranoside A and rubranoside B were the nine diarylheptanoids that were isolated. Additionally, the papain-like protease was inhibited by these compounds. They also demonstrated that the most powerful inhibitor of the papain-like protease was hirsutenone. Additionally, investigation revealed that the compound included catechol and an, -unsaturated carbonyl group, which are essential for inhibiting the cysteine protease of the SARS-Co virus (Park et al. 2012).

To avoid viral infections like influenza in humans and other mammalian and avian species, *A. japonica* extract is helpful. The extract had significant antiviral activity but very little harm in normal cell conditions. The *A. japonica* extract can also be utilized to combat the influenza virus in the food and pharmaceutical industries (Tung et al. 2010).

3.1.3. *ALLIUM SATIVUM*

A. sativum is a member of *Amaryllidaceae* family. It is an annual flowering plant with a tall flowering stem that may grow up to 1 m in height. It originates from a bulb. Garlic, also known as *Allium sativum*, is acomponent of Indian meals. The garlic bulb has an odd odor, which is caused by the presence of sulphur compounds. *A. sativum* exhibits antiviral qualities in addition to antibacterial action. The coronavirus, avian infectious and bronchitis virus, is the single-stranded RNA, is inhibited by an extract of *A. sativum*. Herpes simplex virus 1 and virus 2, cytomegalovirus, influenza A and B, and other viruses have all demonstrated their effectiveness (Ali et al. 2021).

Garlic has been shown through molecular docking experiments to be able to suppress SARS-Co virus 2. The major protease (PDB6LU7) of the SARS-Co virus has been found to combine with the amino acid of the ACE-2 and organosulfur compounds from garlic essential oil using molecular docking. Allyl disulfide and allyl trisulfide showed the most effectiveness. Additionally, it was projected that SARS-CoV-2 might be treated with garlic essential oil or extract (Thuy et al. 2020).

3.1.4. *HOUTTUYNIA CORDATA*

Houttuyniacordata is primarily restricted to damp habitat and is belong to *Saururaceae* family. It is fragrant medicinal herb with a rootstock that creeps. The dengue virus (DENV) can be effectively inhibited by using an ethyl acetate extract of the *H. cordata* plant. Some researchers have demonstrated that ethyl acetate extract of the *H. cordata* plant inhibits DENV-2 (Chiow et al. 2016).

The avian infectious bronchitis virus was likewise suppressed by the extract of *H. cordata*. In the early phases of infection, *H. cordata's* quercetin 3-rhamnoside demonstrated anti-influenza action and prevented viral proliferation (Choi et al. 2009).

H. cordata extract's effects on SARS might be biphasic. The extract of *H. cordata* may trigger the immunity mediated by cell to stop infection from virus prior to the invasion of SARS-Co virus. When a person is infected, HC extract may disrupt crucial viral replication enzymes and start the immune system's negative feedback loop. On SARS-CoV, *H. cordata* significantly inhibited it. The 3CLpro and RdRp were effectively suppressed by the extract of *H. cordata* (Lau et al. 2008).

3.2. *SALVADORA PERSICA* (ARAK)

The *Salvadoraceae* family includes *Salvadoraperscia* (Arak). It is widely recognized as a medicinal herb. As a sunnah of the Prophet, arak has been used for generations as the natural toothbrush (as Mesiwak or Siwak), notably in the Muslim nations. The World Health Organization has promotes the use of its fibrous branches for oral hygiene (Almas and Almas 2014).

Echinococcosis, also known as hydatidosis, is a dangerous zoonotic infection that is spread around the world by the larval phases of cestodes from the genus *Echinococcus*. All continents have *Echinococcusgranulosus* infections, which are the cause of cystic echinococcosis (McManus et al. 2003). Humans and other intermediate hosts' internal organs, particularly the liver and lungs, generate hydatid cysts of *E. granulosus* as unilocular fluid-filled bladders (Thompson and McManus 2002).

Numerous significant phytoconstituents, including indole alkaloids, flavonoids, the sulfur-containing substance tropaedoin, triterpenes, phytosterols, and isothiocyanates are said to be present in the*S. persica*ethanol extract (Sofrataet al. 2008). Results indicated that *S. persica* root extracts had a strong scolicidal impact against the protoscolices of *E. granulosus*, which may be caused by the presence of the anthelmintic isothiocyanates. The results of this investigation demonstrated that HepG2 cells are not cytotoxic when exposed to the *S. persica* ethanol extract. In conclusion, the ethanol extract of roots of *S. persica* is a safe and effective protoscolicide that may be used to treat hydatid cysts and prevent secondary cyst recurrence before surgery (Abdel-Baki et al. 2016).

3.3. *FOENICULUM VULGARE*

The plant *Foeniculumvulgare* is indigenous to the Mediterranean region and is a member of the Umbelliferae (Apiaceae) family. Fennel is grown in several parts of Europe and Asia, with the majority coming from Egypt, India, and China (Ostad et al. 2001). The parasite that causes Leishmaniasis, a zoonotic illness, is treated with by *F. vulgare*. *F. vulgare* is well recognized for having immunomodulatory effects and for having antimicrobial, anti-inflammatory, anti-diabetic, and antitumor properties. As the study demonstrate the therapeutic benefits of *F. vulgare* aqueous and alcoholic extracts as herbal medicines without significantly harming the host cells. The study shows that the alcoholic extract of *F. vulgare* is highly effective against *L*. major promastigotes and amastigotes while having no negative effects on host macrophages. Trans-anethole and bis (2-ethylhexyl) phthalate are primarily responsible for the majority of the anti-leishmanial effects (Maryam et al. 2019).

