

REVIEW ARTICLE

Herbal Immunomodulators: An Adjuvant Symptomatic Therapy for Covid-19

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ABSTRACT

Millions of people have lost their lives due to the new coronavirus, also known as severe acute respiratory syndrome coronavirus 2 (SARSCoV2). Droplets and close human contact are the primary modes of transmission for this newly discovered virus. Its effects change from one country to the next based on factors including latitude, humidity, typical diet, and cultural practises. Multiple preventative strategies, as well as several medications, are used in various combinations to control the spread of disease. Those affected in the earliest stages of the disease will feel some respite as a result. Natural herbs have been proposed as a substitute treatment option; they have little if any negative side effects and are known to boost the immune system as a whole. This article discusses the immunomodulatory properties of some key herbs and offers advice for strengthening one's defences.

Keywords: Herbal Medicine, Immunity, SARS, and COVID-19

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INTRODUCTION

COVID-19, commonly known as Severe Acute Respiratory Syndrome (SARS), is a virus that causes severe respiratory illness. The SARS-CoV-2 virus has inflicted approximately 190 million confirmed illnesses and over 4 million deaths worldwide, as of July 2021. This disease spreads quickly through close direct contact with infected people, mostly by respiratory droplets from sneezing or coughing, as well as through touch and aerosol transfer. COVID-19 exhibits a variety of symptoms that range from mild to severe. Fever is by far the most frequent symptom reported by patients followed by cough and myalgia or tiredness, etc.[1] Additionally, there have been some fatalities due to increasing respiratory failure.

Viruses kill cells via two mechanisms: through cytopathogenic effects and through immunological reaction mediated death.[2] COVID-19 is unable to directly lyse cells since immune-mediated cell death is the most common mode of cell death.[1]

The virus merges with the host cell's membrane, crosses the airway epithelial layer, and multiplies within host cell.[1] Adults with strong innate cellular and humoral immunity can restrict virus replication and reduce viral load in the alveoli, allowing for a quick recovery with minimal symptoms in 2 to 3 weeks.[3] Humoral immunity prevents viruses from infecting new cells, whereas cell-mediated immunity targets virus-infected cells for destruction.

The virus travels to the lower respiratory tract once the immune system has been weakened, where it permeates and reaches systemic circulation.[3] Cell-mediated immunity becomes more powerful and different pro-inflammatory cytokines are released which cause inflammatory cells to flock to the area and destroy the tissue. This series of events is known as the Cytokine storm.[1]

Grave symptoms observed frequently in immunocompromised patients, elderly, as well as those with underlying medical conditions, several asymptomatic instances, all suggest that immunological response plays a vital part in COVID-19 pathogenesis. The fatality rate among these patients implies that measures that boost the immune system could avoid extreme COVID-19 infection symptoms.[4,5] Our immune system is thought to lack memory against such a virus, providing it an edge over human beings. It has

been stated that, unlike adults, children's alveoli have a weaker cell-mediated immunological reaction, rendering the majority of the cases asymptomatic.[1]

Many herbal preparations have been shown to have immunomodulatory and antiviral properties; therefore, their discovery could be a turning point in COVID-19 prevention and control. Immunity modulation and antiviral therapies are described in Ayurveda and Traditional Chinese Medicine, including remedies for the coronavirus family. Their immunomodulatory activities are based on selectively stimulating cytokines, activating lymphocytes, increasing natural killer cell counts, and enhancing macrophage actions and stimulation of phagocytosis. However, these observations must be verified through scientific or clinical trials.[6]

In this article, herbal agents with antiasthmatic, antitussive, anticoagulant, and antioxidant properties that can help with symptoms of SARS-CoV-2 infection, were also reviewed. Because COVID-19 is a respiratory infection, those with a history of asthma may experience severe symptoms such as trouble breathing, which could lead to an asthma attack, pneumonia, or other lung disorders. Coughing is the second most prevalent symptom of COVID-19, as previously noted, and an antitussive may assist to lessen frequent coughing and reduce patient pain.

The current review focuses on six herbal medicinal agents and their phytoconstituents that have potential to help patients with COVID-19 illness, avoid infection by strengthening immunity or supplementing treatment. With regard to these 6 herbal agents, the individual COVID-19 symptom-relieving effects have been discussed. In addition to this, 25 plants with potential to treat key symptoms of COVID-19 have also been compiled and presented as a table. Fig 1 mentioned hereafter demonstrates the pathophysiology of COVID-19 along with the accompanying effects of herbal agents at various infectious stages.

