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Phytochemicals and Medicinal Plants: A Promising Frontier for Antiviral Research in the Age of Pandemics: *REVIEW*

Radhika Baheti[1]; Diksha Tapsale[1]; Jayashri Mahore[2,]; Rashmi Trivedi[3] & Vinita Patole[1]*

[1] Department of Pharmaceutics, Dr. D.Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, Maharashtra, India- 411018. [2] Department of Pharmaceutics, Sinhgad College of Pharmacy, Vadgaon (Bk.), Pune, Maharashtra, India- 411041. [3] Department of Quality Assurance, Smt. Kishoritai Bhoyar College of Pharmacy, New Kamptee, Nagpur, Maharashtra, India- 441002.

*Corresponding author: jayashri.mahore.scop@sinhgad.edu

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ABSTRACT

The recent outbreaks of viral infections have underscored the urgent need for effective antiviral agents. While synthetic antivirals are frequently employed, they may have limited efficacy and cause negative side effects due to their synthetic nature. An alternative approach that holds promise is phytotherapy, which employs medicinal plants and their secondary metabolites to treat various infections. Herbal remedies offer several advantages, such as lower toxicity and increased efficacy in some viral outbreaks. As extraction technology and customized delivery systems continue to advance, herbal-based therapies are gaining greater popularity. The current review article summarizes the various phytoconstituents isolated from medicinal plants that have demonstrated effectiveness against viral diseases, such as hepatitis B (HBV), human immunodeficiency virus (HIV), coronavirus, and influenza virus. The review comprehensively examines the scientific literature on phytoconstituents, antiviral activity, and viral diseases found on Google Scholar, PubMed, Science Direct, and Research Gate databases using significant keywords and a duration window set between 1995 and 2022. The analysis suggests that the aerial parts of plants have been primarily screened for their antiviral properties, while the tubers/roots still need to be extensively explored. There is significant potential for the formulation of herbal extracts, and research in this area could lead to the development of new therapeutic options.

Keywords: Natural antiviral, HIV, SARS, HBV, Medicinal plants, DNA viruses, RNA viruses.

INTRODUCTION

Viruses are tiny parasites that have either RNA or DNA as their genetic material. These tiny parasites require a host cell to divide and forms as complete virus particle, called a virion. Viruses are classified on their shape, size, structure, chemical composition, and replication mechanism [29]. Most of infecting viruses have helical and icosahedral geometry. The helical filament of nucleic acid is surrounded by helical capsid proteins. Nucleocapsids of spherical viruses have icosahedral morphology [62]. The identification and classification of viruses can be done by observing the arrangement of capsomers, which are morphological subunits of an icosahedron [43]. Viral molecules consist of DNA or RNA, which can be single-stranded, double-stranded, circular, or linear. Viruses replicate using the host's reproductive machinery, causing tissue damage and eliciting an immune response [64].

New antiviral agents are needed due to the emergence of new viral infections caused by mutating viruses and the ineffectiveness of current treatments. Examples of viral infections such as Lassa virus, HIV, Ebola virus, and COVID-19 highlight the need for new antiviral agents [94]. The antiviral agents available in the market are synthetic and involve adverse side effects. To overcome these drawbacks, new antiviral agents need to be explored and developed [1].

Herbal plants have been used for centuries to treat viral infections. These include the treatment of herpes simplex virus type 2 (HSV2) [1], hepatitis B virus (HBV), human immunodeficiency virus (HIV) [7], pox virus [15], and other emerging viral infections such as COVID-19 [54; 16]. Research in this area shows that little effort

has been made to identify the active antiviral agent, and more focus was given to studying the use of water-soluble or alcohol extracts of medicinal or herbal plants [18].

Many herbal remedies have been suggested for various medical conditions, alone or in conjunction with diverse preparations such as powdered leaves, ointments, concentrated liquids, brewed concoctions, and oral tablets. Many biologically active substances have been recognized for their diverse therapeutic properties. In recent times, extensive investigations into the antiviral properties of phytochemicals have gained immense importance worldwide [73]. The diverse range of herbal plants contains various phytoconstituents, such as flavonoids, terpenoids, lignans, polyphenolics, sulfides, coumarins, saponins, proteins, alkaloids, furyl compounds, polyenes, peptides, etc. With the increasing trend of synthetic and semi-synthetic drugs causing adverse effects, people are turning to the use of herbal and medicinal plants for the treatment of various diseases and disorders [18].

Herbal medicine is safe, and cost-effective compared to synthetic alternatives [25]. The World Health Organization (WHO) is promoting the use of herbal medicine [101]. Approximately 40% of the antiviral agents available today have been derived from natural sources and are among the best-selling medicines. Given the advantages of herbal antiviral agents, phytotherapy presents an innovative idea for developing safe, effective, and affordable medicines.

The review summarizes the role of herbal antiviral agents in combating various deadly viral infections. It also provides a comprehensive overview of the various species of medicinal plants used for different viruses, their scientific names, families to which they belong, phytoconstituents they consist of, and their mechanism of action in controlling viral infections [28].

VIRAL INFECTION CONTROL

Understanding the structure and function of a virus is crucial for controlling viral infections. When the structure of the virus is well known, it becomes easier to target and control the infection. Unlike bacterial, fungal, or parasitic infections, viral infections are unique because the virus relies entirely on host cells for replication and propagation. In contrast, bacteria, parasites, and fungi do not require host cells to survive. During a viral infection, the virus uses the host cell's normal metabolic process to replicate, making it challenging to design a treatment that targets the virus without harming the host cells [30].

Modern research has revealed unique properties of viruses, such as their structure and replication mechanisms, that can be targeted with antiviral therapies. The critical factor that initiates viral diseases is the viral enzymes. Therefore, the target for controlling viral infections is the viral enzyme. Neutralization of viral enzymes is essential for inhibiting viral replication. During the maturation process, the viral polyprotein precursors are processed by a viral proteinase. Therefore, designing an inhibitor for individual viral proteases is desirable for controlling viral infections [32].