Both aqueous and alcoholic extracts include active substances with anti-microbial action, such as oleic acid and coumarin. According to this score, macrophages are less toxic to the *L*. major parasite than the alcohol extract of *F. vulgare*. In fact, the alcohol extract shows exceptional anti-leishmanial activity and possesses the ability to reduce the survival rate of amastigotes at host cell-safe doses. Leishmania parasites can be killed using methanolic extract rather than aqueous extract. As a result, further research into *F. vulgare* alcoholic extract might lead to the development of innovative herbal medications against leishmaniasis and other neglected tropical illnesses (Badgujar et al. 2014).

3.4. *PICRORHIZA KURROA*

Picrorhizakurroa is a member of the Scrophulariaceae family, and its ethanol and methanol extracts include essential bioactive substances that may have antibacterial effects. Several harmful microbes, including *E. coli*, *S. aureus*, *S. pyrogens*, and *Salmonella typhi*, have been shown to be inhibited by the ethanol extract of *P. kurroa*. *Yersinia enterocolitica* is a source of the zoonotic illness yersiniosis. The *P. kurroa* extract has antibacterial action against the pathogen *Y. enterocolitica* (Thapaet al. 2022).
The primary chemical component of *P. kurroa* is picroside-1, which is also a component utilized in the manufacture of herbal medicines. *P. kurroa* is particularly important in medicine since it contains a lot of picroside-1 and picroside-11 (Rathee et al. 2016). Comparing the *P. kurroa* ethanolic extract to the control antibiotic (ciprofloxacin), the number of bacterial cells was dramatically decreased. Compared to antibiotics, *P. kurroa* rhizome had high antibacterial activity. This highlights its significant antibacterial properties (Thapa et al. 2022). Table 1 highlights the list of some medicinal plants that have potential against different zoonotic diseases.

4. PLANTS AS SOURCE OF NEW ANTIMICROBIAL AND RESISTANCE MODIFYING AGENTS

The term "natural products" refers to chemical substances derived from living things like plants, fungus, molds, bacteria, marine life, terrestrial animals, and invertebrates. Natural goods have been used by people as their main source of medicine throughout the history of civilization (Rasul et al. 2013).

Table 1: List of some medicinal plants that have potential against different zoonotic diseases

Plant	Compound	Disease	Activity	Reference
Glycyrrhizaglabra	Glyasperin A and glycyrrhizic acid	SARS-CoV-2, influenza and hepatitis	Protects against influenza A virus, inhibit replication of virus, effect on SARS-Co virus.	(Sinha et al. 2021)
Alnus japonica	Diarylheptanoid,platyphyllenone, hirsutenone, hirsutanonol and oregonin	SARS-CoV-2	Antiviral activity against SARS-Co virus, inhibitory effects against papine like protease	(Park et al. 2012)
Allium sativum	Organosulphur compounds, allyl disulfide and allyl trisulfide	SARS-CoV-2, Influenza virus	Anti-bacterial activity, antiviral effects on SARS-CoV and influenza A and B virus.	(Thuy et al. 2020)
Houttuyniacordata	Quercetin 3-rhamnoside	SARS-CoV-2, Influenza virus	Anti-viral, Anti-influenza effects	(Choi et al. 2009)
Salvadorapersica	tropaedoin, triterpenes, phytosterols, alkaloids and flavonoids	Hydatidosis	High Scolicidal effect against protoscolices of *E. granulosus*	(Abdel-Baki et al. 2016)
Foeniculumvulgare	Olic acid, trans-anethole	Leishmaniasis	Antileishmanial effect, anti-microbial	(Badgujar et al. 2014)
Picrorhizakurroa	Picroside-1, Picroside-11	Yersiniosis	Anti-bacterial Activity	(Thapa et al. 2022)

Drug development has a lot of potential for natural products that are enhanced with various antibacterial, anticancer, antioxidant, and neuroprotective chemicals. Antimicrobial resistance (AMR) is a severe global public health concern that impacts people, animals, and the environment. It occurs when pathogens such as bacteria, viruses, fungi, and parasites can survive antimicrobial treatments, leaving them ineffective for treating infections. Numerous infectious diseases, especially those brought on by germs resistant to antibiotics, can be transferred from animals to people (Sarfraz et al. 2017).
An international search for novel therapeutic approaches has been sparked by the rising occurrence of diseases that are multidrug resistant. The growing ineffectiveness of antimicrobial medications

highlights the urgent need for novel therapeutic strategies. The Apocynaceae family, also referred to as the dogbane family and recognized for the wide variety of plants it contains, has recently drawn a lot of attention due to its potential as a source of antibacterial medications. The ability of natural resistance-modifying compounds, phytochemicals, and antimicrobial botanicals derived from various Apocynaceae species to counteract multidrug resistance in pathogenic bacteria (Anand et al. 2020). Recently, there has been a lot of focus on plants as potential sources of novel antibiotics and compounds that can change resistance. the many compounds obtained from plants and how they may be used to combat germs with antibiotic resistance. Alkaloids, terpenoids, flavonoids, phenolics, and essential oils are just a few examples of the many different antimicrobial substances that have been studied. In order to solve the problem of worldwide antimicrobial resistance, it is interesting to investigate plants as sources of antimicrobials and chemicals that change resistance (Abreu et al. 2012). The demand for cutting-edge treatment approaches has increased as multidrug-resistant pathogens like Bacillus anthracis and superbugs have become more prevalent. The potential of phytoextracts as inhibitors of antibiotic resistance has been demonstrated. Development of effective and long-lasting treatments against these deadly infections is possible due to phytoextracts' capacity to alter antibiotic resistance (Dassanayake et al. 2021).

5. NATURAL PRODUCTS DERIVED ANTIMICROBIAL COMPOUNDS

Following are some antimicrobial compounds derived from natural products.

