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Enhancing Immune Responses To Combat Viral Infections: A Phytoconstituents Approach

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Viral infections like AIDS, COVID-19, Zika, Nipah, Chikungunya, Dengue, and M-Pox pose significant global health challenges, impacting public health and causing systemic complications. Viral entry, immune evasion, and tissue damage lead to severe consequences, including immune dysregulation, lung injury, and multi-organ failure.COVID-19 has affected 600 million people, with 6 million deaths, while Dengue and Chikungunya affect millions annually in India. Phytoconstituents from natural plants, such as Withania somnifera, Tinospora cordifolia and Curcuma longa, demonstrate immunomodulatory properties, enhancing T-cell activity, reducing inflammation, and stimulating antibody production. Immunoboosting through phytoconstituents offers a promising avenue for preventing viral infections and strengthening the body's ability to combat pathogens. On 27th May 2020, WHO declared SARS (Severe Acute Respiratory Syndrome)-CoV-2 or COVID-19 caused by Corona virus as pandemic. During this tough time herbal remedies came to rescue when used as an adjunct therapy. Thus best strategy to boost immunity and provide safe antiviral therapy is use of herbal remedies available naturally and abundantly. The objective of this article is to identify and explore the potential of 25 naturally occurring plants rich in immune-boosting phytoconstituents to combat viral infections and mitigate their pathogenic effects.

Keywords: Antiviral; Corona Virus Disease 2019 (COVID-19); Herbal remedies; Immunity boosting; Monkey Pox (M-Pox); Severe Acute Respiratory Syndrome (SARS).

In recent years viral infections such as AIDS, COVID-19, Zika, Nipah, Chikungunya, Dengue and M-Pox have posed severe health challenges globally, significantly impacting public health. The pathophysiology of these diseases involves viral entry into host cells, evasion of immune responses, and subsequent tissue damage, leading to systemic complications. For instance, in AIDS, HIV attacks CD4+ T cells, depleting the immune system.[1] Pathophysiology of COVID-19 involves the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binding to the Angiotensin-Converting Enzyme 2 (ACE2) receptors on host cells, leading to immune

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dysregulation, lung injury, and multi-organ failure in severe cases.[2] Dengue and Chikungunya viruses induce a cytokine storm leading to inflammatory damage.[3-4] Similarly, Zika and Nipah viruses cause neurological damage[5-6], and M-Pox, a zoonotic infection caused by enveloped monkeypox virus is raising alarms due to its rapid spread globally leading to its declaration as a Public Health Emergency of International Concern by WHO on 23-July-2023.[7]

Global statistics highlight the devastating impact of these viral diseases. The COVID-19 pandemic alone has affected over 600 million people worldwide, with over 6 million deaths as of 2023.[8] In India, viral diseases such as Dengue and Chikungunya affect millions annually, and with the emergence of M-Pox, another potential pandemic is looming.[9] Recent outbreaks in South Africa further emphasize the urgent need for preventive strategies.

The immune system, already burdened by environmental stressors, is further compromised during viral infections. For instance, COVID-19 leads to lymphopenia, T-cell exhaustion, and reduced interferon response. Such weakening of the immune response is similarly observed in other viral infections like AIDS and Dengue.

Preventive measures, such as immune boosting, have gained significant importance, especially in light of recent pandemics like COVID-19.[10] Phytoconstituents from naturally occurring plants provide a promising avenue for enhancing immune responses and combating viral infections.[11-12]

Immunoboosting is crucial in the prevention of such infections, as it strengthens the body's ability to combat pathogens.[13] Numerous plant species, including *Withania somnifera, Tinospora cordifolia*, and *Curcuma longa*, have demonstrated immunomodulatory properties by enhancing T-cell activity, reducing inflammation, and stimulating the production of antibodies.[14-15]

MATERIALS AND METHODS

Initially, literature search for identification of widely used herbs with antiviral activity was performed using terminologies like "anti-viral" or "antiviral", "herbs" or "medicinal plants" or "plants". Later, the mechanism of antiviral action of their phytoconstituents was retrieved by using the key words "mechanism of action" plus "name of the herb" or "name of the phytoconstituents" plus "virus" as search terms. Additional searches for literature articles that demonstrated anti-viral efficacy of the herbs using *in silico* studies, cell line studies, *in vivo* studies, clinical studies were included. The results were screened for application of phytoconstituents with respect to viral diseases. Literature articles published by renowned databases like PubMed (Advanced Search Results - PubMed), ScienceDirect (https://www.sciencedirect.com/), Scopus (http://www.scopus.com/), Google Scholar (https://scholar.google.com/) were considered. Exclusion criteria: Literature articles published in the language other than English were excluded due to language barrier.

Herbs Used For Preventing And/Or Treatment Of Viral Infections

A comprehensive list of 25 naturally occurring plants rich in immune boosting phytoconstituents has been identified and each of them are discussed for their role in improving immune responses, reducing viral replication, and mitigating the pathogenic effects of viral diseases.[16,17] Retarding the virus from adhering to the host cells or limiting its intracellular replication are the key mechanisms to curb the infection [Figure 1]. In this review, multiple herbs, plants, spices that show the ability to limit these pathways are discussed with respect to detailed profile, active phytoconstituents with their chemical structures and mechanism of antiviral activity [Table 1].

Herein, an account of 25 naturally occurring plants rich in immune-boosting phytoconstituents to combat viral infections and mitigate their pathogenic effects is presented. This details their therapeutic uses, the phytoconstituents present in them and responsible for these effects along with their chemical structures and chemical abstract services registry numbers.

Clove

Eugenia caryophyllus (Myrtaceae), *lavanga or laung*, is indigenous to Spice Islands of Indonesia and cultivated in India, Sri Lanka, Tanzania, Malaysia and Pakistan. The buds and flowers contain active phytoconstituent eugenol (9-14% w/w). The mechanism of action of clove in the treatment of viral diseases is primarily by the virtue

of eugenol. Eugenol exhibits antiviral properties by inhibiting viral replication and disrupting viral membranes. Additionally, its anti-inflammatory and antioxidant effect help to modulate immune response, thus reducing the severity of symptoms.

Therapeutic Uses

Clove oil alleviates respiratory conditions; asthma, cold, cough, sinusitis, and bronchitis, and is used to treat dental caries, inflammation, manage hepatic diseases and cell damage. It possesses antiviral, anticoagulant, neuroprotective, antioxidant and antifungal properties.[18-21]

Turmeric

Curcuma longa Linn (Zingiberaceae) or haldi or halud, is found in India, Indonesia, and Southeast Asia. Its roots and rhizomes are therapeutically active, containing curcumin, which inhibits virus growth and replication by targeting various cellular pathways like SARS-CoV-2 protease, PD-ACE2 receptors and spike glycoproteins (RBD). Curcuminoids, sesquiterpenes, steroids, and polyphenols are active constituents of turmeric. Curcumin (60–70%) is the most prevalent, followed by demethoxycurcumin (20–27%) and bis-demethoxycurcumin (10–15%). Due to its broad-spectrum activities *viz*; imunomodulatory, antioxidant, anti-inflammatory, antifungal, and antiviral, it helps control the replication of dengue and hepatitis viruses. It is a key component of Ayurvedic decoctions (Kadha), to boost immunity, as recommended by the Ministry of AYUSH. Golden milk (hot milk with turmeric) is regularly consumed to maintain immunity.[22-24] Moreover, molecular docking studies carried out by Banik and co-workers, demonstrated that curcumin showed strongest binding affinity with M-Pox profilin-like protein, that plays a key role in viral replication and assembly.[25]