MEDICINAL PLANTS

Due to the drawbacks associated with synthetic antivirals and antibiotics, there has been a growing global trend for using bioactive compounds extracted from natural sources. These drugs often exhibit resistance to various microorganisms and have adverse side effects. Many traditional plants have demonstrated potent antiviral and antibacterial properties, increasing interest in herbal remedies [96].

The pursuit of more effective phytoconstituents will always continue, as numerous herbal plant species are available globally. However, this comes with a drawback, as many medicinal plant species are endangered due to the expansion of human populations and civilizations. Phytoconstituents extracted from medicinal plants have always provided abundant active ingredients and lead compounds to the pharmaceutical industry. In addition, 40% of modern, synthetic, or semi-synthetic drugs have been derived from medicinal plants, either by using them in their original form as a natural drug or converting them into derivatives [96]. The applications of medicinal plants from the middle east are summarized in (Table 1).

Table (1): Medicinal plants of the Middle East having antiviral efficacy.

Sr. No.	Source	Sample Studied	Country	Phytoconstituent	Antiviral activity	Ref.
1	*Rhazya stricta*, commonly called Harmal, belongs to the family Apocyaneace	Water extract	Saudi Arabia	Strong base alkaloids, weak base alkaloids, and non-alkaloids.	SARS-CoV-2	[21]
2	*Lavandula angustifolia* L., commonly called Lavender, *and Salvia officinalis* L., commonly known as Salvia, belongs to the family Lamiaceae.	-	Egypt	camphor, α-thujone, 1,8-cineole and β-Thujone and borneol	Avian influenza H5N1 virus	[2]
3	*Rosmarinus officinalis*, commonly called Rosemary, belongs to the family Labiatae.	Water extract	Palestine	Polyphenols	Herpes viruses 1 and 2	[10]
4	*Psidium guajava (*Linn*)*, commonly called Guava, belongs to the family Myrtacea	Tea Infusion	Palestine	Polyphenols (Tannins)	Clinically isolated H1N1 viruses	[88]
5	*Mistletoe (Viscum album L) or Viscum cruciatum Sieb*, commonly called European Mistletoe, belongs to the family Santalaceae	Water extract	Jordan	Polyphenols	Human parainfluenza virus type 2 (HPIV-2)	[49]
6	*Quercus infectoria Olivier (Fagaceae)*, commonly called Gall oak, belongs to the family Fagaceae	methanol and water extracts	Jordan	Polyphenols (Tannins)	Hepatisis C virus (HCV) protease	[81]

Sr. No.	Source	Sample Studied	Country	Phytoconstituent	Antiviral activity	Ref.
7	*Rhus coriaria Linn*, commonly called Sumac, belongs to the family Anacardiaceae.	Aqueous extract, Alcoholic extract	Syria	Bioflavonoids, Hinokiflavone ,Myrecetin	HIV, HSV-1, HBV, SARS-CoV 2	[26]
8	*Thymus eigii (syn. T. syriacus subsp. eigii*	Essential oil	Turkey	carvacrol, p-Cymene, β-Caryophyllene, γ-Terpinene, Isoborneol	SARS-CoV-2	[23]
9	*Coridothymus capitatus*, commonly called Conehead-thyme, belongs to the Lamiaceae family.	Essential oil	Lebanese	phenolic compounds, terpenes, and terpinenes	Cystic fibrosis	[97]
10	*Salvia officinalis*, commonly called Sage, belongs to *the* Lamiaceae family	Extract	Middle east	Phenols	SARS-CoV-2	[13]
11	*Cupressus sempervirens*, commonly called Mediterranean cypress, belongs to the Cupressaceae family	ethanolic extracts	Lebanon	proanthocyanidin	Herpes infection (HSV-1)	[24]
12	*Cedrus libani*, commonly called the cedar of Lebanon, belongs to the family Pinaceae	Essential oil	Lebanon	himachalol (22.5%), β-himachalene (21.9%), and α-himachalene (10.5%)	Herpes infection (HSV-1)	[78]
13	*Vitis vinifera*, commonly called grapes, belongs to the Vitaceae family	Lyophilized powder	Palestine	Derivatives of quercetin, luteolin, kaempferol, apigenin, isorhamnetin, myricetin, chrysoeriol, biochanin, isookanin, and scutellarein	HSV-1 and SARS-CoV-2	[106]

Sr. No.	Source	Sample Studied	Country	Phytoconstituent	Antiviral activity	Ref.
14	*Teucrium polium*, commonly called felty germander, belongs to the Lamiaceae family	Essential oil	Palestine	sesquiterpene hydrocarbons β-caryophyllene and germacrene D	Cucumber Mosaic Virus (CMV)	[22]
15	*Origanum majorana*, commonly called Oregano, belongs to the Lamiaceae family.	Supercritical extract	Palestine	Carvacrol, thymol, sabinene hydrate	HSV-1	[80]
16	*Viola odorata L.*, commonly called sweet violet, belongs to the Violaceae family.		Lebanon	tannins, methyl salicylate, alkaloids, glycosides, coumarin, apigenin, luteolin, anthocyanins, flavonoids, flavonol glycosides (Kaempferol), poly-saccharides	SARS-CoV-2	[3]

OVERVIEW OF MEDICINAL PLANTS USED IN THE TREATMENT OF VARIOUS VIRAL INFECTIONS

Aglaia andamanica Hiern (AA)

Aglaia andamanica (AA) (Meliaceae) is distributed in Southeast and South Asia. The major phytoconstituents of AA involve limonoid 24-epi-mellanodiol, tirucallane aglaidiol, and the two cyclopenta tetra hydro-benzo-pyran derivatives (pyramidaglan A and B). Traditionally, the leaves of AA were used for the treatment of headaches. Benzofuran derivatives isolated from the plant show engaging pharmacological activities such as antiviral, antileukemic, and insecticidal. N-methyl-trans-4-hydroxy-L-proline showed a marked anti-HIV effect, causing hydrogen bond formation with Thr 66, Asn 155, and Lys 159 enzymes. [75].