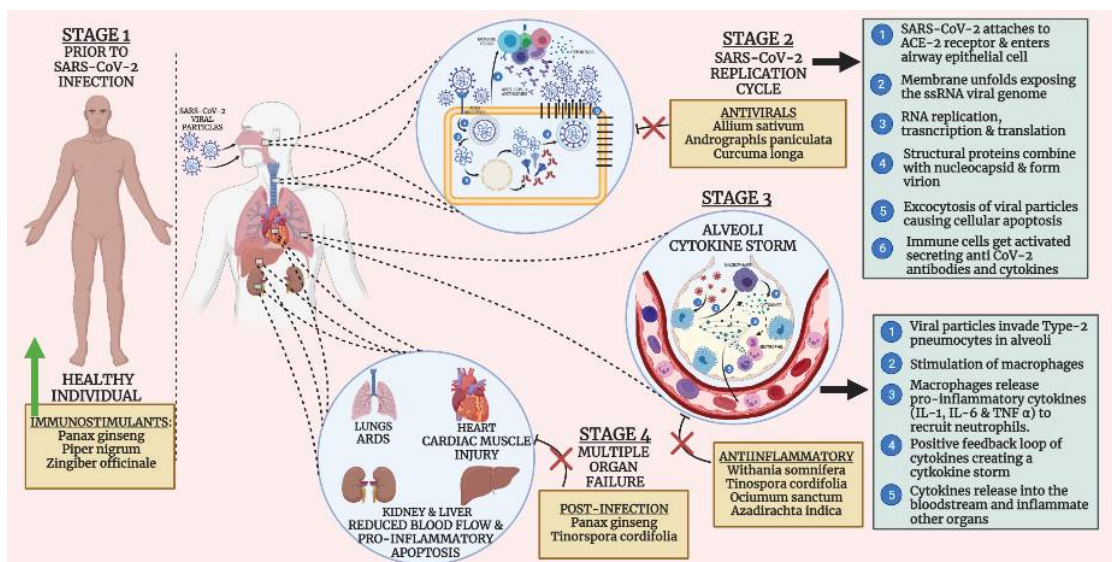


Fig 1: Pathophysiology of COVID-19 and role of herbal agents in different infectious stages

ALLOPATHIC MEDICINES FOR COVID-19:

Antivirals, chloroquine and hydroxychloroquine, and convalescent plasma transfusion are amongst the prospective therapeutic agents for COVID-19 treatment, but have variable results.

Remdesivir can be introduced into the RNA genome of viruses, causing them to deactivate prematurely. It is one of the antiviral medications used for COVID-19. Davies et al. investigated remdesivir's systematic benefit-risk assessment. Nevertheless, a randomized, double-blind clinical trial of Remdesivir was prematurely terminated owing to substantial adverse effects. Since Remdesivir could not evidently reduce patients' mortality risk (8%) in comparison with the placebo group (11.6%), the experiment was terminated by NIAID.[7]

Lopinavir or Ritonavir, are antivirals used for the treatment of HIV. In a clinical trial, lopinavir/ritonavir lowered the rate of intubation, steroid use, and mortality in SARS patients. Its treatment for COVID-19 it could reduce mortality, ARDS, incidence of respiratory failure or the necessity for invasive mechanical ventilation, according to the above study, but the certainty of this data is poor. The use of lopinavir or ritonavir was also connected to a number of adverse effects, according to these trials.[8]

Chloroquine and hydroxychloroquine are two more therapies that have been studied. In COVID-19 patients, SARSCoV-2 viral load in nasal passages and pharynx can be completely cured through a 3-6-day

regimen of hydroxychloroquine and azithromycin.[9] Furthermore, an adverse event occurred following the treatment of macrolide in conjunction with chloroquine or hydroxychloroquine, indicating that the incidence of COVID-19 infection may not be minimized.[10]

PLANT DERIVED-TREATMENT STRATEGIES AGAINST COVID-19:

A wide range of phytochemical constituents are extracted from a single herb, and these components may work alone or in combination with other components to produce desired therapeutic action.[11] Compared to current synthetic pharmaceuticals, 70-80 percent of people in developing nations rely on treatment via medicinal herbs.[12]The active compounds of medicinal plants, particularly secondary metabolites such as alkaloids, triterpenes, and glycosides, have a therapeutic effect.[13]

Owing to viral tolerance, latency, and prolonged infections in immunocompromised patients, the search for novel phytochemicals with antiviral activity has typically been subpar and ineffective.[14] The traditional Indian herbal medicines network is an ancient healthcare system, and is critical in battling and meeting worldwide healthcare requirements.[15]

In the south Asian subcontinent, some 25,000 herbal preparations and extracts have been utilized in traditional medicine.[16] Furthermore, while the total number of Indian medicinal herbs was recently approximately 3000, about 8000 different kinds of plants are used by traditional ayurvedic practitioners for therapy.[16]

The Ministry of AYUSH, with its long history, has a tradition of maintaining the health of the nation, and its involvement in the COVID-19 pandemic issue has grown exponentially.[17] Traditional ayurvedic medicine is normally recommended by all ayurvedic healthcare professionals. AYUSH-64 is a unique formula developed by Central Council for Research in Ayurvedic Sciences (CCRAS), confers protection against malaria and acts as an antipyretic.