Giloy (Halden)

Tinospora cordifolia (Menispermaceae) or gulvel or giloy is found in Sri Lanka, India, Myanmar, Thailand and China. Its leaves, stem, root, flower, and seed are therapeutically active. Key constituents include berberine, â-sitosterol, choline, and tinocordiside. Tinocordiside acts by inhibiting main protease of the virus SARS-CoV-2. Other constituents include octacosanol, N-methyl-2-pyrrolidone, cordifolioside A, 11-hydroxymustakone, magnoflorine, N-formylannonain, and syringin. Giloy is the main constituent of the Ayurvedic drug CORONIL®, approved by the Ministry of AYUSH, India for prevention of COVID-19.[26]

Therapeutic Uses

Giloy has immunomodulatory, antioxidant, anti-arthritic, anti-osteoporotic, hepatoprotective, cardioprotective, neuroprotective, anti-diabetic, antipyretic and cytotoxic properties. It is used for treating severe infections, neurological disorders, and AIDS[27]. The methanolic extract of Giloy possesses broad-spectrum antimicrobial and antibacterial activities.[28,29] Batista and co-workers reported the use of berberine in inhibiting entry and replication of many viruses like human cytomegalovirus, herpes simplex, influenza virus, Chikungunya virus and other *Alphaviruses*. Activity of berberine and emodin was tested against Zika virus on Vero E6 cells and virucidal assay. It was proved that berberine inhibited uncoating and replication of virus at later stages of the viral cycle.[30,31]

Lemon

Citrus limon (Rutaceae), or lemon has its peel and juice therapeutically active, with the key constituent L-ascorbic acid, which binds to SARS-CoV-2 receptors, boosts WBC count, enhances immune response, and acts as a potent antioxidant.

Therapeutic Uses

Lemon juice is rich in phytochemicals like vitamin C, citric acid, polyphenols, naringin, naringenin, hesperidin, and hesperetin. The antioxidant properties of citrus fruits enhance the body's natural defense, while citrus peel exhibits antimicrobial activity. Vitamin C is a potent antioxidant that boosts the body's defense mechanisms, aids in wound healing, and enhances iron absorption. These properties help to combat COVID-19 and other viral infections.[32]

Betel Vine (Pan)

Piper betel (family Piperaceae), Nagavallari, or Pan is found in India, Malaysia, Sri Lanka, Bangladesh, Nepal, Burma and China. Leaves and fruits, contain eugenol, chavibetol, and chavicol. Methanolic extract of chavibetol cause lymphocyte proliferation, interferon-C receptor activation, and nitric oxide production, thus has immunosuppressive effects on cellular and humoral responses.[33]

Therapeutic uses

Volatile oils are used in treating respiratory disorders, serve as antiseptic, appetite stimulant, laxative, carminative, and aphrodisiac. They also possess anti-inflammatory, anticancer, anti-apoptotic, antioxidant and antimicrobial activities. The leaf juice is used to treat bronchitis, dyspnea and boost the immune system against bacterial and viral infections while the fruit with honey is an excellent cough remedy. [34]

Adulsa (Malabar nut)

Justicia adhatoda (Acanthaceae) or Malabar nut or Adulsa, or Vasa is native to the India, Bangladesh, Nepal, Sri Lanka, Laos, and Myanmar. Phytoconstituents, Vasicine is a cardiac-depressant while Vasicinone is a weak cardiac stimulant. Combining these alkaloids normalizes the effect, and Vasicine also possess a uterine stimulant effect. It also has tannins, saponins, phenolics, and flavonoids that are effective against respiratory disorders. The active compounds in Adulsa, such as vasicine, may enhance immune response and exhibit some antiviral activity by inhibiting viral replication and promoting respiratory health.[35]

Amla (Indian gooseberry)

Emblica officinalis Gaerth (*Phyllanthusemblica Linn*.) or Indian gooseberry is found in India, Pakistan, Uzbekistan, Sri Lanka, Southeast Asia, China, and Malaysia. Fruit, leaves, seed, root, and bark contain active constituent like ellagic acid, exhibiting antioxidant and anti-cancer effects by enhancing Natural Killer cell activity in tumor cells. It contains ellagic acid, amino acids (alanine, arginine, ascorbic acid), vitamins (â-carotene, niacin, riboflavin), minerals (boron, calcium, copper,), carbohydrates (fructose, glucose, sucrose,), fats, fiber, pectin, flavonoids, tannins, and various acids (gallicacid, chebulagic acid). It also includes growth hormones (gibberellins, phyllemblinics), polysaccharides, proanthocyanidins, proteins, and other beneficial compounds like rutin, tannins, and kaempferol found in its leaves. Research suggests that it may have activity against various viruses, including SARS-CoV-2.Amla is rich in vitamin C and antioxidants, which may enhance immune function and inhibit viral replication by reducing oxidative stress and modulating immune responses.[36]