Andrographis paniculate (AP)

Andrographis paniculata (AP), also known as Green Chirata and part of the Acanthaceae family, is an ancient annual herb that is exceptionally bitter and is cultivated in India and Sri Lanka. This herb has been used for centuries to treat various conditions such as cancer, diabetes, bronchitis, high blood pressure, malaria, influenza, and leprosy. The significant phytoconstituents of AP include lactones, diterpenoids, diterpene glycosides, flavonoids, and flavonoid glycosides [46]. Recent clinical trials have indicated that it is effective against Dengue virus-1 and upper respiratory tract infections. Andrographolide, one of the major phytochemicals of AP, has exhibited antiviral activity against the Ebola virus, Dengue virus, and SARS-CoV-2, or the novel coronavirus. It has been shown to inhibit the growth of all three viruses and has an immunomodulatory effect. Its non-toxicity

at high concentrations has promoted its evaluation of anti-COVID-19 activity [46]. The modalities of its effect in impeding viral infections can be classified into multiple categories, encompassing the control of the viral entrance stage, genetic duplication, and the production of fully developed operative proteins [4].

Ardisia chinensis Benth *(AC)*

Ardisia chinensis Benth (AC), a flowering plant from the Myrsinaceae family, is found in America, Asia, Australia, and the Pacific Islands. Ardisia species are known for their rich phytoconstituents with strong antiviral properties. Bergenin and norbergenin, extracted from Ardisia japonica, have been identified as anti-HIV agents. The crude aqueous extract of AC has demonstrated potent anti-hepatitis B virus (HBV) activity. [70].

Moreover, studies have shown that AC also exhibits antiviral activity against CoX B3. This antiviral activity is primarily attributed to the naturally occurring polysaccharide present in the plant. The isolated polysaccharide from AC is a neutral polysaccharide, with D-glucose as its main sugar. It inhibits viral replication by interfering with the early stages of viral absorption and entry into the target cells. Therefore, this suggests that polysaccharides or plant extracts containing polysaccharides could be promising antiviral agents for future research [89].

Azadiracta indica (AI)

Azadirachta indica (AI), commonly known as neem, neem tree, or Indian lilac, belongs to the Meliaceae family and is native to the Indian subcontinent. The leaves, stems, fruits, and flowers of this plant have specific medicinal uses. The significant phytoconstituents of AI include azadirachtin, Nimbin, palmitic acid, gedunin, linoleic acid, salannin, and phytol. Neem leaves are used to treat skin ulcers, hair fall, bacterial infections, cardiovascular diseases, diabetes, liver problems, and viral infections. Interestingly, the aqueous extract of neem leaves has proven to be effective against DENV-2. This effectiveness is attributed to its mechanism of action, which involves the inhibition of viral replication. [14].

Bergenia ciliate (BC)

Bergenia ciliata, commonly known as Pasahanbheda, is a small perennial herb that belongs to the Saxifragaceae family. It is found throughout the Himalayas and has traditionally been used to treat diarrhea, dysentery, and stomachache. Phytoconstituents found in BC include flavonoids, glycosides, saponins, terpenoids, sterols, and phenolic compounds. The polyphenols in BC have been shown to inhibit nucleic acid synthesis and viral protein synthesis of influenza virus A. It is also found to inhibits the growth of HSV-1 [77].

Bupleurum kaoi (BK)

Bupleurum kaoi (BK) is an herbaceous perennial plant that belongs to the Umbelliferae family. It is a crucial traditional Chinese medicine used to treat hepatitis, inflammation, nephritis, and bacterial and viral infections. BK is found locally in Taiwan. The active phytochemicals in BK include saponins, sterols, coumarins, flavonoids, lignans, polysaccharides, and essential oils. [19]. Various species of Bupleurum have shown antiviral activity against several viruses. For instance, saikosaponins (A, B2, C, D), isolated from different species of Bupleurum, exhibited antiviral activity against HIV, hepatitis B virus, measles virus, herpes simplex virus, influenza virus, and varicella-zoster virus.

Moreover, BK has proven effective in treating coxsackie B virus type 1 (CVB1) infection [19]. The aqueous extract of BK roots neutralized the CVB1-induced cytopathic effect in the human neonatal foreskin fibroblast cell line. It also inhibited the early stage of viral replication by inducing type I interferon expression. Hence, BK has been proven to be one of the most potent natural agents against CVB1 infection. [33].

Centella asiatica L. *(CA)*

Centella asiatica L. *(CA)* is a perennial creeper belonging to the Umbellifere (Apiceae) family. It is commonly known as Gotu kola or Brahmi. It is cultivated in various regions including India, Pakistan, Sri Lanka,

Madagascar, and South Africa. The plant is rich in significant phytoconstituents such as triterpenoids and saponins, which are known for their medicinal properties. Traditionally, CA has been used to treat wounds and various skin conditions like leprosy, lupus, varicose ulcers, eczema, and psoriasis. In addition, CA has been evaluated for its antiviral activity, particularly against HSV-1 and HSV-2. Asiaticoside, a glycosidic triterpene isolated from the aqueous extract of *C. asiatica*, is the major phytoconstituent responsible for this activity. The mechanism of action is believed to involve the inhibition of HSV-1 and HSV-2 replication in infected Vero cells. [45].