- Coumarin-6-ol, 3,4 dihydro-4, 5, 7, tetramethyl-, a Streptomyces VITAK1 antibacterial agent, inhibits drug-resistant MRSA (ATCC 33591) as well as other Gram-positive and Gram-negative bacterial pathogens (IC50, 40 g/mL) (Brylev et al. 2021). Streptomyces spp. SCSIO 11594 produces two further new compounds. Only dehydroxyaquayamycin (3) suppressed MRSE-shhs-E1 (16.0 g/mL) in addition to other biological activities, but it has no effect on other organisms resistant to other medicines (Song et al. 2015).
- The S. zhaozhouensis CA-185989 (Equatorial Guinea) strain produces ikarugamycin (1-3) derivatives as well as four other recognised compounds that are efficacious against pathogens such as MRSA MB5393 (1–64 g/mL) (Lacret et al. 2014).
- Micromonospora spp. CA-214671 (Gran Canaria, Spain) has been known to develop the chemical phocoenamicin (3), which displayed antimicrobial efficacy against specific diseases such as MRSA MB5393 but was ineffective against *E. faecium* (VRE) MB5570 (Pérez-Bonilla et al. 2018). Diakylresorcins from Zobelliagalactanivorans OII3 are known to be isolated from a Kappeln, Germany, isolate. These compounds had a MIC value of 4.0 g/mL against MRSA LT-1334 and MRSA COL strains (Harms et al. 2018).

6. CLASSIFICATION OF BIOACTIVE NATURAL COMPOUNDS AGAINST ZOONOTIC DISORDERS

Scientists employ the varied pharmacological properties of secondary metabolites, which are phytochemicals produced by plants, to create new medications utilizing their active moieties in the preparation of synthetic pharmaceuticals. Plants utilize their secondary metabolites like polyphenols, alkaloids, saponins, tannins, terpenes,flavonoids, sterols, limonoids, glucosinolates along with several other bioactive substances that are used to ward off herbivores and insects (Şenkal 2020). Because of their numerous pharmacological properties, natural chemicals originating from plants are well-known. Different vegetables, fruits, and herbs contain these chemicals. The majority of these substances are efficient in treating a range of zoonotic diseases (Ashrafizadeh et al. 2021). Fruits, vegetables, spices,

and herbs are the potential sources of polyphenols including phenolic acids. Secondary metabolites are ingested on a regular basis and offer numerous health benefits to humans, including ROS scavenging, cytotoxic affects, anti-inflammatory, anti-allergic, antihypertensive, and antiviral capabilities.Numerous studies have shown how effective polyphenols are at fending off many viruses that are known to cause serious health issues. Antiviral drugs, like polyphenols, have a wide range of action mechanisms that can be used as a therapy or prophylactic method for viral infections (Montenegro-Landívar et al. 2021). Invading human body cells and using their constituent parts for their replication, viruses are comprised of DNA or RNA encased in protein capsules. Frequently, this procedure kills or injures infected cells, which results in a viral illness (Rouse and Sehrawat 2010). Due to their potential health advantages, bioactive substances like polyphenols have recently been suggested as an alternative therapy. These compounds can be obtained through secondary sources, such as agri-food residues (Tapia-Quiróset al. 2020). More than 400 food components include more than 500 different types of polyphenols, according to scientific research (Galanakis and Galanakis 2018).
Here we reviewed a few polyphenolic compounds and their antiviral activity against zoonotic illnesses. The basic chemical structure of polyphenols comprises of one or more hydroxyl groups bound to a benzene ring. Polyphenols can be divided into various classes that range from simple to highly polymerized substances (Ignat et al. 2011).

6.1. POLYPHENOLS

A class of phytochemicals known as polyphenols may have positive health effects. They make up the largest and most diverse collection of bioactive chemicals. The collection of physiologically active substances found in plant-based diets is called polyphenols. These substances, which come from plants including fruits, vegetables, grains, and coffee, are ingested by humans every day. Polyphenols may be further classified into two broader categories namely; phenolic acids and flavonoids. Degenerative disorders are known to be prevented by polyphenols. Phenolic acids are found abundantly in vegetables and fruits (kale, onions, and broccoli). Moreover, polyphenols may also be found in the extracts of various fruits like pomegranate, tea, and grapes(Abbas et al. 2017).
Phenolic acids are typically categorized into hydroxycinnamic andhydroxybenzoic acids while flavonoids among them are further broken down into flavones, isoflavones, flavononse, flavonols(Di Lorenzo et al. 2021). Fruit peel is one of the rich sources of flavonoids, and the amount found in it varies depending on the species and how much light the fruit peel has been exposed to (Abbas et al. 2017).

6.2. *PHENOLIC ACIDS*

The two broad categories of phenolic acids include Hydroxybenzoic acid (Galic acid and Protochatechuic acid), Hydroycinnamic acid (Coumeric acid and Caffeic acid). These subclasses comprise of C1-C6 and C3-C6 backbones. As hydroxybenzoic acids are uncommon in the human diet, it is not thought that these substances have any impact on health. Phenolic acids can also be found in the seeds, hull and bran in addition to fruits and vegetables. Alkaline, acidic as well as enzymatic hydrolysis of aforementioned food items yield phenolic acids in considerable quantities (O'Leary et al. 2004).

6.3. *ANTIVIRAL ACTIVITY OF POLYPHENOLS*

Tannic acid TA ($C_{76}H_{52}O_{46}$), shares characteristics with the two phenolic ligands, TCG (1,3,6-tri-O-galloyl-D-glucose) ($C_{27}H_{24}O_{18}$) and corilagin ($C_{27}H_{22}O_{18}$), as well as other phenolic compounds. It is a naturally occurring polyphenol which is found in a variety of plant species (Gaudreault and Mousseau, 2019).