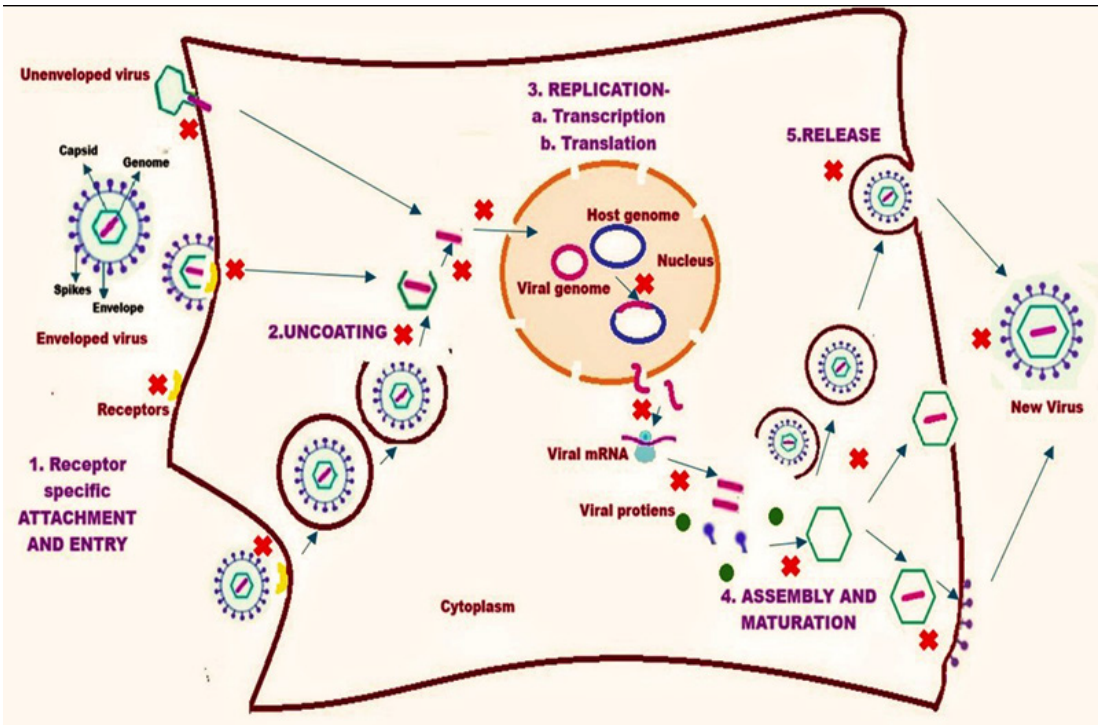
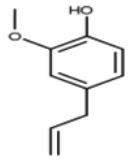
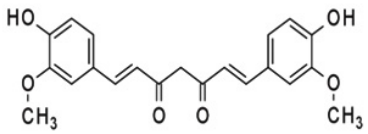
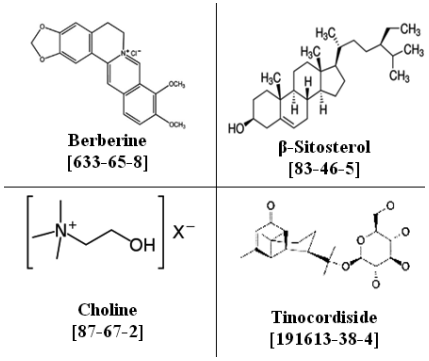
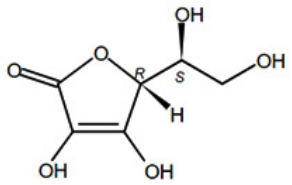
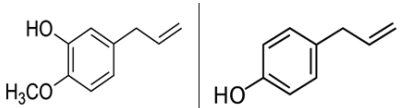
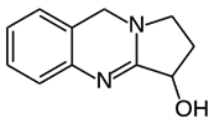
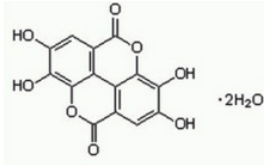
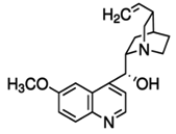
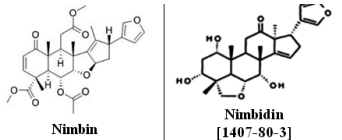
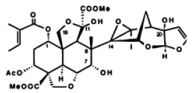
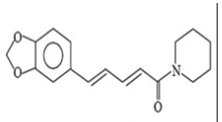
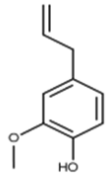
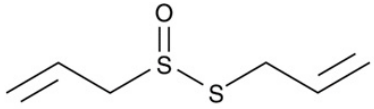


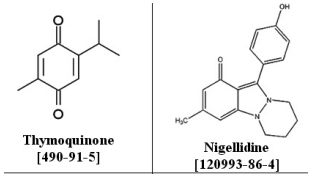
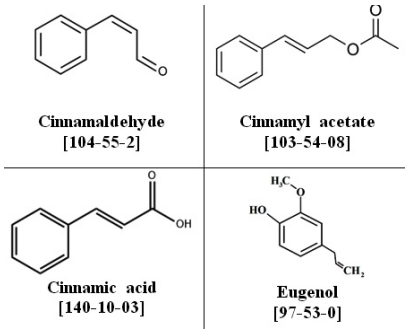
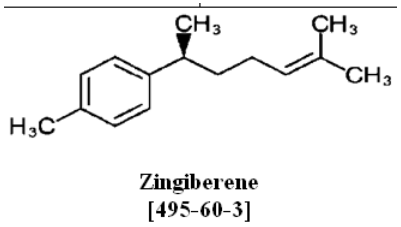
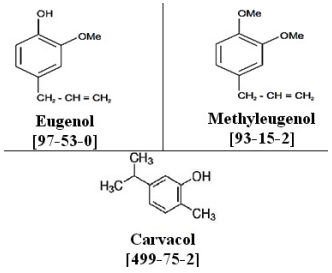
Fig. 1. Mechanism of antiviral activity of phytoconstituents from medicinal plants-Multiple sites of blockage

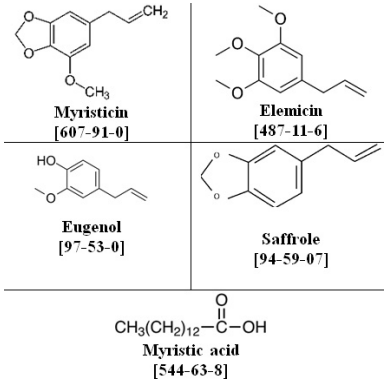
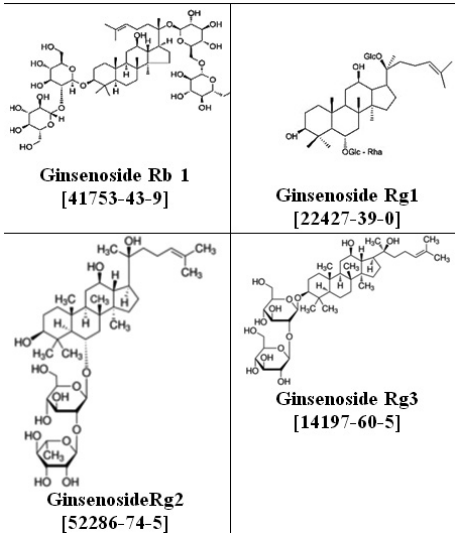
Table 1. Important naturally occurring plants, their immune-boosting phytoconstituents, with chemical structures, CAS registry nos., and their MoA

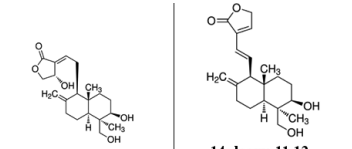
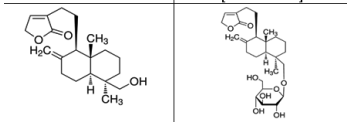
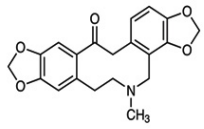
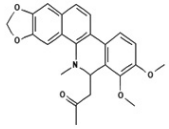
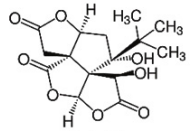
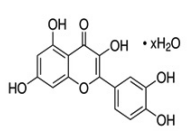
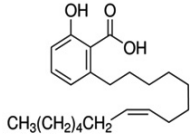
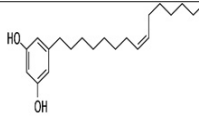
Sr. No.	Plant Name	Phytoconstituent/s & CAS Registry Number	Mechanism of Action (MoA)	References
1	Clove	 **Eugenol [97-53-0]**	Eugenol exhibits antiviral activity by inhibiting HSV-1 DNA polymerase and damaging the outer envelope of newly synthesized viruses. It shows efficacy against Ebola, influenza A, herpes simplex virus types 1 and 2, and feline calicivirus. Eugenol derivatives have also demonstrated potential against flaviviruses like dengue, Zika, and yellow fever. Additionally, eugenol may inhibit HIV-1 replication and boost lymphocyte production, showcasing its anti-HIV-1 potential.	75
2	Turmeric	 **Curcumin [458-37-7]**	Curcumin inhibits HIV replication by targeting viral proteins, including integrase, protease, and Tat protein. It also binds to the active site of HIV-1 protease. Additionally, curcumin exhibits antiviral activity against various viruses, including Zika, chikungunya, influenza A, dengue, hepatitis B and C, HIV, SARS-CoV-1, and others. Its antiviral mechanisms include virucidal effects, inhibition of viral entry, replication, and egress, as well as viral protein degradation	76
3	Giloy (*Halden*)	 **Berberine [633-65-8]** **β-Sitosterol [83-46-5]** **Choline [87-67-2]** **Tinocordiside [191613-38-4]**	In-silico studies revealed that compounds Berberine, Isocolumbin, Magnoflorine, and Tinocordiside exhibit high binding affinity for SARS-CoV-2 proteins, including surface glycoprotein and main protease. Additionally, these compounds may modulate host immune responses by inhibiting NF-ºB and MAPKs, key regulators of transcription and protein phosphorylation.	77