Glycyrrhiza glabra L. *(GG)*

Glycyrrhiza glabra (GG), a perennial herb also known as licorice, belongs to the Fabaceae family. The roots of this plant are dried, processed, and utilized for various purposes. Licorice has been used in many traditional preparations and formulations for a long time, particularly for treating symptoms of viral respiratory tract infections such as cough and hoarse voice, as well as symptoms of hepatitis. The active phytoconstituents of licorice root are triterpene saponins, with glycyrrhizin being the most abundant component. The concentration of glycyrrhizin ranges between 1% and 9%, depending on the species, geographical location of cultivation, and extraction methods. Glycyrrhizin, also known as glycyrrhizic acid, is a glycoside that contains a mixture of sodium, calcium, and potassium salts of glycyrrhizic acid.

Glycyrrhizin is effective against various viruses such as Human Immunodeficiency Virus (HIV) [105], influenza virus, Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Hepatitis A Virus (HAV), SARS-related coronavirus, herpes viruses (VZV, HSV-1, EBS, CMV), and flaviviruses. In HIV, it works by inhibiting the replication of the virus and improving the CD4/CD8 ratio. For influenza viruses, it acts by increasing the production of IFN-gamma.

Glycyrrhizin also normalizes serum transaminases in HBV and acts as an immunomodulator. In HCV conditions, it inhibits immune-mediated cytotoxicity, normalizes serum transaminases, and reduces the risk of hepatocarcinoma. It also helps inhibit viral expression in HAV conditions [85]. SARS-related coronavirus induces cellular NO-synthase and inhibits viral replication in humans. [42]. Herpesviridae family viruses can also be treated by glycyrrhizin; it inhibits the replication of viruses such as VZV, HSV-1, EBS, and CMV. Glycyrrhizin shows the inhibition of viral replication in Flavivirus conditions.

Glycyrrhizic acid, another essential phytoconstituent of GG, is effective against many viruses such as influenza virus, Vaccinia Virus (VV), Newcastle Disease Virus (NDV), Vesicular Stomatitis Virus (VSV), and Respiratory Syncytial Virus. The glycyrrhizic acid ethanol extract of *G. uralensis* is effective against the Influenza virus, and its mechanism of action involves inhibition of the inflammatory cytokines and the virus growth. Vaccinia Virus (VV) and Newcastle Disease Virus (NDV) can be treated using glycyrrhizic acid by inhibiting the growth of the virus. It also inhibits kinase P enzyme and virus growth in Vesicular Stomatitis (VSV) conditions [42].

Gossypium herbaceum L. *(GH)*

Gossypium herbaceum L., also known as the cotton plant, belongs to the Malvaceae family. It is widely distributed across western India, several Middle Eastern countries, Africa, Central Asia, Iran, Russia, Afghanistan, and Turkey. A qualitative analysis of the phytochemicals indicates the presence of carbohydrates, saponins, glycosides, steroids, and phenolic compounds, which include flavonoids and tannins [74]. Gossypol, a phenolic compound, is the primary pigment found in cotton seeds. Research has confirmed that this compound displays antiviral properties against enveloped viruses, which include HIV-1, HSV-2, influenza, and parainfluenza [55]. Different versions of gossypol with varying characteristics exhibited enhanced efficacy against the immunodeficiency virus known as type 1 (HIV-1).

Conversely, the racemic mixture and the enantiomers of gossypol hindered the replication of the type 1-HIV-1 (Tai- Shun et al., 1993). Aqueous extracts derived from the leaves of *Gossypium hirsutum* have been examined regarding their potential antiviral

properties against the yellow fever virus in a tissue cell culture utilizing Vero cells. These extracts exhibited notable antiviral efficacy against the yellow fever virus by impeding its progression, as indicated by the observed minimum inhibitory concentration of 0.079 mg/mL (Esmail, 2023).

Kaempferia parviflora (KP)

Kaempferia parviflora (KP) is known as Krachai dam and is a traditional Thai herb belonging to the Zingiberaceae family. It is an herbaceous plant and is native to Thailand. *KP* has been used for medicinal purposes for a long time. KP therapeutic activities include anti-inflammatory, anti-allergic, antidepressant, anticancer, antimicrobial, antiviral, and anti-obesity [31]. It contains 2 major phytoconstituents, 5,7-dimethoxyflavone and 5,7,4-trimethoxyflavone. The virucidal activity against dengue virus type 2 (DENV-2) was observed using KP leaves and stem extracts. The mechanism of action involves inhibition of the propagation of the dengue virus. A study showed that KP was also effective against avian influenza virus (H5N1). Upregulation of TNF-α and IFN-β mRNA expression by the ethanolic and aqueous extract causes inhibition of the H5N1 virus. Further investigation also proved that the extract showed no cytotoxic effect on the cells at high concentrations. Hence, KP is an excellent herbal alternative to synthetic or conventional medicines for fighting the anti-avian influenza virus [87].

Myrica rubra (Lour.) Siebold and Zucc. (MR)

Myrica rubra (Lour.) Siebold and Zucc. *(MR)* is an evergreen shrub and is commonly known as Chinese Bayberry. It belongs to the Myricaceae family and is mainly distributed in China and Japan [90]. The polyphenolic compound is the major phytochemical of MR. Its bark was used for arsenic poisoning, skin diseases, and ulcers. However, its fruit is carminative and astringent. The antiviral effects of MR were discovered, and the ethanolic extract of the leaves exhibited strong anti-influenza virus type A (H1N1) activity. The extract was added to the Madin-Darby Canine Kidney (MDCK) cell culture medium inoculated with the influenza virus. It showed the activity by inhibiting influenza virus replication. Further studies proved that MR is also effective against the subtype of influenza virus, i.e., H3N2 and type B [63].