These three phenolic compounds act on the SARS-CoV-2 target receptor on the cell membrane of host organism and block the chemical bond between SARS-CoV-2 spike RBD (protein receptor binding domain) and ACE2 (angiotensin converting enzyme 2). The entry and replication of SARS-CoV-2 is reported to have been inhibited by phenolic ligands, TMPRSS2 (Transmembrane protease serine 2) and 3CLpro (3-chymotrypsin like protease), respectively (Haddad et al. 2022).

7. *FLAVONOIDS*

Plants produce flavonoids as 2-phenyl-benzo-pyrone derivatives as secondary metabolites. In flavonoids, there are two benzene rings (often referred to as A and B) that are joined by a pyrene ring (C) that contains oxygen, forming a C6-C3-C6 system (Panche et al. 2016).

7.1. *FLAVONOLS*

Flavonoids with a ketone group are called flavonols. The 3-position of the C-ring on flavonols has a -OH group; the hydroxyl group may be glycosylated. Two significant members of the flavonol sub-class of flavonoids include quercetin and kaempferol. Vitexicarpin, fisetin, Galangin and myricetin are other prominent members (Panche et al. 2016).

8. *MYRICETIN*

Flavonols, a subclass of flavonoids that includes myricetin as bioactive natural compound.

9. *ANTIVIRAL ACTIVITIES OF MYRICETIN*

According to reports, it has an IC50 value of 8.4 M for inhibiting the protease of the African swine fever virus (ASFV). Another substance that suppressed ASFV was myricitrin, a myricetin derivative with a rhamnoside moiety (Jo et al. 2020).

Herpes simplex virus 2 (HSV-2)'s highly immunogenic glycoprotein D (gD) is crucial for viral entrance into host cells.Myricetin blocks viral adsorption and membrane fusion to host cells by interacting directly with the viral gD protein. Myricetin also suppresses viral infection and replication by down-regulating the host EGFR/PI3K/Akt (epidermal growth factor receptor/phosphoinositide 3-kinase/Akt or protein kinase B) signaling pathway (Li et al. 2020).

Elderberry extract contains dihydromyricetin, which has antiviral properties against the influenza H1N1 virus in MDCK cells (Roschek et al. 2009).

The synthesis of viral RNA was almost entirely suppressed by myricetin, which also prevented Zika virus multiplication (Zou et al. 2020).

Myricetin from the Dioscoreaceae plants *Marcetiataxifolia* and *Dioscoreabulbifera* L. has been found to have potent inhibitory effects on HIV-1 (RT) and HIV-1 integrase. Myricetin's glycosylated moiety may favourinternalisation within cells and increase anti-HIV-1 efficacy (Ortega et al. 2017).

9.1. *PHLORETIN*

The Puerto Rican strain PRVABC59 and the African strain MR766 are the two ZIKV strains that phloretin is effective against; their respective EC50 concentrations are 22.85 and 9.31 M.Phloretin's inhibitory effects are thought to be due to its ability to prevent cells from absorbing glucose, which prevents the spread of viruses (Lin et al. 2019).

9.2. ANTHOCYANIN

A subclass of flavonoids called anthocyanins gives flowers, vegetables, and fruits different colours like red, blue, pink, or purple. They possess the flavylium ion (2-phenylchromenylium), which bears a positive charge at the oxygen atom of the flavonoid basic structure's C-ring(Khoo et al. 2017). Anthocyanins, from a structural perspective, are anthocyanidins that have been altered by acyl acids (acylated) or sugars (glycosylated).The degree of blue colour of anthocyanins is determined by the quantity of hydroxyl groups on the B ring; methylation results in a red colour (Alappat and Alappat 2020).
The anthocyanidinscyanidin, delphinidin, pelargonidin, peonidin, malvidin and petunidin are widespread in plants and have varying concentrations in fruits and vegetables (Hernández and Elena 2009).

9.3. DELPHINIDIN

According to studies, delphinidin (3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-1--4-chromen-1-ylium) inhibits flaviviruses such the West Nile virus, Zika virus, and dengue virus (DENV). There is evidence that the substance interferes with viral entrance and adhesion to host cells. Delphinidin also lowered ZIKV and DENV infectivity by having a virucidal impact, which was also noted (Vázquez-Calvo et al. 2017).

9.4. MECHANISM OF ACTION OF DELPHINIDIN

This unique mechanism of action for preventing viral entrance directly binds to viral particles and hinders viral (HCV) adhesion to the host cell surface. The virus is also susceptible to it in primary human hepatocytes (Calland et al. 2015).
The influenza virus that is hostile to human numerous phytochemical components, notably delphinidin-3-O-sambubioside, have been linked to the action of Hibiscus sabdariffa L. (sorrel) (Lowe et al. 2021).
Delphinidin-3,5-diglucoside interacts with the main protease Mpro of SARS-CoV-2 via hydrogen bonds with Gly143, His163, His164, Glu166, Gln189, Thr190, and Gln192 as well as via -interaction with His41, according to in silico studies. This suggests that the compound may be helpful in preventing viral replication by inhibiting Mpro (Gahlawatet al. 2020).The substance is also said to be able to bind to ACE-2, which is the human receptor for the SARS-CoV-2 spike protein.Delphinidin 3-O-D-glucoside 5-O-(6-coumaroyl-D-glucoside), one of the flavonoids examined, was found to be a powerful inhibitor of all three protein targets of SARS-CoV-2 (Marimuthu Ragavan et al. 2020).

9.5.FLAVANONES

With roughly 350 flavanone aglycones and 100 flavanone glycosides found in naturally occurring sources, flavanones—previously thought to be a minor group of flavonoids—are now thought to be a large group (Iwashina 2000).