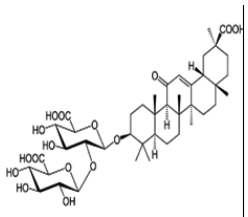
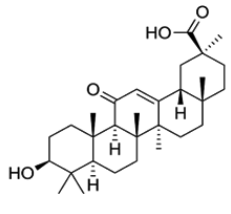
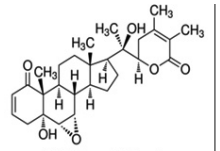
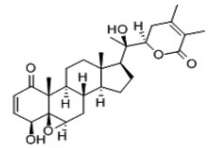
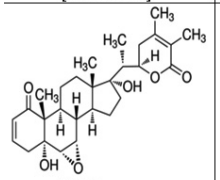
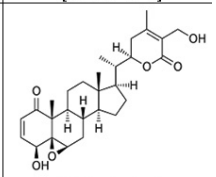
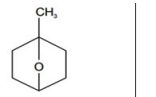
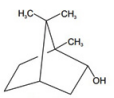
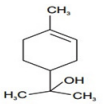
4	Lemon	 **L-Ascorbic acid (Vitamin C) [50-81-7]**	L-Ascorbic acid (Vitamin C) binds to SARS-CoV-2 receptors, mitigating the immune system's pro-inflammatory response. It boosts WBC count, immune response, and antioxidant defenses. Citrus fruits, rich in Vitamin C and secondary metabolites (phenolic acid, flavonoids, etc.), exhibit antiviral properties. D-limonene, a citrus compound, may inhibit SARS-CoV-2 replication by targeting the spike protein and viral polymerase. Vitamin C and citrus compounds also show antiviral activity against various viruses, including influenza, enterovirus, and coronavirus.	78
5	Betel Vin (*Pan*)	 **Chavibetol [501-19-9]** **Chavicol [8015-73-4]**	*Piper betle (P. betle)* extract exhibits immunosuppressive effects, decreasing antibody titres and suppressing inflammation, suggesting potential therapeutic applications for autoimmune and immune disorders. These can be attributed to Chavibetol andChavicol.	79
6	Adulsa (*Malabar nut*)	 **Vasicine [6159-55-3]**	This Ayurvedic plant is traditionally used to treat respiratory issues like cold, cough, asthma, and tuberculosis. It exhibits antiviral activity against influenza type-B virus, with its methanolic and aquesous extracts both containing, Vasicine responsible for inhibiting viral attachment disrupting the viral protein envelope.	80
7	Amla (*Indian gooseberry*)	 **Elagic acid [476-66-4]**	Bhui amla containing elagic acid exhibits antiviral activity against various viruses, including hepatitis B virus (inhibiting DNA polymerase and binding to surface antigen), HIV, dengue virus (aqueous and methanolic extracts), and Herpes Simplex Virus types 1 and 2 (acting at early stages of infection and replication).	81

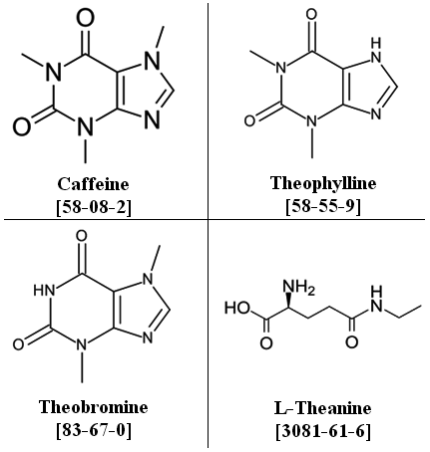
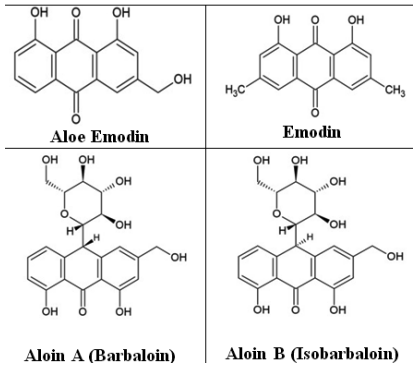
8	Cinchona (*Red Bark*)	 **Quinine** **[130-95-0]**	Hydroxychloroquine, a quinine derivative, was explored as a COVID-19 therapy. Cinchona bark is a natural source of quinine, which was historically used to create anti-viral chloroquine analogs, being studied against SARS-CoV-2. This article revisits the potential of CB as a monotherapy against COVID-19.	82
9	Neem	 **Nimbin** **[5945-86-8]** **Nimbidin** **[1407-80-3]**  **Azadiractine** **[11141-17-6]**	Neem has been traditionally used to treat viral infections, including smallpox, chickenpox, and warts. Studies have shown its efficacy against various viruses, including hepatitis B, herpes, HIV, and dengue. Neem extracts may exhibit antiviral effects by inhibiting replication, blocking entry into host cells, and enhancing immune responses, primarily through compounds like nimbin, nimbidin, and azadirachtin.	83
10	Black pepper (*Sweet Pepper*)	 **Piperine** **[94-62-2]**  **Eugenol** **[97-53-0]**	Piperine, a compound in black pepper, has antiviral properties that can inhibit viral replication, making it a potential treatment for COVID-19. Similarly, Eugenol, found in essential oils, has shown potency against Ebola virus in vitro and exhibits antiviral, anti-inflammatory, and immunomodulatory effects against various viruses and conditions, including coxsackie virus type B3 and cancer.	84
11	Garlic	 **Allicin** **[539-86-6]**	Allicin, garlic's main active component, interacts with cellular -SH groups, modulating macrophage activity and inhibiting pro-inflammatory cytokines. Garlic has been used for thousands of years as a food, spice, and traditional medicine to combat various ailments, including viral diseases.	85

12	Black Cumin		Nigella sativa has shown antiviral activity against cytomegalovirus, attributed to its constituents thymoquinone and nigellidine. Treatment with N. sativa oil demonstrated a significant antiviral effect against MCMV infection, linked to increased CD4 cell response.	86
13	Cinnamon		Cinnamon's essential oil containing cinnamaldehyde, cinnamic acid, cinnamyl acetate and eugenol has shown antiviral activity against SARS-CoV-2. These ingredients, may target proteins involved in viral proliferation. Molecular docking analysis predicts that C. Zeylanicum essential oil components interact with SARS-CoV-2 protein targets, potentially inhibiting the coronavirus through synergistic effects.	87
14	Sunthi		*Zingiber officinale* (ginger) extracts show potential in treating CHIKV. Dry ginger may also be an effective, affordable treatment for preventing COVID-19 infection and managing symptoms. Additionally, ginger has a high binding affinity to the main protease of SARS-CoV-2, essential for viral replication The activities are attributed to zingiberene.	88
15	Tulsi		Tulsi exhibits antibacterial, antiviral, and antifungal properties, effective against various pathogens causing human infections. These activities are attributed to its active constituents, including Eugenol, Methyleugenol, and Carvecol.	89