Ocimum basilicum (OB)

Ocimum basilicum (OB) is an aromatic perennial herb from the Lamiaceae family. It is a basil genus and a traditional Chinese herb used in the preparations of Chinese medicines. It is cultivated in China, India, Mexico, Russia, South America, and various oceanic islands. The significant phytoconstituents found in *Ocimum basilicum* are linalool, methyl chavicol, eugenol, apigenin carvone, cineole, geraniol, farnesol, α-thujone and ursolic acid [48]. The aromatic oils present in OB showed antimicrobial, antifungal, anticonvulsant, hypnotic, antioxidant, and insect-repelling activities. Various fractions of a phytochemical extract isolated from OB showed activity against different viruses [48]. The aqueous and ethanolic extract, as well as ursolic acid and apigenin, showed significant antiherpetic activity.

In contrast, it was reported that the aqueous extract of OB was more effective than the ethanolic extract. Apigenin showed its action by inhibiting the multiplication of both HSV types but had significantly lower activity in the inhibition of HSV-2 replication. Ursolic acid showed the same action as apigenin against the HSV-1 virus. The ethanolic extract of the plant showed inhibitory activity against adenovirus (ADV-3 and ADV-8). However, apigenin, ursolic acid, and linalool showed activity in inhibiting the secretion of HBV virus. Hence, due to the above findings, OB proves effective against HSV-1, HSV-2, ADV-3, ADV-8, and HBV viruses [34].

Punica granatum (PG)

Punica granatum, commonly known as pomegranate, is a shrub that bears fruit and is widely cultivated in countries such as India, the USA, Japan, Argentina, China, France, Spain, Russia, Egypt, and Iran. The fruit cortex of PG contains phenolic compounds, including flavonoids, tannins, and phenolic acids. PG has been reported to have various pharmacological activities, such as antioxidant, antibacterial, antidiabetic, and

anti-carcinogenic properties. The aqueous extract of PG exhibits antiviral activity against HSV-1 due to its high tannin content [56]. The hydro-alcoholic peel extract of PG displayed the highest inhibitory effect against the influenza A virus, reducing virus production and aiding in its cure. These findings suggest that PG is an effective antiviral agent against both HSV-1 and influenza virus [50].

Salvia miltiorrhiza Bunge *(SM)*

Salvia miltiorrhiza Bunge *(SM)* is known as red sage, Chinese sage, or Danshen. It is a perennial plant and belongs to the Lamiaceae family. This plant is cultivated in China and Japan. The major phytoconstituents of SM include tanshinones and phenolic compounds. sSven phenolic compounds extracted from its roots have shown hepatoprotective, antibacterial, antioxidant, and antiviral activity [99]. It was found that the crude ethanolic and aqueous extract obtained from dried roots of SM showed anti-enterovirus 71 (EV 71) activity. The ethanolic and aqueous extract fraction inhibited EV71 replication, cytopathic effect (CPE), and EV71-induced cell death in Vero cells. The plaque formation in EV71-infected Vero cells was also inhibited due to the reduced virus production. Further studies also revealed that the SM extract prevented the virus entry into the host cells. As a result, due to the reduction in virus entry, there was a gradual decrease in the viral RNA and protein synthesis and a decline in the cell sub-G1 phase [103].

Satureja thymbra (ST)

The herbaceous plant known as *Satureja thymbra*, called the savory of Crete, thrives primarily in the Middle East. It has been documented to possess noteworthy antiviral properties. [93]. The botanical species comprises various chemical constituents, including thymol, carvacrol, p-cymene, γ-terpinene, borneol, caryophyllene, and bicyclogermacrene, which constitute the principal compounds. (Tepe & Cilkiz 2015). Ethanol extract from savory Crete leaves has been used against monkey kidney cell line infected with Herpes simplex virus type 1 [40]. The study found that ethanolic extract at a concentration of 0.25 mg/mL can inhibit 50% of the viral growth, indicating the extract's ability to be utilized as an antiviral agent. The result obtained was confirmed by another researcher, who identified that 50% of the viral growth of Herpes simplex virus type-1 was inhibited at a concentration of 0.22 mg/mL [61]. Phenolic compounds present in the extract exert their effects on the viral particles through their interaction with the glycoprotein of the viral envelope or through their inhibition of the polymerase of the viral particles. As a result, the synthesis of the viral genome is disrupted. On the other hand, terpenes impede the virus by interfering with the structure of the envelope, which is essential for the attachment of the viruses to the host cells and the subsequent initiation of infection. [95].

Verbascum thapsus L. *(VT)*

Verbascum thapsus L. *(VT)* is commonly known as mullein and is a hairy biennial plant. It belongs to the Scrophulariaceae family and is native to Europe, Northern Africa, and Asia. It is a very reputed plant due to its various medicinal properties. The significant phytoconstituents of VT include saponins, iridoid and phenylethanoid glycosides, flavonoids, vitamin C, and minerals. The pharmacological activities shown by this herb are antioxidant, anticancer, anti-inflammatory, antimicrobial, antiviral, antihepatotoxic, and anti-hyperlipidemic. Traditional uses of VT involve wound healing, urinary diseases and edema, and antiviral activity. Another study demonstrated that the methanolic extract of VT showed antiviral activity against the pseudorabies virus strain RC/79 (PrV). It mainly inhibited plaque formation and showed dose-dependent inhibition on the growth of Vero cells, which eventually resulted in reduced infectivity [41].