9.6. NARINGENIN

Naringenin ((S)-5, 7-dihydroxy-2-(4-hydroxyphenyl) chroman-4-one), a flavourless and colorless flavanone, is one of the primary flavanones.In grapefruit, it is the predominant flavanone. It's noteworthy to note that naringenin may be able to treat bronchial pneumonia in children, even though COVID-19 pneumonia is distinct from bronchopneumonia because the latter is caused by a bacterial infection (Chrzan et al. 2021).

Naringenin has been evaluated against a replicon of the Chikungunya virus (CHIKV) that was transfected into BHK cells. The replicon contains markers for Rluc, EGFP and viral replicase proteins with puromycin acetyl transferase. It was discovered that naringenin inhibits the expression of the CHIKV replicon-expressed marker genes Rluc and EGFP. Naringenin's anti-alphaviral activity against the Semliki forest virus (SFV) was also verified. Naringenin prevented the generation of SFV virion and further decreased the cytopathic effect caused by SFV and Sindbis viruses.By displaying strong binding affinity to nonstructural protein 2 (nsP3), a protein thought to be crucial for the virus's intracellular replication, naringenin demonstrated potential as a CHIKV inhibitor in silico tests (Pohjala et al. 2011).
Table 2 shows the list of some natural compounds, with the class of the compound, their natural sources from which compound obtained and their antiviral activity.

10. PLANT BASED VACCINE

Vaccination establishes a major advance in the prevention of zoonotic diseases. This process is based on the principle to induce defense against a pathogen through imitating its natural interaction with the immune system of human (Canouï and Launay 2019). Since 1940, several vaccines are being industrialized by the use of attenuated, inactivated as well as live viruses. Among these vaccines, live attenuated or recombinant proteins or killed live attenuated pathogens are the ones that are licensed and the most commonly used vaccines against several infectious animal diseases. Porcilis-PCV2 and also, Suvaxyn PCV2 for pigs, AquaVacFuruvac, AquaVac Vibrio for fish, Periovac for dogs AquaVac ERM, are marketed and also approved vaccines against numerous veterinarian diseases (Meeusen et al. 2007).
There are four main types of vaccines including subunit vaccines, conjugate, recombinant as well as polysaccharide vaccines.

- Subunit vaccines are the ones that separate specific antigens from a virus or germ so that it can be used in the vaccine. However, these specific antigens are accurately chosen in accordance to immune response strength they generate. These vaccines are not known do not cause many drastic effects as they are so precisely targeted (Khalaj-Hedayati et al. 2020).
- Conjugate vaccines are the ones that use specific parts from the superficial antigen coat of the virus or bacteria and these are the ones that are not strong enough to be the basis of illness or even to generate any immune response in body (Bremer and Janda 2017).
- Recombinant vaccines are the one that are made through process of genetic engineering. The protein creating gene is precisely isolated and then placed inside genes of another cell. When this new cell reproduces, it yields vaccine proteins, which means that the immune system will identify this protein and then look after the body against it.These vaccines mostly use two varied components (Yadav et al. 2020).
- Polysaccharide vaccines are the ones that use complex sugar molecules (such as polysaccharides) from external layer of a virus or bacteria. These polysaccharides are chemically linked to that of carrier proteins and also work in the same way as conjugate vaccines (Sun et al. 2018).

An innovative trend of plant-based vaccine has attracted a lot of attraction. A number of these plant derived vaccines against animals' and human infections and diseases have recently been recognized which undergo regulatory and clinical approval. These vaccines have potential to serve as ideal boosters (Shahid and Daniell 2016a). Approximately 200 different proteins have been formed in plants, and according to their expected results, they are known to be new competitors in t recombinant protein field. Plant based vaccine has variety of benefits over different eukaryotic production arrangements. They are largely cost effective as well as safe and thus can be produced productively in bulky amounts. By using systems of plant based production, the expensive usage of fermenters can easily be replaced by a plot of land or a glasshouse (Daniell et al. 2016). The preference of technology as well as the plant

Table 2: Some natural compounds, with the class of the compound, their natural sources and their antiviral activity

NaturalCompounds	Class of the compound	Plant source	Type ofvirus	References
Tannic acid	Phenol	Tarapods (Caesalpiniaspinosa), gallnutsfrom Rhussemialataor Quercusinfectoriaor Sicilian sumac leaves (Rhuscoriaria).	SARS-CoV-2	(Haddad et al. 2022)
Kaempferol	Flavonol (type of flavonoid)	Berries, tea, almonds,beans, tomato,Ficuscarica, cloves, cumin	Corona virus, rotavirus, HSV-1, -2, coxsackie B virus	(Russo et al. 2020)
Catechin	Flavonol	E. cooperi, M. alba, R. succedanea	HIV, HSV-1	(El-Toumy et al. 2018)
Quercetin	Flavonol	Citrus spp., fish mint (H. chordata), Spondiasmombin, S. tuberosa	Rabies virus, poliovirus, HSV-2, SARS-CoV-2, DENV	(Zandi et al. 2011); (Chiow et al. 2016)
Rutin	Flavonol	Spondias spp., Pavettaowariensis (bark)	Rabies virus, influenza virus	(Cushnie and Lamb 2005)
Curcumin	Flavonoid	Turmeric	HIV	(Praditya et al. 2019)
Hesperidin	Flavonone	Citrus spp., grapefruit	Influenza virus, SARS-CoV-2, poliovirus, HSV, syncytial virus,	(Mhatre et al. 2021)
Caffeic acid	Phenolic acids	Pappaya, peach, avocado	HIV, HSV	(Sytar et al. 2021)
Luteolin	Flavone	Broccoli, lentils, pistachio, artichoke, olive, lemon	HSV-1, HSV-2	(López-Lázaro 2009)
Ellagic acid	Phenolic acid	Berries, pomegranate, walnuts, pecans	DENV, hepatitis A and B	(Kang et al. 2006)
Resveratrol	Stilbenoid	Grapes, berries, peanuts	Influenza A, hepatitis C virus, respiratory syncytial virus, HSV, HIV	(Docherty et al. 2006)
Myricetin	Flavonol	Guierasenegalensis leaves, MarcetiataxifoliaandDioscoreabulbiferaL.	African swinefevervirus (ASFV), Herpes simplex virus 2 (HSV-2), Influenza H1N1 virus, Zika virus, Hepatitis B virus (HBV), HIV-1	(Sun et al. 2022);(Mammen 2022)
Phloretin	Chalcone	Apple andStrawberries	Two strains of Zika virus (ZIKV)	(Lin et al. 2019)