16	Nutmeg (*Jayphal*)		Its strong anti-inflammatory and antioxidant effects, due to compounds like Myristicin, Elemicin, and Eugenol, may help boost immune health.	90
17	Ginseng		Ginsenosides, particularly Rg2, exhibit 91 antiviral activity by inhibiting oxidative stress and stimulating nitric oxide production. Specific ginsenosides have shown efficacy against: • Human Rhino virus (Rg1) • Influenza virus (Rb1) • HIV-1 (Rb1, Rh1) • Hepatitis virus (Rb1, Rg1) • Hepatitis C virus (Rg3) • Herpes Simplex virus (Rg3 isomers) • SARS-CoV-2 (Rg3) Ginseng's antiviral properties make it a potential treatment for various viral infections, including Monkeypox.	

18	Indian Echinacea (*Kalmegh*)	 **Andrographolide [5508-58-7]** **14-deoxy-11,12-didehydroandrographolide [42895-58-9]**  **Andrograpanin [82209-74-3]** **Neoandrographolide [27215-14-1]**	Active constituents of Kalmegh, particularly Andrographolide, exhibit antiviral activity against: • Influenza A Virus (IAV), inhibiting gene replication and protein maturation • Herpes Simplex Virus (HSV), blocking entry into host cells • HIV, suppressing CCR5 and CXCR4 co-receptors • SARS-CoV-2, interacting with viral proteins • Dengue Virus, inducing heme oxygenase-1 (HO-1) to counteract oxidative stress • Chickengunia virus, Zika virus, and Epstein Barr Virus, inhibiting replication and transcription.	92
19	Mexican Poppy	 **Protopine [130-86-9]**  **6 – Acetonyl dihydro chelerythrine [22864-92-2]**	*A. mexicana's* aqueous leaf extract inhibited HIV-1 reverse transcriptase activity. The benzo[c] phenanthridine alkaloid, (±)-6-acetonyl dihydrochelerythrine, demonstrated potent anti-HIV activity. Molecular docking studies showed that four protopine alkaloids (protopine, allocryptopine, argemexicaine A, argemexicaine B) and one benzophenanthridine alkaloid (6-acetonyl dihydrochelerythrine) inhibited SARS-CoV-2 RNA polymerase (RdRp), preventing viral contamination in Vero E6 cells, and potentially acting as SARS-CoV-1 and SARS-CoV-2 inhibitors.	93
20	Ginkgo biloba	 **Bilobalide [33570-04-6]**  **Quercetin [849061-97-8]**  **Ginkgolic acid [22910-60-7]**  **Bilobol [22910-86-7]**	Ginkgo biloba's Ginkgolide A irreversibly inhibited SARS-CoV-2 papain-like protease (PLpro). Quercetin from the extract inhibited SARS-CoV-2 3CLpro and PLpro, preventing replication. Ginkgolic acid (GA) inhibited: • HSV-1 viral protein synthesis and genome replication • HCMV genome replication • ZIKV, IAV, EBV, HIV, and EBOV infections Ginkgo biloba extract also showed antiviral activity against HHV-1, HHV-2, VZV, HSV-1, and HSV-2, attributed to flavonoids, especially isorhamnetin.	94

21	Liquorice	 **Glycyrrhizin [1405-86-3]**  **Glycyrrhetinic acid [471-53-4]**	Liquorice's triterpenoids, particularly glycyrrhizin, exhibit antiviral activity through: • Inhibiting virus replication and inflammation • Blocking ACE2 and spike proteins • Inhibiting M-pro, S-protein, and 3C-like protease Glycyrrhizin effectively inhibits: • SARS-CoV-2 adsorption, penetration, and replication • HIV replication and entry into cells • Hepatitis B virus surface antigen secretion Computer-aided design and biological verification confirm glycyrrhizin as a non-toxic, broad-spectrum anti-coronavirus molecule.	95
22	Ashwagandha	 **Withanolide A [2911-62-9]**  **Withanolide D [30655-48-2]**  **Withanone [27570-38-3]**  **Withaferin A [5119-48-2]**	Withanone and Withaferin-A block SARS-CoV-2 entry into host cells by interacting with TMPRSS2 and viral proteins (Mpro). Withanolides and Withaferin-A inhibit SARS-CoV-2 replication and transmission by disrupting spike glycosylation. Withaferin A: • Alters Herpes Simplex Virus DNA polymerase • Suppresses Hepatitis C virus (HCV) replication by enhancing Th1 cytokines, CD4/CD8 counts, and NK cell activity • Inhibits TNF-± activity and PKC substrate peptide phosphorylation in HCV-infected lymphocytes Withanolide suppresses HIV-1 transcription and replication.	96
23	Cardamom	 **Cineole [470-82-6]**  **Borneol [507-70-0]**  **α-Terpineol [10482-56-1]**	Treatment with the terpenes, particularly, 1,8-Cineol reduced influenza virus-induced inflammation in mice by: • Decreasing NF-kB p65, ICAM-1, and VCAM-1 expression in lung tissues • Lowering inflammatory cytokines (IL-4, IL-5, IL-10, IL-1², IL-6, TNF-±, and IFN-³) in nasal lavage fluids and lung tissues 1,8-Cineol also potentiated the antiviral transcription factor IRF3 in human cell lines and nasal mucosa. In-silico analysis confirmed the antioxidant and	97

			anti-inflammatory potential of *Elettaria cardamomum* essential oils.	
24	Tea		Tea's functional components, including catechins, theaflavins, theanine, and caffeine, exhibit antiviral effects against influenza, rotavirus, hepatitis, HPV, HSV, and HIV. These compounds: • Inhibit viral replication and disrupt viral envelope integrity • Modulate immune responses • Block viral attachment and entry (catechins) • Enhance immune function (theanine) • Modulate inflammation (caffeine) Resveratrol: • Reverses RNA replication of Rotavirus • Disrupts adenovirus replication • Inhibits HIV reverse transcriptase • Induces NTCP endocytosis, reducing viral DNA replication • Prevents coronavirus attachment to host cells • May inhibit coronavirus RNA synthesis or 3CLpro activity Theaflavins and theanine also enhance immune response by changing viral capsid protein conformation and boosting natural killer cell and macrophage activity. Flavonoids inhibit viral enzymes and interfere with viral RNA synthesis.	98
25	Aloe Vera		Aloe vera compounds, emodin, Aloin A & Aloin B, show potential as antiviral agent against HSV-2. Previous studies have demonstrated Aloe vera's antiviral activity against: • Herpes simplex virus type 1 (HSV-1): Aloe vera extract gel (0.2-5%) inhibited HSV-1 growth on Vero cells. • H1N1 subtype influenza virus: Aloe polysaccharides decreased viral replication and adsorption by interacting with virus particles.	99

Cinchona (Red Bark)

Cinchona officinalis (*Rubiaceae*) or Red bark, is native to countries including India, Bolivia, Colombia, Peru, Tanzania, Indonesia, and Sri Lanka., Thearpeutically active constituents are Quinine, Quinidine, Cinchonidine, Cinchonine. It also contains Flavonoids, phytosterols, quinoline, essentials oils, minerals, triterpine (quinovic acid), quinic acids) and caffeic acid.