Ventilago denticulata (VD)

Ventilago denticulata (VD) is a climber commonly known as Raktavalli. It belongs to the Rhamnaceae family and is cultivated throughout India, mainly in hotter parts. The stem bark of VD contains friedelin and several anthraquinones. In contrast, the root contains anthraquinones, ventinones A, and B. Emodin is the significant phytoconstituent in its root bark and is used for atonic dyspepsia, mild fever, and debility. Evaluated VD for its antiviral activity, which is effective against Herpes simplex virus type 1 infection (HSV-

1). The ethanolic extract of VD inhibited plaque formation of HSV-1, and the action was determined using a plaque reduction assay. It was also effective against thymidine kinase-deficient HSV-1 and phosphonoacetate-resistant HSV-1 strains, and the activity was characterized using cutaneous HSV-1 infection in mice. The plant extract did not show any toxicity in mice; thus, it may be a candidate for anti-HSV-1 agents [59].

***Salvadora persica* L. (SP)**

Salvadora persica L., a botanical species renowned for its association with oral hygiene, is commonly called Meswak. This plant thrives in Saudi Arabia and is also prevalent in other parts of the Middle East. [37]. The benzylisothiocyanate, an isothiocyanate, is responsible for the antiviral activity [5]. The botanical extract influences the viral entity by rendering the viral particles inactive. This mechanism is achieved by impeding the initial stage of viral attachment to a host cell. [47]. The efficacy of the ethanol extract derived from the plant was examined on baby hamster kidney cells that had been infected with the Herpes simplex virus. The investigation determined that all variations of the ethanol extract, containing different concentrations of Meswak, successfully impeded the growth of the herpes simplex virus. The presence of the extract at concentrations of 0.5%, 1.0%, and 1.5% exhibited a decrease in the virus cytolytic activity after a 10-minute treatment period. [91]. However, the cytolytic activity was significantly diminished when the concentration of Meswak extract reached 5.0%. Consequently, the replication of the virus can be effectively impeded by the ethanol extract of Meswak. The active components that account for the antiviral properties are likely benzyl nitrate and benzyl isothiocyanate [91].

Clinical or preclinical studies of medicinal plants have found to be effective against specific viral infections. Some of the herbal antiviral agents are discussed below, and some are summarized in (Table. 2)

Table (2): Antiviral effects of herbal plants against various viruses.

Sr. No	Herbal plant	Major phytoconstituents responsible for the activity	Active against Virus	Mode of action	Ref.
1	Roots of *Astragalus membranaceus* belonging to the family Fabaceae	Flavonoids, astra-isoflavanin	HSV-1	Inhibition of HSV-1-induced cytopathic effect	[84]
2	Stem barks of *Calophyllum brasiliense* belonging to the family Clusiaceae	Tricyclic coumarin	HIV	Inhibits viral replication in acute as well as chronic infections via suppression of NF-κB activation	[53]
3	Leaves of *Carica Papaya* belongs to the family Caricaceae	Papain	Dengue fever	Increases platelet count (PLT) and WBC (white blood cells) count	[6]
4	Leaves of *Cassia javanica* belonging to the family Fabaceae	Epiafzelechin-(4α→8) -epiafzelechin	HSV-2	Inhibits the viral replication	[32]
5	Fruit of *Chaenomeles sinensis* belonging to the family Rosaceae	Polyphenols	Influenza virus	Neutralizes influenza virus by inhibition of hemagglutinin action activity and via suppression of NS2 protein synthesis	[82]

Sr. No	Herbal plant	Major phytoconstituents responsible for the activity	Active against Virus	Mode of action	Ref.
6	Rhizomes of *Curcuma Longa* belongs to the family Zingiberaceae	Curcumin	Hepatitis B virus (HBV)	It suppresses viral transcription by downregulation of the coactivator PGC-1α	[65]
7	Roots of *Glycyrrhiza inflate* belonging to the family Fabaceae	Chalcones	Influenza virus	Influenza virus A NA inhibitor	[38]
8	Roots of *Isatis indigotica* belonging to the family Brassicaceae	Phenolic compounds	SARS-CoV-2	It inhibits the protease enzyme of SARS-CoV-3CL	[57]
9	Leaves of *Moringa oleifera Lam.* belonging to the family Moringaceae	Zeatin, quercetin, beta-sito-sterol, caffeoyl-quinic acid and kaempferol	HSV-1	A combination of the flavonoids present provides an antiviral activity by inhibition of viral replication	[17]
10	Leaves of *Ocimum sanctum* belonging to the family Lamiaceae	Terpenoids	H9N2	Inhibits the replication of virus	[44]
11	Aerial parts of *Prunella vulgaris L.* belonging to the family Lamiaceae	Tannins	HIV-1	Inhibits HIV-1 gp41 six-helix bundle formation and also inhibits HIV-1 entry by disruption of the gp41 six-helix bundle formation	[60]
12	Fruits of *Prunus mume* belonging to the family Rosaceae	Polysaccharide	H1N1, H3N2	Inhibits viral hemagglutinin attachment to host cell surfaces	[104]
13	Aerial parts of *Raoulia australis Hook* belonging to the family Asteraceae	Raoulic acid	Human (HRV-2)	rhinovirus 2	[36]
14	Seeds of *Silybum marianum* belonging to the family Asteraceae	Flavonolignans and Silymarin	HepatitisC virus (HCV)	Antioxidant effect of flavonolignans gives antiviral action	[98]
15	Dried fruits of *Terminalia chebula* belonging to the family Combretaceae	Chebulagic acid and Punicalagin	Hepatitis C virus (HCV)	Interferes with viral binding, Inactivates the virus particles which are free, and interferes with the post-infection cell-to-cell spread	[58]

HERBAL MEDICINES SHOWING ANTI-SARS-COV-2 ACTIVITY

As worldwide travel and urbanization are increasing, the emergence of pandemic outbreaks is also increasing extensively. Human health is at risk, especially when vaccines and antiviral agents are not developed during pandemic outbreaks. Examples of such viruses include dengue,

influenza, measles, human immunodeficiency, adenovirus, etc. [11].