species regulate the administration route of vaccine as few plants can only be consumed when they are processed, despite the fact that pressure or heat treatments may abolish the antigen. There are mainly two choices for administration of vaccine including mucosal (nasal or oral) and injection (subcutaneous or intramuscular) administration. However, injection type vaccines can prompt robust protective immunity by favorably inducing production of IgG. Such vaccines are considered the most appropriate against several pathogens that are reported to infect through a respiratory and or systemic route, but antigens need to be highlypurified before they are administered (Takeyama et al. 2015). Various bacterial and viral subunit vaccines production have been practiced in several transgenic plants. Many recombinant subunit vaccines are usually safer as compared to traditional vaccines as they comprise pathogen that are not alive. Vaccines that are produced inside the seeds are usually stable for extended period of storage, due to this reason cereal crops are considered appropriate for production of subunit vaccine (Hefferon 2013). However, the prime plant-made vaccine made commercially wasan accomplishment against NDV by Dow Agro Sciences, which lighted the path for the commercialization of these plant-made vaccines (Yusibov et al. 2011).

11. ZOONOTIC DISEASES AND PLANT-BASED VACCINES

Plant based vaccine offer great results for zoonosis.

Rabies is one of the many zoonotic infections and is most common and circulates amongst wild bats and dogs. Virus belonging to family *Rhatbdoviridae*is the cause of rabies. Vaccines that are currently available give reasonable results but are thoughtful limitations in developing countries due to a number of restrictiohns including high cost and requirement for refrigeration at temperature of 4 °C. Whereas, vaccines that are developed through plant sources can offer effective explanations to such issues (Loza-Rubio et al. 2012).The nucleoprotein of this rabies virus is transiently expressed and can produce remarkable expression and is reported to be immunogenic in case of mice and also confers protection against challenge of rabies viral (Perea Arango et al. 2008). The researchers have fused glycoprotein with ricin toxin -B chain (rgp–rtxB) in roots of tomato, which after intramucosal immunization produced high immune response. The great efficacy of CTB to GM1 receptors assured its anti-rabies antibodies and anticholera toxin (Rosales-Mendoza et al. 2010;Singh et al. 2015). Rabies vaccines which are also plant-based, expressed transitorily in spinach plant, and occurs in phase I of its clinical trials; about five out of nine volunteers expressed neutralizing antibodies against that virus causing rabies (Takeyama et al. 2015).

- Swine flu is a contagious disease that is common in pigs and the virus responsible for this disease belongs to the family *Flaviviridae*. This disease is a major load in the industry of livestock. Plant based oral vaccine proposes key to this disease.E2 protein articulated in chloroplasts of tobacco plant deliberated immune response in animals like mice after oral delivery (Shao et al. 2008). Researchers have also created transgenic rice calli which expressed E2 structural protein, in addition to noticing protective immune response in mice that is immunized orally; pigs also generated cellular, systemic as well asmucosal immune responses that is E2-specific (Jung et al. 2014).
- Pasteurellosis is also one of the commonly occurring infections found in humans as well as animals, and is caused as a result of bacterium called *Pasteurella*. This disease is accountable for loss in pig as well as cattle industry on a large scale, and this infection can be transmitted to humans through an animal's bite in addition to contaminated food. In order to make low-cost and edible vaccines against this Pasteurellosis infection, a remarkable immune response has been the result in plant-based GS60 fed rabbits (Lee et al. 2008).
- Anthrax is reported to be the most commonly emerging zoonosis that is caused by the bacterium called *Bacillus anthracis*. In 2001, anthrax was considered as a biological weapon as it killed 5 people in the US. Recent vaccines obtained from *Bacillus anthracis* by culture filtrate are injectable protective antigen against human anthrax as well as animal anthrax. There are numerous restrictions to this vaccine which include necessity of numerous boosters (approximately eight) as well as withdrawal of specific batches because of occurrence toxin contamination in that culture filtrate. The transplastomic tobacco has been designed by articulating the antigen (PA) which is anthrax protective and detected

immune response by producing high-titre IgG antibodies against anthrax disease (1 : 320 000) in immunized mice and give out to 100% defense after treated a dose of *Bacillus anthracis* which is lethal (Gorantala et al. 2011).