Therapeutic uses

It acts by virtue of its alkaloids inhibiting glycolysis as well as nucleic acid and protein synthesis in the *Plasmodium falciparum*, and it binds with hemazoin in parasitized erythrocytes. Cinchona is used to enhance appetite, stimulate the release of digestive juices, and alleviate digestive discomfort. It also acts as immunity booster, anti-obesity, anti-cancer, anti-oxidant, anti-microbial, anti-inflammatory, anti-pyretic and anti-cancer activity. The cinchona, particularly its active compound quinine possesses antiviral and antimalarial properties. Quinine may inhibit viral replication by interfering with the virus's ability to enter and infect host cells. [37,38]

Neem

Azadirachtaindica (*Meliaceae*) or Neem is native to the Indian subcontinent and widely found across Africa. Neem oil, extracted from its seeds and fruits, contains nimbin, a triterpenoid known for its anti-inflammatory, antipyretic, fungicidal, antihistaminic, and antiseptic effects.

Therapeutic uses: Neem bark contains gallic acid, (–) epicatechin, catechin, and various polysaccharides (GIa, GIb, GIIa, GIIIa, NB-II peptidoglycan). The fruit contains phytosterols, seed oil contains nimbidin, sodium nimbidate, nimbin, nimbolide, gedunin, azadirachtin, and mahmoodin. It possesses immune-stimulant, antiviral, hypoglycemic, and antifungal activities. The neem has antiviral, anti-inflammatory, and immune-modulatory properties. Some research suggests that neem extracts may exhibit activity against viruses, including HIV and potentially SARS-CoV-2 and M-Pox virus. Neem may exert antiviral effects by inhibiting viral replication, blocking viral entry into host cells, and enhancing immune responses, particularly through its active compounds like azadirachtin and nimbolide.[39]

Black pepper (Sweet Pepper)

Piper nigrum L.(*Piperaceae*) or black pepper is native to Kerala, India, and widely cultivated in tropical regions. Its fruit contain piperine (majorly), ascorbic acid, beta-carotene, camphene, carvacrol, eugenol, methyleugenol, gammaterpinene, lauric acid, linalyl acetate, myrcene, myristic acid, myristicin, palmitic acid, piperine, terpinen-4-ol, and ubiquinone.

Therapeutic Uses

It exhibits cytotoxic effects against various cancers and inhibits coxsackie virus type B3. It also acts as an anti-inflammatory agent by modulating macrophages and suppressing inflammatory mediators like NO and cytokines. It has immunomodulatory, anti-allergic, antitussive, bronchodilator, and antidiarrheal activities. The MOA of black pepper in the treatment of COVID-19 is primarily attributed to its active compound piperine. Piperine has antiviral properties that can inhibit the replication of the virus. Additionally, its anti-inflammatory and antioxidant effects help modulate the immune response and reduce the severity of inflammation and oxidative stress associated with viral diseases.[40-41]

Garlic

Allium sativum Linn.(*Liliaceae*) or garlic is cultivated extensively in Central Asia, Southern Europe, USA, and throughout India. Both the bulb and leaves of garlic possess therapeutic properties. The bulb contains allicin, alliin, diallylsulfide, diallyldisulfide, diallyltrisulfide, ajoene, and S-allyl-cysteine. The leaves contain ajoene, allicin, alliin, diallylsulfide, diallyldisulfide, Sodium 2-propenyl thiosulphinate, and S-methyl1-cysteine sulfoxide.

Therapeutic uses

Allicin can permeate cell membranes and modulate macrophage activities, inhibiting the secretion of pro-inflammatory cytokines like TNF-á. It has anti-inflammatory and immunomodulatory properties. Its constituents contribute to various activities like antiviral, antioxidant, natural blood thinner and natural immunity booster.[42] These properties promote the use of garlic as preventive therapy against Corona virus and M-Pox virus.[43]

Black Cumin

Nigella sativa (*Ranunculaceae*) or black caraway is native to southwestern Asia, parts of the Mediterranean, and Africa. The seeds contain therapeutically active constituents-thymoquinone and nigellidine. Seed oil contains

nigellidine, thymoquinone, thymol, 4-terpineol, thymohydroquinone, t-anethole, linoleic acid, oleic acid, p-Cymene, á-pinene, á-thujene, and ã-terpinene.

Therapeutic uses

Thymoquinone-rich oil inhibits cytokine signaling molecules and PGE2 in T-lymphocytes, suggesting anti-inflammatory effects. Molecular docking studies indicate that bioactive compounds in Nigella sativa may inhibit COVID-19, highlighting its potential therapeutic value in combating viral infections and modulating immune responses. It possess activities like antiviral, immune system strengthening, antihistamine activity, cough and cold.[44]

Cinnamon

Cinnamomumverum (*Lauraceae*) or Ceylon cinnamon or dalchini is primarily found in Sri Lanka, the Malabar Coasts of India, South America, and the West Indies. The therapeutic properties reside in its bark, which contains essential oils and compounds with antimicrobial effects.

Therapeutic Uses

Cinnamon bark's volatile oil contains 60-70% cinnamaldehyde, 5-10% cinnamyl acetate, eugenol, benzaldehyde, cuminic aldehyde, phellandrene, pinene, and cymene. These constituents exhibit various activities such as anticancer, antimicrobial and in respiratory treatment. Its constituents act by damaging cell membranes, altering lipid profiles, inhibiting ATPase, and disrupting cell division. Additionally, they can affect bacterial membrane porins, motility, biofilm formation, as well as exhibit anti-quorum sensing effects, contributing to its medicinal applications in treating various infections and promoting health. Active compounds, such as cinnamaldehyde exhibit antiviral properties by interfering with viral replication and entry into host cells. Additionally, cinnamon has anti-inflammatory and antioxidant effects, which help reduce inflammation and oxidative stress.[45-47]

Sunthi (Dry Ginger)

Zingiber officinale (*Zingiberaceae*), known as ginger or sunthi in India, is widely cultivated in countries like Jamaica, India, Haiti, Hawaii, and Nigeria. Its rhizome contains bioactive compounds such as zingiberene. It exhibits antioxidant effects, protection against DNA damage and oxidative stress. Like NSAIDs, it acts by interfering with prostaglandin biosynthesis, leading to anti-inflammatory effects. It also inhibits the main protease (R7Y) essential for the replication and reproduction of SARS-CoV-2, indicating its possible role in combating COVID-19.

Therapeutic Uses

Dry ginger possesses, shogaol, zingiberol, and gingerol and also exhibit anti-ulcer, anticholinergic, rheumatologic, anticancer, antioxidant, antimicrobial activities.[48-51]

Tulsi

Ocimum sanctum (Labiatae) or Tulsi or Holy Basil, is native to the Indian subcontinent, thriving throughout Southeast Asia. It is valued for its therapeutic properties found in its leaves, seeds, and roots, containing eugenol, methyleugenol, and carvacrol. It scavenges free radicals, reducing oxidative damage and inflammation. It binds with viral and host proteins like SARSCoV-2 main proteases, spike proteins, human ACE_2 and furin proteins, combating viral infections.