Approximately 209 countries have been affected by the virus. However, despite the efforts of many researchers and scientists from different countries to develop an anti-SARS-CoV-2 vaccine, no therapeutic molecule has fully impacted the virus. The complex structure of SARS-CoV-2 is the most likely reason for delayed development of the vaccines.

Single-stranded RNA with symmetric helical nucleocapsid virus can encode twenty proteins (90). Structural proteins involved are S: spike, E: envelope; M: membrane, N: nucleocapsid, while non-structural proteins involved are RNA-dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro) and papain-like protease (PLpro). The most crucial receptor for SARS-CoV-2 attachment to human cells was the angiotensin-converting enzyme-II (ACE-2) receptor. The virus reproduction is also dependent on this receptor. SARS-CoV-2 interacts with host cells primarily through the spike protein-receptor binding domain and the ACE 2 receptor and this contact between the binding site and the host cell generates conformational changes in the spike protein C-terminal S2 subunit, which leads to virus-cell membrane fusion. The complex S protein-ACE is proteolytically processed by the host cell type II transmembrane serine protease TMPRSS2, resulting in ACE 2 cleavage and viral entrance into the host cell [39].

Traditional herbal remedies have been used alone or in combination with pharmaceuticals to treat viral infections effectively. Herbal medicine has a long history of treating infectious diseases and has shown promise in treating SARS-CoV-2 (43). There is hope that herbal remedies will be a breakthrough in treating COVID-19 (44). Alternative medicine systems, such as herbal remedies, have proven effective and safe against viral infections, leading to a global search for alternative COVID-19 therapies. Various herbal remedies are available to stop the viral infection process, with some directly suppressing the SARS-CoV-2 life cycle, blocking the ACE2 receptor, or inhibiting the serine protease TMPRRS2 receptor. Reviewed the applications inhalations of the essential oils (*L. nobilis, J. oxycedrus, Rosemary, Ravensara, Ravintsara, Tea Tree, Bergamot, Eucalyptus, Lemon Balm, Thyme, Oregano, Fennel, Peppermint, Cinnamon and Clove*) as an adjuvant therapy for Covid-19 [72]. It was summarized that inhalation of these essential oils could help to get rid of respiratory infections.

Ecklonia cava (EC)

Ecklonia cava (EC) is an edible marine brown algae species. It belongs to the Lessoniaceae family and is found in the oceans of Japan and Korea. It is extracted and contains Seanol, a polyphenolic compound, and Ventol, rich in phlorotannins [52]. The ethanolic extract of *E. cava* contains nine phlorotannins, eight of which showed anti-SARS-CoV-2 activity. The phlorotannins are triphloretol A, phlorofucofuroeckol A, dieckol, fucodiphloroethol G, eckol, dioxinodehydroeckol, 2-phloroeckol, 7-phloroeckol. The mechanism of action of phlorotannins involves inhibition of SARS-CoV-3CL (pro). Moreover, six phlorotannins (dioxinodehydroeckol, 2-phloroeckol, 7-phloroeckol, fucodiphloroethol G, dieckol, and phlorofucofuroeckol A) exhibited significant dose-dependent inhibition of SARS-CoV-3CL (pro) cis-cleavage activity. However, diekcol (possessing two eckol groups linked by a diphenyl ether) showed the best inhibitory effect of SARS-CoV-3CL (pro). In treating COVID-19, *Ecklonia cava* has proven to be a promising candidate. Bioavailability and metabolism problems associated with the phlorotannins can be improved with the advancement in the drug delivery [69].

Paulownia tomentosa (Thunb). Steud. (PT)

Paulownia tomentosa (Thunb). Steud. (PT) is an aggressive ornamental and showy tree and is commonly known as paulownia. It belongs to the Paulowniaceae family and is primarily cultivated in European countries. The primary five flavonoids identified from PT ethanolic extract are geranylated flavonones: tomentin A, tomentin B, tomentin C, tomentin D, and tomentin E. These flavonoids showed significant activity against SARS-CoV-2 by inhibiting SARS-CoV-2 PLpro. However, of all the five flavonoids,

tomentin E exhibited the highest inhibitory action. Further preclinical studies were performed, and the results proved that PT flavonoids were reversible and mixed inhibitors [35].

Salvia miltiorrhiza Bunge. (SM)

Salvia miltiorrhiza Bunge (SM) is a perennial plant commonly known as red sage or danshen. It belongs to the Lamiaceae family and is majorly grown in China and Japan. It is reported that SM has inhibitory activity against SARS-CoV-3CL (pro). The ethanolic extract contained tanshinones, the major phytochemicals of *Salvia miltiorrhiza*, and showed significant anti-COVID-19 action. From the research and studies done, it was found that the six tanshinones present in the plant exerted strong inhibitory action against SARS-CoV-3CL (pro) in a dose-but not time-dependent manner. Moreover, it was also found that dihydro tanshinones exhibited the most potent inhibitory action against the virus out of the six tanshinones. Concerning the kinetic mechanism of SARS-CoV-3CL (pro) inhibition, the tanshinones isolated from SM were found to be non-competitive inhibitors [71].

Torreya nucifera (L.) Siebold and Zucc. (TN)

Torreya nucifera (L.) Siebold and Zucc. (TN), commonly known as kaya, is an evergreen shrub. It belongs to the Taxaceae family and is primarily found in central and southern Japan and Korea. The phytoconstituents of TN, which are helpful for anti-SARS-CoV-2 activity, are four bioflavonoids. These bioflavonoids (amentoflavone, ginkgetin, sciadopitysin, and bilobetin) were isolated from the ethanolic extract of TN leaves, and they exhibited a strong inhibitory effect of SARS-CoV-3CL (pro). However, amentoflavone exhibited the most vital inhibitory activity of all the bioflavonoids. Furthermore, molecular docking studies proved that amentoflavone has more affinity with SARS-CoV-3CL (pro) and forms strong hydrogen bonds [79].