- Listeriosis is also infectious zoonosis in animals and humans. *Listeria monocytogenes* is the causative agent of this disease. Uncooked food is the common reason of this disease transmission to human. Newborn, individuals with weak immune system as well as pregnant women are highly susceptible to severe infection. Extreme complications lead to encephalitis. The causative bacterium of listeriosis is reported as a neglected zoonotic pathogen and several plant derived vaccines might propose the finest solution for this disease. An effort was made to make plant based vaccine against this disease in which transgenic potato is used to orally immunize mice and it showed very auspicious results by notably dropping the bacterial load in liver and spleen after treated with *Listeria monocytogenes*(Ohyaet al. 2005).
- Plague in humans is an infectious disease caused by a bacterial as well as zoonotic pathogen *Yersinia pestis*. Plague can occur in blood vessels (septicaemic infection), in lymph node (bubonic infection) or in lungs (pneumonic infection). In humans, plague causes dreadful infection with approximately 90% mortality rate if continued untreated (Sinclair et al. 2008). The high levels of F1-V have been articulated in chloroplasts of tobacco plant and mice that were fed orally were reported to be extremely immunogenic, and when treated with deadly dose of *Y-pestis* showed 88% protection. When F1-V expressed in chloroplast in lettuce plant, it produced considerably decreased level of antigens but it also revealed immunogenicity (Arlen et al. 2008). Table 3 shows the vaccines antigens expressed in plants against zoonotic diseases.

12. RECENT TRENDS IN THE USE OF NATURAL PRODUCTS AS ANTI-ZOONOTIC AGENTS

12.1. NANOTECHNOLOGY-BASED APPLICATIONS OF NATURAL PRODUCTS AGAINST ZOONOTIC DISEASES

Many zoonotic illnesses have been successfully treated using products produced from plants (Ali et al. 2021). According to sources, the source is zoonotic pathogens 75% of new infectious illnesses in humans(Shahid and Daniell 2016b).Zoonosis, often known as illnesses of animal origin, is the term used to describe diseases that spread from animal to human by direct touch, indirect environmental contact, or ingested food(Chlebicz and Śliżewska 2018).

The advancement of nanotechnology, which has made it possible to comprehend the molecular operations of living cells, has made it possible to design practical technologies that allow early diagnosis and treatment of illnesses (Chakravarty and Vora 2021). Innovations powered by nanotechnology give patients and medical professionals hope for solving the issue of medication resistance.

The domains of medicine and veterinary science both hold great promise for nanomaterial. (Khalaj-Hedayati et al. 2020). Nanoparticles are divided into four categories: 1) nanoparticles made of metals (such as Fe, Zn, Ag, Cu, and Au); 2) oxides of metals and nonmetals(such as ZnO, AlO, VO,and FeO); 3) nanoparticles of semiconductors(such as, CdS, CdSe, and ZnS); and 4) nanoparticles of carbon (From theSociety of NeuroInterventional Surgery (SNIS), American Society of Neuroradiology (ASNR), American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), European Society of Neuroradiology (ESNR),European Stroke Organization (ESO), Cardiovascular and Interventional Radiology Society of Europe (CIRSE), Canadian Interventional Radiology Association (CIRA), European Society of Minimally Invasive Neurological Therapy (ESMINT), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Interventional Radiology (SIR), and World Stroke Organization (WSO) et al. 2018).

Table 3: Vaccines antigen expressed in plants against zoonotic diseases.

Disease	Expressed Antigen	Host plant	Immune response	References
Rabies	Rabies virus G protein	Tomato roots	mice immunized with RGP-RTP showed explicit immune response in the form of IgG1, IgG2 as well as TH2 lymphocyte against RGP-RTP	(Takeyama et al. 2015)
Swine flu	E2 glycoprotein	Tobacco	Subcutaneous immunization produces CSFV-specific serum IgG In comparison to subcutaneous immunization, mice didn't show any specific response after oral immunization	(Shao et al. 2008)
Avian flu	H5 of (HPAI) A	Arabidopsis	When mice immunized orally educed elevated level of HA specific systematic IgG as well as mucosal IgA, sturdy Th1 retorts together with IgG2b production was detected, as well as 72% defense was observed in immunized mice after treated with virus	(Lee et al. 2015)
Pasteurellosis	GS60	Alfalfa/Tobacco	Rabbit Immunized through transgenic plant alfalfa formed antibodies against GS60	(Lee et al. 2008)
Anthrax	PA (protective antigen)	Tobacco	Mice immunized with transplastomic tobacco formed broad range of IgG antibodies against anthrax disease (almost 1: 320 000) as well as 100% protection was noted in immunized mice after treated with lethal dose of *Bacillus anthracis*.	(Gorantala et al. 2011)
Listeriosis	IFN-α	potato	Transgenic potato is used to orally immunized mice it showed very auspicious outcomes by noteworthy dropping the bacterial load in liver and spleen after treated with bacterial pathogen	(Ohya et al. 2005)
plague	F1-V	Tobacco	After oral immunization, mice formed high-titre IgG1, IgG2a, IgA as well as showed 88% protection after treated with fatal dose of *Y. pestis*	(Arlen et al. 2008)

The most prevalent metal nanoparticles are those that are nanosized silver and gold. The improved antibacterial action of AgNPs against a variety of harmful microorganisms, including bacteria, fungi, and viruses, is well recognized. Given that AgNPs and composites have shown efficient antiviral effects against well-known viruses, such as influenza and the human immunodeficiency virus (HIV), they have been suggested by several researchers as possible antiviral medicines to treat a variety of viral illnesses (Jeevanandam et al. 2022).

12.2. APPLICATIONS OF NANOPARTICLES

Gene delivery and drug, the use of fluorescent biological labels, the proteins detection, infections, and tumours, the separation and purification of biological molecules and cells, tissue engineering, the raising of MRI contrast, and pharmacokinetic investigations are some of its uses (Chakravarty and Vora 2021).
Due to their inherent antipathogenic qualities and capacity to photothermally or through the generation of reactive oxygen species (ROS) by photocatalysis inactivate viruses, fungi, bacteria, or yeasts, nanoparticles (NPs) can provide alternatives to conventional disinfection protocols used in healthcare settings. SARS-CoV-2 inactivation techniques using nanotechnology may also be investigated (Weiss et al. 2020).