Sunthi (*Z. officinale*), lavanga (*S. aromaticum*), and maricha (*P. nigrum*) decoctions are advised for both healthy and people infected with SARS CoV-2, since it supports B and T-lymphocyte mediated responses and reduces airway hyperresponsiveness and nasal congestion.[18,19]

Traditional ayurvedic medicines and saturated fatty acids have been linked to enhanced resistance. Suppression of cytokine release is an important development linked to influenza trials and various viral infections. These trials have been correlated with COVID-19, which has a comparable cytokine storm.[20] Furthermore, warm extracts of *T. cordifolia* (for chronic fever), *C. oblonga*, *Z. jujube*, and *C. myxa* (antioxidant, immunomodulatory, anti-influenza), have been suggested by AYUSH for the prophylaxis of COVID-19.

The most prevalent and effective herbal medicines with immunomodulatory, antiviral, and anti-inflammatory properties are included in Table 1.

SN	NAME OF THE PLANT AND DESCRIPTION	IMMUNOMODULATORY CONSTITUENTS	MECHANISM OF IMMUNOMODULATORY ACTION	APPLICATIONS IN COVID-19 TREATMENT	OTHER THERAPEUTIC USES
1	<i>Azadirachta indica</i> (Meliaceae) - NEEM (Seeds and leaves)	Glucosamine, Glycoproteins (NLGP)	Significantly increases concentration of IL-2 and enables proliferation of T-lymphocytes.[21] Rectifies CD8+ T-cell mediated tumor killing & reduces the frequency & suppressive properties of regulatory immune cells.[22]	Neem derived compounds- Nimboline A, Nimocin and cycloartanols have activity against SARS CoV-2 by binding to enveloped (E) and membrane (M) glycoproteins of the virus and act as inhibitors.[23]	Anti-Inflammatory (<i>A. indica</i> has its effect on proinflammatory cell signaling) [24]
2	<i>Asparagus racemosus</i> (Asparagaceae) -SHATAVARI (Roots)	Shatavarin (steroidal saponins), Aspargamine A (Polycyclic alkaloid), Oligospirostanoside (Immunoside)	Shatavarin stimulated immune cell proliferation and IgG secretion. It initiated IL-12 production and inhibited IL-6 production. It	Asparoside-C, D and F, were most efficacious against the SARS-CoV-2 spike RBD and NSP15 endoribonuclease established by their docking score and	Anti-inflammatory (<i>A.racemosus</i> extract suppressed topical edema in the mouse ear, leading to reductions in inflammatory cytokine production and various

			strongly modulated the Th1/Th2 cytokine profile.[25]	affinity. <i>A. racemosus</i> is a promising SARS-CoV-2 (S) and (N) protein inhibitor.[26]	histopathological indicators.) [27] Antitussive (Methanolic extract of <i>A.racemosus</i> roots showed remarkable antitussive activity on SO ₂ induced cough in mice)[27]
3	<i>Curcuma longa</i> (Zingiberaceae) - HALDI (Rhizome)	Curcuminoids, sesquiterpenes, turmeronols, curdione, polysaccharides	Curcumin reduced IL-6, and IFN- γ levels via reactivating NF- κ B within the lungs.[28] HMGB1 expression and LPS-induced acute lung damage was reduced by curcumin treatment.[29]	SARS-CoV 3CL protease activity, crucial for viral replication, is blocked by curcumin. It also combines with protein S and ACE2 and may interfere with passage of virus into lung tissues. [30]	Anti-inflammatory (Suppresses production of mature IL-1 β and reduces pulmonary inflammation by preventing inflammasome activation via pyrin domain-containing 3 (NLRP3)) [31] Anticoagulant (Inhibiting TNF- α -induced endothelial tissue factor and by directly inhibiting thrombin activity.)[32]
4	<i>Zingiber officinale</i> (Zingiberaceae) - SUNTHI (Rhizomes)	[6]-gingerol, zingerone, paradol, shogaols	<i>Z. officinale</i> restored the decreased humoral immunity in cyclophosphamide suppressed Mice.[19]. Ginger oil influences both cell-mediated immune response and nonspecific proliferation of T lymphocytes. [33]	<i>Z. officinale</i> might benefit in reducing the severity of COVID-19 by inhibiting SARS-CoV-2 in the nasal passages. It also has the ability to stimulate antiviral cytokines. At high concentration, it could stimulate mucosal cells to secrete interferon- β to counteract viral infection. [34]	Anti-asthmatic (Aqueous and alcoholic extract showed antiasthmatic effect by decreasing inflammation by suppressing Th2-mediated immune response.)[35]
5	<i>Aloe vera</i> (Liliaceae)- GHRIT KUMARI (Gel from the leaves)	Acemannan, Anthraquinone glycosides, Aloctin A	Release of IL-1, IL-6 and TNF- α and augmentation of secondary humoral immunity. Stimulates cytokine selectively, reduces keratinocyte derived immunosuppressive cytokine.[36]	Anthraquinones work with the SARS-CoV-2 protease 3CLpro to kill SARS-CoV-2. <i>Aloe vera</i> contains zinc, which when present in enhanced levels inside the cells, hinders the reproduction of retroviruses.[37] Acemannan activates the generation of CTLs specific to viral antigens and hence can be used as adjuvants in viral	Anti-inflammatory (<i>Aloe vera</i> extracts can weaken the expression of inflammatory mediators which produce ARDS (major cause of death in COVID-19 infected patients) [37] Anti-allergy (polysaccharide inhibited type 2 helper T cell (Th2) immune response, increased IL-10 production) [39]