(Table 3) describes the anti-SARS CoV-2 action of several natural compounds.

Table (3): Antiviral effects of herbal plants against SARS-CoV-2.

Sr. No.	Scientific Name	Phytoconstituent responsible for the activity	Category	Mode of action	Ref.
1	Leaves of *Angelica keiskei (Miq) Koidz* belongs to the family Apiaceae	Alkylated Chalcones and Coumarins	Herbal product targeting the chymotrypsin-like protease [3CL (pro)]	Inhibitory action towards chymotrypsin-like protease [3CL (pro)]	[70]
2	Seeds of *Cullen corylifolium (L.) Medik* belongs to the family Fabaceae	Flavonoids (Bavachinin, neobavaisoflavone, isobavachalcone,40 – O-methylbavachalcone, psoralidin, and corylifol A)	Herbal products which target Papain-like proteinase (PLpro)	Inhibits SARS-CoV-2 Plpro activity	[51]
3	Fruits of *Quercus infectoria* belongs to the family Fagaceae	Phenolic compounds and condensed tannins	Herbal product as ACE 2-blockers	Blocks ACE 2 receptor and also shows antioxidant activity	[83]
4	Stem of *Sambucus javanica* belongs to the family Adoxaceae	Phenolic acids (caffeic, chlorogenic, and gallic acid)	Herbal product with anti-SARS-CoV-2 effect	Inhibits NL63 replication and virus attachment to the host cell	[100]

Sr. No.	Scientific Name	Phytoconstituent responsible for the activity	Category	Mode of action	Ref.
5	Fruits of *Tribulus terrestris* belongs to the family Zygophyllaceae	Cinnamic amides (N-trans-Feruloyloctopamine, N-trans Coumaroyltyramine, N-trans-Caffeoyltryamine, Terrestrimine, N-trans-Feruloyltryamine and Terrestriamide)	An herbal product that targets Papain-like proteinase (PLpro)	Inhibits SARS-CoV-2 PLpro activity	[86]

CHALLENGES AND FUTURE ASPECTS:

In recent times, there has been the emergence of many viral diseases that can be fatal. Although the use of synthetic antiviral drugs can control some of the viral infections, many developing countries need help to afford such expensive antiviral drugs. Hence, there is a need of the hour to develop effective, safe, and cost-effective antiviral drugs. There are many antiviral agents available across the globe. There is need to extract the phytoconstituent responsible for the antiviral activity and convert inro suitable dosage form.

Moreover, the long-term use of antiviral drugs for diseases such as HIV is causing issues of viral resistance. Hence, it becomes necessary to keep searching for natural novel antiviral agents. Nowadays, researchers are paying much attention to developing natural antiviral agents that are safe, efficacious, and cost-effective. Various species of herbal plants that can provide a cure against various viral infections are screened. Many aspects need to be given attention while developing novel natural antiviral agents. The extraction techniques and evaluation parameters for the activity shown by that specific plant extract must be studied in detail. For instance, the extraction method used for antiviral activity against HIV-1 and HIV-2 was achieved using the acetone extract of *Combretum paniculatum*. In contrast, *Dodonaea augustifolia*'s methanol extract showed only anti-HIV-2 activity [20].

Another example is of Pokeweed antiviral protein (PAP). These PAP isoforms were isolated from the leaves of *Phytolacca americana.* This showed activity against HIV [76]. Therefore, while screening medicinal plants for their antiviral activity, it becomes essential to identify the method for extraction, which part of the plant needs to be used, and the correct and appropriate climatic conditions and season to collect that plant. Numerous medicinal plant species contain proteins that can inactivate the ribosomes (RIPs), alter the ribosomal functioning in infected cells, and further inhibit viral protein synthesis [67]. For instance, trichobitacin an RIP isolated from *Trichosan theskirilowii* showed action against HIV-1 by reducing the expression p24 antigen. These observations provide the base ground for further research on PAP as a potent therapeutic agent for HIV. *Phyllanthus niruri* was found to be effective against Hepatitis B. It also provides activity against HIV-1 RT inhibition [27]. The antioxidant potency of several phytoconstituents also contribute to their antiviral potential. One such example is *Bituminaria bituminosa* L. commonly found in Palestine. The extracts from *Bituminaria bituminosa* L. showed potent antioxidant effect owing to the presence of flavonoids, anthocyanin and hydrolysable tannin using various solvents for extraction [12]. In another study the extracts (n-hexane, chloroform, and methanol) of *B. bituminosa* were found to be effective against HSV-1 and HSV-2 [66].

Considering the alarming condition predicted by the UK professional about Disease X, which could be 20 times more potent than Covid-19 [102], there is an urgent need to develop natural and novel antiviral agents that can be effective against various

viral proteases and help reduce their expression by inhibiting viral replication.

CONCLUSION

A wide variety of traditional herbs and medicinal plants have demonstrated antiviral activity against diverse viruses. With the emergence of new types of viruses, the development of novel antiviral agents has become a priority. While synthetic and semi-synthetic antiviral agents exist, they can also cause adverse effects and develop resistance. In such situations, antiviral agents derived from natural sources gain increasing importance. Numerous herbal plant extracts have shown promising results in managing viral infections. However, a comprehensive understanding of the plant is necessary to develop effective herbal antiviral agents. This includes deciding which extract, extraction method, and part of the plant to use.

Moreover, the active ingredient must be characterized. Active phytochemicals encompass coumarins, tannins, flavonoids, alkaloids, lignans, polysaccharides, peptides, and proteins. Various herbal formulations effective against numerous viruses can be formulated. Although many potent phytochemicals are available, only a few are marketed as pharmaceutical products. Some phyto-compounds are still undergoing various stages of clinical trials. Therefore, the use of traditional plants in treating viral infectious diseases is justified.

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