12.3. BIOFILMS

Bacteria can develop into planktonic, free-floating bacteria or into complex communities known as biofilms. It encourages the variety and proliferation of bacteria and provides them with special habitats that include both aerobic and anaerobic layers. Bacteria are given greater resistance to antimicrobial treatments via biofilms (Johnjulio et al. 2012). By creating biofilms, microorganisms are able to survive with high or low temperatures, antibiotic treatments, and a lack of nutrition. Zoonotic and environmental diseases utilize biofilm development as a method of infection in both animals and people (Clutterbuck et al. 2007).

- Propolis is a beneficial natural product, however some beekeepers have reported allergic reactions including contact dermatitis to this substance. Biofilm development is a significant contributor to poor wound healing; propolis, an anti-microbial substance, can decrease biofilm production and speed up healing (Oryan et al. 2018).
- Herbal essential oils, such as rosemary oil, lime oil tea, tree oil, and, have become more important in dermatology. These are the oils aromatic secondary metabolites are plentiful, particularly terpenes and phenolic compounds, which have strong antibacterial effects and prevent the growth of biofilm (Jain et al. 2022).

12.4. MULTIDRUG EFFLUX

Pathogenic infections caused by multidrug-resistant bacteria are becoming more common quickly over the globe and are in danger of becoming incurable. Numerous studies suggest that efflux pumps have a role in the virulence and adaptive responses that result in the rise of antimicrobial resistance during infection, and moreoverin the process of drug extrusion(Du et al. 2018).

The tet (tetracycline) determinants, which were encoded on plasmids or transposons, were responsible for this resistance, which could be transferred across strains (Roberts 2005).

The "smoke tree," Daleaspinosa, was used to make the isoflavone and pterocarpanarylbenzofuran aldehyde (spinosan A), which had a potential effect when berberine was present (Tagaand Okabe 1991).By reducing the MIC 4- to 8-fold, all three substances improved berberine's efficacy against the wild-type strain of *S. aureus*. An isogenic NorA mutant's MIC was reduced by 2- to 15-fold increaseas a result of these compounds, however none were potent against the NorA overexpressing mutant. Agents 15–17 are expected to block a different efflux pump than NorA (Stavriet al. 2007).

12.5. SYNERGISTIC EFFECTS

Synergistic effects are the collective effects of at least two substances making an influence that is more substantial than both of them could have revealed by themselves. Greek “synergos”, meaning “working together” (Anand et al. 2021).

In order to effectively combat infectious diseases, new strategies must be implemented right now due to the growing global problem of medicine resistance. Recent years have seen a rise in interest in the study of natural compounds, particularly phytochemicals derived from plants, because of their potential to increase the effectiveness of antimicrobial drugs. the expanding idea of synergistic interactions between phytochemicals and traditional antibiotics as a possible countermeasure to drug resistance. Discussions of the mechanics behind these beneficial interactions offer important new information for developing combination medicines (Ayaz et al. 2019). Numerous plant-based essential oils have recently come to light as potential candidates to boost the effectiveness of traditional antibiotics due to their strong antibacterial properties. Essential oils work synergistically with conventional antibiotics when combined. Specifically, the capacity of essential oils to revert bacterial resistance pathways, regaining antibiotic sensitivity in species that have developed bacterial resistance. In order to prevent antibiotic resistance and improve the outcomes of therapy for challenging infectious diseases, synergistic interactions provide significant promise (Lahmar et al. 2017). In the era of antimicrobial resistance, the synergistic antibacterial activity of essential oil-nanoparticle combinations creates new opportunities for the creation of effective and long-lasting antimicrobial treatment methods (Rai et al. 2017).

Among the potential agents being looked at to replace synthetic antimicrobials and traditional antibiotics are plant-based solutions. Numerous investigations on the antibacterial activity of herbal extracts and essential oils were conducted in order to create safer medications. *Myrtuscommunis L.*, sometimes known as the common myrtle or true myrtle, is one of the plants whose essential oils have been thoroughly studied. It is an evergreen shrub from the Myrtaceae family and is frequently seen in typical Mediterranean vegetation. One of the significant fragrant and therapeutic species in this family, *M. communis* has a high concentration of essential oils in the glands of its leaves, flowers, and fruits. Although myrtle essential oils have been shown to have both in vitro and in vivo biological activity (Harikrishnan et al. 2003).

A top goal for global health is the discovery of new, powerful antibacterial agents against MDR microorganisms. It has been demonstrated that certain phytochemicals can make bacteria more susceptible to the effects of antibiotics, inactivating or weakening antibiotic resistance systems. Because of this capacity, some phytochemicals and antibiotics, whose efficiency would be very poor in the absence of phytochemicals, work together synergistically. Some phytochemicals are inactive when taken alone; they only exhibit meaningful action when given together with an antibiotic. Other substances exhibit synergistic action through other ways (Álvarez-Martínez et al. 2021).

13. CONCLUSION

The progress of plant-based vaccines against zoonotic diseases holds great promise in revolutionizing disease control. These innovative vaccines offer advantages such as ease of administration, stability, and reduced production costs. With the increasing global threats posed by zoonotic infections, the research and development of plant-based vaccines are becoming more critical than ever. Continued efforts in this field may pave the way for effective, scalable, and environmentally sustainable solutions for zoonosis control, benefitting both human and animal health.

Plant-based vaccines have shown tremendous potential in addressing zoonotic diseases. The recent progress in this field provides hope for more effective and accessible solutions to prevent zoonotic infections. This review emphasizes the importance of continued research and collaboration between scientists, policymakers, and stakeholders to harness the full potential of plant-based vaccines for safeguarding human and animal health.

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