				vaccinations.[38]	
6	Glycyrrhiza glabra (Fabaceae)- MULETHI (Roots, rhizomes and leaves)	Polysaccharides ,18β-glycyrrhetic acid, Isoliquiritigenin, glycyrrhizin and glabridin	Leukocyte and phagocytic counts were enhanced upon administration of aqueous liquorice extract (ALE). Positive significant action was observed on spleen weight and increase in foot pad thickness indicating stimulated DTH reaction. Combination of ALE with Zinc showed elevated HA titre and antibody secreting cells. [40]	Glycyrrhizic acid brings about cholesterol - dependent disorganization of membrane lipid rafts, vital for the entry of SARS CoV-2 into cells. Intracellularly, it can trap box 1 protein and blocks the alarming functions of HMGB1. In Vero cells, it reduced the reproduction of two SARS-associated coronavirus clinical isolates (FFM-1 and FFM-2) and also adsorption and penetration of the virus into cells. [41]	Anti-asthmatic (Saponin fraction of G. glabra inhibited mast cell degranulation in triple antigen sensitized rats) [42] Anti-inflammatory (Liquorice extract, 3 triterpenes and 13 flavonoids decrease TNF-α, MMPs, PGE2 and free radicals. This is also found to be useful in eliminating phlegm, relieving cough) [43]
7	Nigella sativa (Ranunculaceae)- KALONJI (Seeds)	Thymoquinone (TQ)	TQ controls cell immunological responses such as dendritic cell maturation and NK-cell cytotoxicity, phagocytic involvement, chemotaxis, as well as the activation of T-cells. [44]	N sativa's active components TQ and nigellimine inhibit the SARS CoV-2 entry into pneumocytes, supplying ionophores to increase zinc intake and therefore boost the host immune system response to SARS-CoV-2, and stopping the virus from replicating. [45]	Anti-inflammatory (TQ decreases concentration of inflammatory mediators (IL-1β, IL-6, TNFα), and prevents pulmonary inflammation.) [46] Antioxidant (TQ increases mRNA expression and stimulates antioxidant enzymes) [47]
8	Cyperus rotundus (Cyperaceae) - NAGARMOTHA (Rhizome)	Polyphenols, flavonoids, tannins.	Total oligomer flavonoid extracts of C. rotundus Modulate humoral-mediated immune response by stimulating B and T cell proliferation. [48]	Two compounds of C. rotundus β-amyrin and stigmasta-5,22-dien-3-ol, showed the best binding interactions and stability for SARS-CoV-2 virus M protein.[49]	Anti-inflammatory (Ethanol extract of C. rotundus showed maximum % inhibition of paw edema, which was similar to indomethacin) [50] Antioxidant (Due to its high content of polyphenols, flavonoids, ascorbic acid, etc.) [50]
9	Punica granatum (Punicaceae) - ANAR (Fruits)	Phenolics, ellagitannins, flavonoids, proanthocyanidins	P. granatum fruit powder stimulates the cell-mediated and humoral immune responses. It also elicited an increase in	P. granatum contains punicalagin and punicalin which showed promising potential for interactions with selected protein targets - SARS-CoV-	Isolated galloyl-hexahydroxydiphenyl-glucose showed protective effect against acute lung injury. [53] Anti-inflammatory (Inhibition of LPS-

			antibody titer to typhoid-H antigen and enhanced the inhibition of leukocyte migration. [51]	2 spike glycoprotein, ACE-2, furin and transmembrane serine protease 2. [52]	induced JNK and NF-κB stimulation and suppression of TNF-α, IL-1β, and IL-6 gene expression in lungs) [53]
10	Psoralea corylifolia (Fabaceae) - BABCHI (Seeds)	Coumarins, flavonoids, meroterpenes	Hydroalcoholic extract of P. corylifolia potentiates NK cell activity. The ADCC activity of spleen cells demonstrated a stimulating response. [54]	P. corylifolia ethanolic seed extract containing aromatic compounds - bavachinin, neobavaisoflavone, etc showed remarkable activity against the SARS-CoVPLpro. [55]	Anti-asthmatic (P. corylifolia inhibited the accumulation of eosinophils into airways and blood and modulated the Th1/Th2 cytokine balance.) [56]

In context to the above-mentioned plant species there are few other medicinal plants which are used as potent immunomodulators and have proven their efficacy in combating Covid-19 infections. The details about the plant constituents, mechanism of immunomodulatory action and their marketed formulations are described below and summarized in Fig 2.