Therapeutic Uses

Tulsi's volatile oil contains 70% eugenol, 20% methyl-eugenol, beta-caryophyllene, carvacrol, cineole, and linalool helping to promote healthy heart, relieves fever, cures respiratory disorders, prevents aging and also acts as immunity booster in COVID-19.[52-54] Immunomodulatory effect of alcoholic extract of Tulsi leaves was studied on healthy volunteers by Mondal and co-workers.[55]

Nutmeg (Jayphal)

Myristica fragrans (*Myristicaceae*) or Nutmeg or Jayphal, is native to the Moluccas (Spice Islands) of Indonesia. It is cultivated in Indonesia, the West Indies, Sri Lanka, and other tropical regions. The kernels of seeds contain therapeutically active constituents like 5–16% volatile oil (myristicin, elemicin, eugenol, safrole) and 30% fat (myristic acid, palmitic acid, oleic acid, and lauric acid)

Therapeutic Uses

It exhibits anti-inflammatory and antioxidant effects, potentially boosting immune health. Myristicin, is known for its weak inhibition of monoamine oxidase (MAO), which plays a role in metabolizing neurotransmitters in the liver. It

regulates blood pressure, stimulate digestion, act as an anti-inflammatory, immunity booster and used in treatment of insomnia.[56]

Ginseng (Man-Root)

*Panax ginseng(*Araliaceae), Chinese ginseng or ginseng root, is primarily found in North America and eastern Asia, including Korea, northern China (Manchuria), and eastern Siberia.The therapeutic properties of ginseng are concentrated in its rhizome and root, which contain active constituents such as Ginsenoside (Rb1,Rg1), paraxosides (major glycosides) and dammarol (aglycone from ginsenosides) that inhibit ROS production, stimulate nitric oxide production, enhance immune function, improve CNS function, and potentially prevent cardiovascular diseases.[57]

Therapeutic Uses

Ginseng may boost immune function by increasing the production of immune cells and cytokines, while also directly inhibiting viral replication and entry into host cells. Many *in vitro* and clinical analysis confirmed that ginseng restricted depletion of CD4 T cells caused due to HIV infection, thus prolonged the survival rate of hosts.[58] Studies by Cho and co-workers demonstrated that Ginseng may augment the elimination of cell replicating *pol* gene and protein *nef* gene of HIV.[59] Pei and co-workers reported that Ginseng spared glioma stem cells by reducing plaque formation and replication of herpes simplex virus (HSV).[60] Efficacy of ginseng is also anticipated for the treatment of monkey pox.[61]

Indian Echinacea (Kalmegh)

Andrographis paniculata Nees (Acanthaceae), Bitterweed, King of Bitters, Creat, Green Chireta is a plant native to South Asian countries spread throughout south India and Sri Lanka. It is commonly used in the traditional Indian medicine system, Ayurveda. *Andrographis* leaf and stem stimulate the immune system and prevent flu viruses from binding to cells in the body. Major constituents of *A. paniculata* are diterpenoids, flavonoids and polyphenols. Among the single compounds extracted from *A. paniculata*, andrographolide is the major compound in terms of bioactive properties and abundance. Other studies have also reported that *A. paniculata* extract increases the lymphocyte cell proliferation at low concentrations, for examples, *A. paniculata* dichloromethane extract significantly augments the proliferation of human peripheral blood lymphocytes (hPBL) at low concentrations.[62] Sa-Ngiamsuntorn and co-workers demonstrated anti-SARS-CoV-2 activity of andrographolide using high-content imaging platform and the plaque assay using Calu-3, human lung epithelial cells.[63]

A. paniculata extracts possess broad spectrum antiviral properties like anti-HIV, anti-dengue virus and chikungunya virus activity. They are also effective against herpes simplex virus type 1 (HSV-1) and were found to reduce the inflammation caused by influenza viruses. They inhibit the division of influenza viruses, hepatitis C virus, and anti-viral mutations that cause resistance to antiretroviral drugs.[64]

Therapeutic Uses

A. paniculata, also called 'king of bitters' is considered as 'natural antibiotic' due to wide range of pharmacological effects, including antiviral, anti-inflammatory, antioxidant, anti-diabetic, anti-infective, and hepatorenal protective activity.[65]

Mexicane Poppy [Kateli ka phool]

Argemone mexicana (Papaveraceae), Mexican Prickly Poppy, is native to southeastern USA (Florida), Mexico, Central America, the Caribbean, and tropical South America. The entire plant possesses therapeutic properties.It is used for treating thrombosis as an antiplatelet agent due to protopine, which acts by inhibiting the release of arachidonic acid and platelet-activating factor from platelet membrane phospholipids. It also inhibits the conversion of prostaglandin G2 to thromboxane A2 and serves as a thromboxane synthetase inhibitor. Other active phytochemical constituents include catechins, flavanols, leucoanthocyanins, phenolic acids, caffeine, theophylline, theobromine, theanine, theaflavins, and polyphenols.[66]

Therapeutic Uses

It shows Antioxidant, Anticancer activities also used in Respiratory Diseases, skin disorders and immunity booster in viral diseases.[67]

Ginkgo Biloba

Ginkgo biloba (Ginkgoaceae), Ginkgo is native to China and Japan and cultivated in various temperate regions. The leaves and seeds possess active constituents like Bilobalide, Ginkgotoxin, Ginkgolic acid, and Bilobol. It also has diterpenes; the ginkgolides A, B, C, J and M; flavonoids and

bioflavonoids, especially, kaempferol, quercetin and amentoflavone. It has antioxidant properties, modulate neurotransmitters and receptors, and exhibit antiplatelet activating factor actions. However, caution is advised when using ginkgo in patients taking anticoagulants due to potential interactions.[68]

Therapeutic uses

It is useful for respiratory disorders like asthma, bronchial spasm. The leaf extract improves blood circulation both peripheral and cerebral to improve memory, hearing and concentration in elderly persons. It is useful to treat anxiety, headaches, vertigo and apathy. The Ginkgo biloba's active compounds, such as flavonoids and terpenoids, help to reduce oxidative stress and modulate the immune response, potentially alleviating inflammation and improving respiratory function in COVID-19 patients.[69]

Liquorice (Black Sugar)

Glycyrrhiza glabra (Leguminosae), Black Sugar or Common Licorice is found in sub-Himalayan tracts, Baluchistan, China, Europe, India, Iraq, Japan, Kurdistan, Spain, Turkey, and United States. Rhizomes and roots possess therapeutically active constituents like Glycyrrhizic acid and Glabridin. Glabridin inhibits melanogenesis by reducing ROS production and suppressing tyrosinase activity, which controls melanin production. Glycyrrhizic acid exhibits anti-inflammatory effects by inhibiting ROS (Reactive Oxygen Species) generation from neutrophils, crucial. Liquorice root's scent is mainly from anethole, and its sweetness from glycyrrhizin, which is 30-50 times sweeter than sugar.