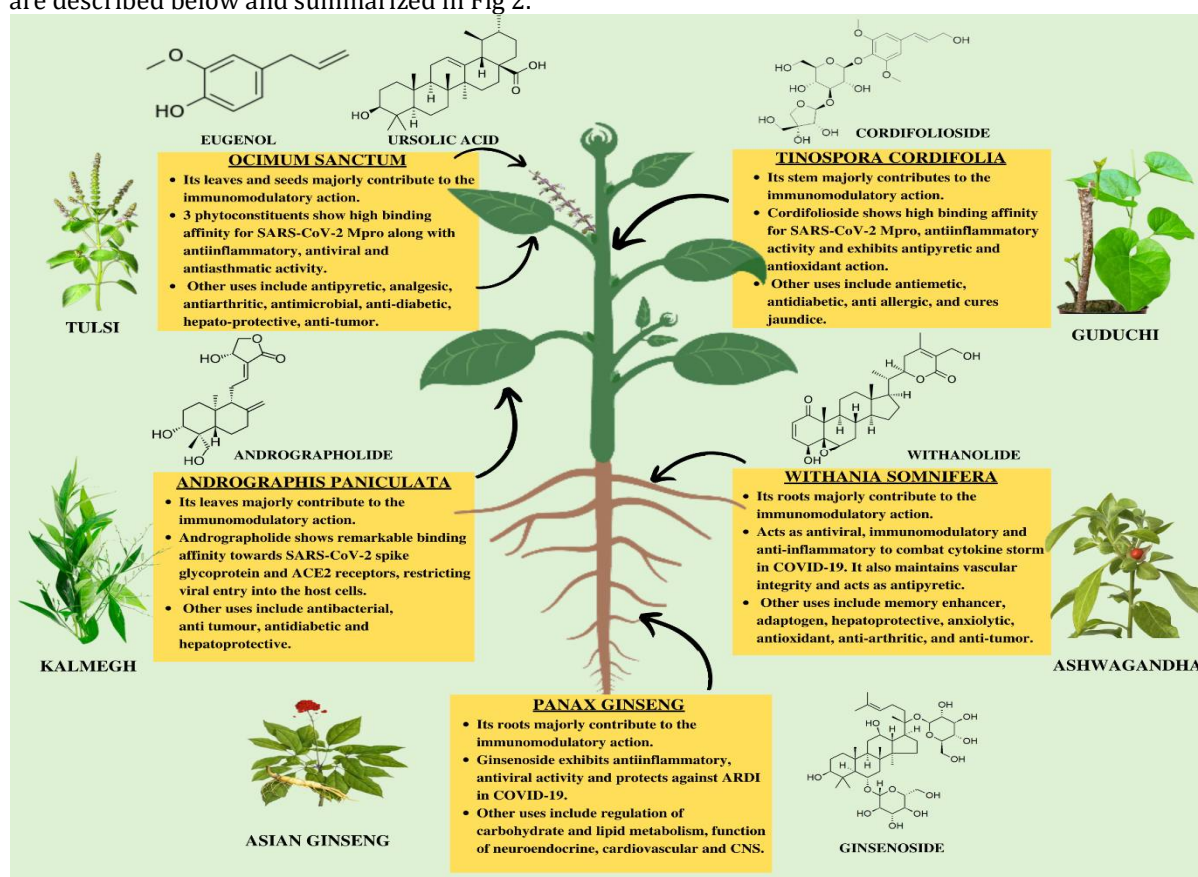


Fig 2: Summary of immunomodulatory agents with their phytochemical aspects used in prophylaxis and treatment of symptoms of COVID-19

WITHANIA SOMNIFERA:

The plant Withaniasomnifera, often known as Ashwagandha, is a member of the Solanaceae/Apocynaceae family. It has several health benefits and is a vital ‘Rasayana’ known as ‘Sattvic KaphaRasayana’ in the Indian school of Ayurveda. It is a memory enhancer, adaptogen, hepatoprotective, anxiolytic, boosts haemoglobin and RBC counts, is an antioxidant that fights free radical cellular damage, and improves the

body's cell mediated immunity. It also possesses anti-inflammatory, anti-neoplastic and anti-arthritis properties.[57]

Constituents:

Over 35 phytoconstituents are found in *W. somnifera* root extract. Ashwagandha's two primary withanolides, withaferin-A and withanolide-D, have different pharmacological actions, withaferin-A having a documented effect on human lymphocyte.[57] 5-dehydroxywithanolide-R, withasomniferin-A, and withanolide A-Y are some of Ashwagandha's other immunomodulating components.[57] The immunomodulation and CNS actions of novel glycowithanolides, sitoindoside IX and X, have been explored.[58]

Mechanism of action:

Immunological homeostasis, rather than immune activation or suppression, is known to be maintained by *W. somnifera*. In healthy mice, a hydroethanolic extract of *W. somnifera* altered B and T cell proliferation and balanced the Th1/Th2 response. It also showed a rise in CD4+ as well as CD8+ T cells, indicating a cell-mediated immunological response. In healthy mice, *W. somnifera* hydroethanolic and aqueous root extract boosted leukocyte and platelet numbers as well as peritoneal macrophage phagocytic activity.[59]

It raises IFN- γ IL-2, and Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) levels, showing immunostimulatory and myeloprotective properties. It has anti-inflammatory and immunosuppressive effects, demonstrated by inhibition of DTH. [57]

Role in COVID-19 pandemic:

- **Prevention of viral entry and replication:**

By disrupting the ACE-2 complex and inhibiting the SARS-CoV-2 Mpro and TMPRSS-2 enzymes, withaferin A impairs the host-virus relationship. Virus spike protein and RdRp enzyme are blocked by withaferin A and withanolide B.

The host receptor glucose-regulated protein 78 was suppressed by withaferin A, which is known to be elevated in COVID-19 patients.[59]

- **Diminution of cytokine storm:**

In vitro, *W. somnifera* aqueous extract reduced IL-6 and IL-1, as well as TNF- α when combined with fatty acids and withaferin A. In PBMCs from healthy people and arthritic patients, an ethanolic extract of *W. somnifera* reduced IL-1 expression.[59]

- **Anti-inflammatory:**

Withaferin A reduces the expression of the NLRP3 inflammasome in monocytes, dendritic cells, and lung tissues, coupled with STAT3-induced macrophage repolarization and M1 macrophage-mediated pro-inflammatory cytokines.[59]

- **Maintaining vascular integrity:**

HMGB1-mediated barrier breakdown, acetic acid-induced hyperpermeability induced by acetic acid and limited transendothelial migration of leukocytes within endothelium was hampered by withaferin A.[59]

- **Therapeutic & vaccine adjunct:**

W. somnifera has cardiorespiratory protective qualities. Hence, it can be used in conjunction with other medications to support cardio-pulmonary function. [(6) ST_11]

Hydroxychloroquine has risks of hepatic failure in a few cases. *W. somnifera* is a hepatoprotective agent effective for regularizing drug induced altered liver enzymes and reducing inflammatory mediators. Its immunomodulatory functions are indicative to explore *W. somnifera* as a vaccine adjuvant for COVID-19.[59]

Commercial preparations:

Ashwagandha is a primary constituent of numerous poly-herbal commercial preparations. These include:

- IMMU-21 (*W. somnifera*, *O. sanctum*, *E. officinalis*, *T. cordifolia*), immunomodulatory effects of IMMU-21 have been reported to show improvements in HIV patients.[57]
- IMMU PLUS (*W. somnifera*, *E. officinalis*, *T. cordifolia*)[60] stimulates blastogenic capacity of T and B cells and in few fishes such as *Labeo rohita*. [57]

ANDROGRAPHIS PANICULATA:

Andrographis paniculata, a herbaceous plant from the family Acanthaceae, is popularly known as Kalmegh. Main pharmacological activities exhibited by this plant include immunomodulatory, antibacterial, antiviral and are attributed to Andrographolide. In addition to this, it displays a variety of therapeutic advantages such as anti-inflammatory, anti tumour, antidiabetic and hepatoprotective.

Currently, this plant is most commonly used to treat infections of upper respiratory tract, sore throat in China, India, etc. [61]

Constituents:

The immunomodulatory phytoconstituent is Andrographolide and is present in all parts of the plant, particularly in the leaves. 14-deoxy-11,12-didehydroandrographolide is one of the analogues of Andrographolide and has immunostimulatory, anti-infective and anti-atherosclerotic properties. The other analogue 14-deoxyandrographolide is immunomodulatory and anti-atherosclerotic. [62]

Mechanism of Action:

In vitro studies of Andrographolide extract from stems & leaves of *A. paniculata* suggest that it stimulates production of antibodies and delayed DTH reaction. It also stimulates innate immune response which is studied via macrophage index. Additionally, it stimulates proliferation of splenic lymphocytes and blood lymphocytes and synthesis of crucial cytokines like IL-2.