Therapeutic Uses

It may exhibit antiviral effects by inhibiting viral replication and modulating immune responses. Glycyrrhizin has been shown to interfere with the replication of various viruses, including SARS-CoV-2, the virus responsible for COVID-19. Glycyrrhizin can inhibit the replication of viruses by blocking viral entry into host cells and interfering with viral RNA synthesis, thereby enhancing the host's immune response.[70]

Ashwagandha (Ajagandha)

Withania somnifera (Solanaceae), Ashwagandha is native to India, Middle East, and parts of Africa. Root, fruit, flowers, and leaves possess active constituents like Withanolide A, D, Withanone and Withaferin A. Withaferin A inhibits motility and invasion capacity of cancer cells by inducing Par-4 and inhibiting MMP-2. Withanone and Withaferin A potentially block the entry of SARS-CoV-2 by interacting with transmembrane protease serine 2.

Therapeutic Uses

It is explored for its potential in treating viral diseases such as COVID-19 and AIDS due to its antiviral, immunomodulatory, and adaptogenic properties. The mechanism of action of Ashwagandha includes enhancing the immune response by promoting the activation of natural killer (NK) cells and macrophages, inhibiting viral replication, and reducing inflammation and oxidative stress through its bioactive compounds, such as withanolides.[71]

Cardamom (Elaichi)

Elettaria cardamomum (Zingiberaceae), cardamom is cultivated in Ceylon, Sri Lanka, Myanmar, Malaysia, and India (Mysore and Kerala). Seeds and fruit have active constituents like Cineole, Borneol, and á-Terpineol. Seeds are also rich in oils, salts, nitrogen, starch, fiber, color, and ash

Therapeutic Uses

However, it has shown some potential due to its antiviral, antioxidant, and anti-inflammatory properties. The mechanism of action of cardamom's bioactive compounds, such as terpenes and flavonoids, includes inhibiting viral replication and reducing inflammation through immune modulation. Its use in these viral infections is largely complementary and supportive for symptom management rather than as a primary treatment.[72]

Green Tea (Tea Plant, Tea Shrub and Tea Tree)

Camellia sinensis L (Theaceae), tea plant or tea shrub is originated in China and is widely cultivated across East Asia, Japan and Korea. Leaves contain active constituents like Caffeine, Theophylline, Theobromine, and L-Theanine. These compounds, particularly catechins, modulate apoptosis by influencing the expression of genes involved in cell death regulation. They also exhibit anti-inflammatory effects by modulating different isoforms of nitric oxide synthase. Major cathechins

in green tea leaves are catechin, epicatechin, epicatechin 3-gallate, epigallocatechin, and epigallocatechingallate.

Therapeutic Uses

The green tea has been studied for its potential in treating viral diseases like AIDS and COVID-19. The active compound epigallocatechin-3-gallate (EGCG) in green tea exhibits antiviral effects by inhibiting viral entry, replication, and viral protein function. Additionally, EGCG's antioxidant and anti-inflammatory properties help modulate the immune response, making it beneficial in managing viral infections.[73]

Aloe vera

Aloe vera (*Aloe barbadensis miller*) is a widely cultivated succulent plant native to the Arabian Peninsula, is now grown in tropical and subtropical regions around the world, including India, China, and Mexico. The phytoconstituents responsible for its antiviral activity include polysaccharides, anthraquinones, and glycoproteins. Among these, acemannan, a polysaccharide, is recognized for its significant antiviral effects. Acemannan demonstrates antiviral properties by enhancing immune function, promoting macrophage activity, and inhibiting viral replication. It interferes with the viral adsorption process and helps in reducing inflammation, which aids in modulating the immune response during viral infections. Aloe vera gel has been found to exhibit antiviral effects against several viruses, including herpes simplex virus (HSV), human immunodeficiency virus (HIV), and influenza virus.

Therapeutic Uses

Aloe vera is widely used for its antiviral, anti-inflammatory, antioxidant, and wound-healing properties. It is used in the treatment of skin infections, herpes simplex, and as a topical application for burns and cuts. Additionally, it alleviates gastrointestinal issues, promotes wound healing, and has been studied for its potential in managing viral diseases such as HIV, HSV, and influenza.[74]

CONCLUSION AND FUTURE PROSPECTS

Viral infections continue to be a significant cause of morbidity and mortality globally, spreading rampantly at an alarming rate. Currently available antiviral therapies are often ineffective due to constant viral mutations, emergence of aggressive strains, drug resistance, and potential side effects. Numerous epidemiological and experimental studies have demonstrated that many medicinal plants and their phytochemicals have been utilized consistently to treat various infections owing to low toxicity and reduced side effects. This review examines 25 herbal medicinal plants, traditional medicines, spices, and herbs recognized for their immune-boosting capabilities and possible therapeutic effects against various viral infections. Herbal remedies have been found to enhance therapeutic effectiveness against a range of viral diseases due to high concentration of immunomodulatory phytochemicals, which can be both immunoinhibitory and anti-inflammatory. They have the potential to obstruct and control viral uptake, bind to surface receptors, and compete with pathways that activate intracellular signaling. Several in silico and in vitro studies have indicated the potential of phytochemicals in treating viral infections. Further exploration into the mechanisms by which these compounds exert their antiviral effects will facilitate the development of effective, target-specific drug delivery systems. Pharmaceutical nanotechnology and targeting strategies can utilized for delivery of phytomedicines thereby bypassing cellular defenses, directing drugs to specific intracellular locations, and releasing them in response to particular molecular signals thereby improving their efficacy against viral infections. Repurposing of already reported phytochemical as an inhibitor for viral diseases or conjunction of traditional medicinal systems with biotechnology can lead to the development of innovative antiviral drugs and therapies. Future collaborations may be beneficial by combining newly identified antiviral phytoactive compounds with existing FDA approved drugs for improved and lasting effectiveness. Furthermore, countries should promote dedicated research into various biodiversity-rich areas and collaborate with ethnomedicine practitioners, pharmacists, chemists, microbiologists, clinicians, and specialists to identify additional phytoactive compounds with antiviral properties to address the global challenges posed by ever evolving viral diseases. Altogether, the evidence presented in this work supports the notion that "Nature provides treatments for every

malady in its flora and fauna, awaiting effective human discovery and utilization" underlines the holistic approach of integrating herbal medicines as preventive and adjunct therapy to support treatment against the deadly viral diseases.

While this review highlights the promising potential of phytoconstituents in combating viral infections, it is crucial to acknowledge certain limitations. Most studies referenced rely on *in silico, in vitro*, or animal models, which may not directly translate to their efficacy in humans, without extensive clinical trials. Furthermore, potential interactions of these herbal remedies with existing medications and their safety profiles in specific populations (e.g., pregnant women, elderly patients) require thorough investigation. Overuse or improper usage of certain herbal formulations may lead to adverse effects. Therefore, these remedies should be used under professional guidance and integrated cautiously with standard treatments to ensure safety and efficacy.

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Each author has contributed significantly to the preparation of this review article and has given approval for its publication; Shamal Daulat Dawange: Data Collection and Writing – Original Draft; Ashish Nandkumar Phuge, & Nilesh Yadav Jadhav: Data Collection, Analysis, Writing & Editing; Neha Manish Munot: Writing, Reviewing & Editing; Kishor Sanchalal Jain: Conceptualization, Correction, Supervision, Expert checking and final approval of the manuscript.

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