In mice, in vivo immunological responses including immunological response to thymus specific antigen and DTH were reduced. It enhanced tolerogenic properties of immature dendritic cells (DCs) by suppressing stimulation of NF- κ B in murine DCs. [61]

Role in treatment of COVID-19:

Andrographolide successfully docked against the inhibitor region of the SARS-CoV-2 virus's primary protease which indicates great binding of the phytoconstituent when analyzed against synthetic compounds docked against Mpro. [63]

On treatment with andrographolide in SARS-CoV-2 infected Calu-3 cells (human lung epithelial cells), the production of infectious virions, viral replication and release were significantly inhibited as determined by plaque assay.

The mechanism of action of andrographolide was to target nonstructural proteins of SARS-CoV-2. Andrographolide exhibits a high affinity for the spike glycoprotein of SARS-CoV-2 as well as ACE2 receptors, suggesting that it could be used as a prophylactic drug to prevent viral entrance into host cells. [64]

Commercial preparations:

Kalmegh herb powder by Bixa Botanical is a marketed product which is widely used as a natural liver tonic. It contains bitters that are used to increase immunity against various pathogens. It is also useful as an anti-inflammatory and reduces body ache.

In Ayurveda, Kalmegh has been used since ages to treat various ailments related to 'Pitta' or 'Kapha' in liver, skin and intestine.

TINOSPORA CORDIFOLIA:

Tinospora cordifolia commonly recognized in Ayurveda as Guduchi belongs to the family Menispermaceae. Its stem is mainly used to treat antipyretic, antiemetic, useful in skin diseases; cures jaundice and its juice are useful for the treatment of enlarged spleen, diabetes, and vaginal discharges. It also possesses numerous properties like antioxidant, immunomodulatory, anti-inflammatory and anti-allergic. [65]

Chemical constituents:

Aqueous extract of *T. cordifolia* contains arabinogalactan and it accounts for the immunological activity. The potential immunomodulatory compounds like N-formylannonain, cordifolioside A, tinocordiside are found in this plant. [65] Seven compounds of classes such as alkaloids, phenylpropanoids and sesquiterpenes were isolated out of which two, cordifolioside A and syringin were reported to have immunomodulatory effect. [66]

Mechanism of Action:

T. cordifolia aqueous extracts were reported for immunostimulation; influence cytokine production, and mitogenicity. In one preclinical in vivo study, its extracts resulted in enhancement of IL-6 cytokine which resulted in B lymphocyte differentiation. [65] The ethyl acetate, water fraction and hot water extract of *T. cordifolia* stem increased the phagocytic action of human neutrophils, indicating potential immunostimulating effect. [66]

Role in treatment of COVID-19:

Cordifolioside, a phytoconstituent of *T. cordifolia*, indicated high inhibitory activity towards the binding pocket of Mpro due to its stable conformations, which suggests immunomodulatory activity. [67] When compared to the built-in ligand N3, tinocordiside, sesquiterpene glycoside of *T. cordifolia*, had the best binding ability for SARS-CoV-2 M protein. [68]

T. cordifolia possesses antioxidant, antipyretic and anti-inflammatory effects which prove to be useful in providing symptomatic relief in the treatment of COVID-19.

T. cordifolia contains alkaloids such as a magnoflorine, isocolumbin, palmatine, choline, tinosporin, tetrahydropalmatine; which have a defense against aflatoxin-induced nephrotoxicity and are capable to scavenge free radicals. The antioxidant saponarin is present in *T. cordifolia* which is characterized as an alpha -glucosidase inhibitor.[65]

Stem extract of *T. cordifolia* inhibited acute inflammatory response induced by carrageenan.[65]

Commercial preparations:

Giloy-Guduchi Powder (*Tinospora Cordifolia*), balances the tridoshas (vata, pitta and kapha) in the body and helps to boost the immune system to combat various diseases.

Guduchi plus tablets reduces joint and muscle pain, prevents nausea, possesses antipyretic action, eases digestion, reduces cholesterol levels, and maintains healthy uric acid levels.

PANAX GINSENG:

Panax ginseng, belonging to the family Araliaceae, has been utilized for thousands of years as a herbal medicine in Asian nations. The roots of *P. ginseng* contain numerous phytoconstituents which have different effects on carbohydrate and lipid metabolism, function of neuroendocrine, immune, cardiovascular and central nervous systems in human beings. *P. ginseng* is popular for its immunomodulatory activity. Ginseng has also been found to have powerful anti-inflammatory properties.[69]

Chemical Constituents:

The vital phytoconstituents of ginseng include ginsenosides, polysaccharides, peptides, polyacetylenic alcohols and fatty acids. Ginsenosides are the steroid saponins, and are the major biologically active phytoconstituents of ginseng. They are responsible for various immunomodulatory and antiinflammatory actions. Ginsan, a polysaccharide extracted from ginseng, has anti-inflammatory activity.[69]

Mechanism of Action:

The cytokine synthesis was modified by *P. ginseng* extract, which generated more IFN- γ , TNF- α , but perhaps less interleukin-4 (IL-4). A Th1-like immune response (cell mediated immune response) was elicited by ginseng extract therapy, but long-term administration potentiates humoral immune response. Ginsenoside Rg1 boosted CD4(+) T-cell activity while also influencing Th1/Th2 differentiation. Apart from PBGA11, all polysaccharides stimulated the generation of IFN- γ and TNF- α . Ginsenosides are believed to be the key molecules that have adjuvant activity among the whole ginseng extract.[70]

Role in treatment of COVID-19:

Anti-Inflammatory

Ginseng enhances phagocytic activity of macrophages and the generation of proinflammatory cytokines is inhibited. This occurs by suppressing the Mitogen-activated protein kinase activity (MAPK).[69]

Influenza and covid

Korean Red Ginseng (KRG) stimulated the production of the antiviral cytokine IFN- γ , which protected tissue following infection with the H1N1 influenza virus.[71] In animal studies, it also reduced proinflammatory cytokines, which protected from bacterial pneumonia-septicemia produced by pneumococcus. Increased phagocytosis, suppression of oxygen radical generation, and decrease of apoptotic signaling and inflammation are all potential ways for KRG to improve vaccination effectiveness.[71]

ARDI -

A study suggests that KRG may be effective in protection from contracting ARI, and may decrease the duration and scores of ARI symptoms.[72]

Antiviral activity of ginseng -

Quinqueginsin, a homodimeric protein from the roots of American ginseng, *quinquefolium*, and xylanase, a homodimeric protein obtained from the roots of *Panax notoginseng*, were found to block reverse transcriptase.

P. ginseng extract displays an immunomodulatory action that shields the host from extreme lung inflammation and RSV infection by regulating Th1 and Th2 immune responses. [768, 71]

Commercial Preparations:

Ginseng root extract capsules manufactured by Health Solution Prime, boosts the immune system, increases energy levels by withstanding physical and mental stress. It enhances memory and reduces age related effects. It also contains antioxidants, vitamins and minerals, helps in enhancing the digestive system and provides appetite support.

OCIMUM SANCTUM:

Ocimum sanctum popularly known as 'Tulsi', belonging to the family Labiateae, has been widely used in Ayurveda for various diseases and possesses adaptogenic activity. The immunomodulatory, anti-

inflammatory, antipyretic, analgesic, and antiarthritic properties of the fixed oil produced from the seeds are well recognized. [73] Anti-diabetic, hepatoprotective, antimicrobial and anti-carcinogenic effects have also been discovered in studies. [74]

Chemical Constituents:

The leaf volatile oil contains eugenol, euginal, urosolic acid, carvacrol while the seed volatile oil has fatty acids and sitosterol. The seed mucilage contains some levels of sugars and the anthocyanins are present in green leaves. Flavonoids are also one of the phytoconstituents possessing immunomodulatory activity [75].

Mechanism of Action:

In young, non-stressed animals, *O. sanctum* seed oil had a beneficial effect on humoral immunity. It seems to regulate both B and T cell-mediated immunological responses, with GABAergic pathways playing a role in these immunomodulatory actions. [75] This implies that the Th1 kind of reaction was polarized first, followed by the Th2 type of response (IL-4). Flavonoids contained in Tulsi leaf extracts also were discovered to be accountable for the immunomodulatory effects. [76]

Role in treatment of COVID-19:

Only three compounds among *O. sanctum*'s 46 active phytoconstituents, Vicenin, Isorientin 4'-O-glucoside 2"-O-p-hydroxybenzoate, and Ursolic acid, exhibited significant binding affinity for SARS-CoV-2 Mpro. The greatest binding energy was discovered in Vicenin. [78]

The *O. sanctum* hydroalcoholic extract has antiviral effects against the H9N2 virus, inhibiting viral intracellular growth and interfering with virus-cell interactions in a non-specific manner. [79]

Alcoholic extracts showed anti-asthmatic potential through inflammatory mechanisms by inhibiting LTC₄, LTA₄ and COX-2 in HL-60 cell lines and reduction in inflammation in asthma mice model. [80]

Commercial Preparations:

Dabur Tulsi tablets provide improved respiratory health and immunity boosting properties. Tulsi enhances immunity by reducing total bacterial count and increasing neutrophils, lymphocytes and phagocytic activity.

ZandulmmU is a paediatric tablet preparation which contains *O. sanctum* extract which provides enhanced immunity by increasing NK cells and phagocytic activity to kill bacteria and viruses and supports lung function.

CONCLUSION

Based on the studies conducted by the researchers worldwide and literature, it is evident that these herbal immunomodulators regulate the release of various inflammatory cytokines and interfere in the viral development cycles by modifying certain molecular pathways. However, for a herbal agent, its purity, quality, chemical stability and pharmacological effects are important. Hence, using these agents without consent and proper examination might prove to be harmful. Comprehensively we have summarized the details about few herbal immunomodulators that have potential in providing symptomatic relief to the patients along with acting as an adjuvant therapy.

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