

# Immunomodulation and anti-viral effect of Herbal compounds: A review on coupled strategy for COVID-19

<sup>1</sup>Satish Kumar Sharma, <sup>2</sup>Ashok Kumar

<sup>1,2</sup>Glocal School of Pharmacy, Glocal University, Mirzapur Pole, Saharanpur, 247121 Uttar Pradesh, India.

<sup>1</sup>satishdipsar55@gmail.com, satish.kumar@theglobaluniversity.in

**Abstract:** *Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an infectious pathogen rapidly spreading throughout the world. The disease has become a global pandemic having approximately thirty four million disease cases with one million reported deaths, worldwide. The immuno compromised and/or old age people are most susceptible to severe form of the disease. The pathogenic virus enters the human body causing numerous changes in the immune system regulation. Several studies report that coronavirus causes 'cytokine storm' leading to adverse effects of host immune response. Thus, it becomes necessary to prevent the pathogen from hijacking the host's immune system. The present study elaborately describes the scope of immunomodulation in COVID-19 along with ayurvedic herbs as potential immunomodulating drugs to curtail the effects of the pathogenic virus. Briefly, the study provides dual strategy of immunomodulation and antiviral herbal compounds as a measure to control the pandemic at current stage.*

**Keywords:** *Ayurveda, COVID-19, Herbs, Immune system, Immunomodulation, Medicinal plants.*

## 1. INTRODUCTION:

The widespread economic downfall caused by the coronavirus disease 2019 (COVID-19) spreading globally through the pathogen severe acute respiratory syndrome coronavirus (SARS-CoV-2) has become unstoppable despite several attempts of social isolation and restrictions. Even after thirty four million disease cases and one million deaths worldwide, there is no direct treatment available for the disease [1]. The common symptoms of the disease include fever, tiredness, dry cough, nasal congestion, runny nose or diarrhea. It has been reported that traditional remedies can provide symptomatic relief in COVID-19. Products of biological origin including plants and animals have been used as pure compounds or crude mixtures to treat variety of diseases. Researchers have been focused on stimulating immunity and eliminating the risk of disease. Ministry of AYUSH has prescribed preventive health measures and immunity boosters for tackling COVID-19.

The state of biological defense for preventing infection, disease progression or any type of harmful biological invasion comes under the term immunity. The immune system helps in protecting human body from biological invasion while preventing damage to the self tissues. Immune system falls under the second line of defense mechanism. The immune system is a combination of cells network, proteins and lymphoid organs strategically working to prevent pathogen invasion or protect the body from infection progression. As per COVID-19 research done so far, hospitalized patients with the disease have been developing problems due to over-activation of systemic immune response. The impaired regulation can cause multisystem

organ failure [2]. Thus, the disease has a scope of immuno-modulation to relieve patients from post COVID effects.

### 1.1 Scope of immunomodulation in COVID-19

The treatment strategy for COVID-19 on which the world is relying on is vaccine based prevention of the disease. Although the strategy is ideal for the pandemic but it is time consuming which requires extensive clinical trials making the strategy inefficient at the current clinical situation. Currently, antiviral drugs have been repurposed to cure the disease by inhibiting viral replication inside the host. However, some studies describe the role of interleukins in pathological improvement of the disease.

It has been observed that during the recovery phase of the disease, patients' body develop hyper inflammatory response also known as 'cytokine storm' that has harmful effects on the acute respiratory syndrome. The response can also lead to multiple organs failure [3] [4]. Thus the study states that inhibition of interleukin-6 (IL-6) can have benefitting effects on pathological manifestations of the disease. Several other types of immune regulators such as IL-1, IL-6, C-reactive protein and lactate dehydrogenase have also been associated with the disease severity [5] [6]. However, systemic data of proof is not available. According to observationa clinical data, macrophage syndrome and haemophagocytic lymphohistiocytosis have also been associated with the disease. It has been suggested that patients who develop sepsis with excessive secretion of transaminases in liver and coagulopathy in COVID-19 can benefit from inhibition of IL-1, IL-6 or JAK [7]. The cytokine storm can be treated by JAK inhibition, specifically inhibiting IL-6 and interferon (IFN-gamma). Although the mechanistic inhibition seem promising in improving disease condition but, clinical trials will reveal the effects in heterogeneous population along with side effects of the inhibition strategy.

The most complex manifestation of the disease lies in the question that whether host immune system is a friend or foe during disease progression. Toll like receptor-7 (TLR-7) present in endosomes are responsible for viral binding to the host and lead to inflammatory cytokines [8]. The binding receptor of the virus is extensively expressed in organs like lung epithelial cells, kidney, heart, gastric tract and bladder, thus these organs are most affected ones [9]. After 7 to 14 days of the infection, the host body stimulates adaptive immune response directed by pro-inflammatory cytokines through NF- $\kappa$ B signaling cascade. The activated B cells secrete antibodies and specific cytotoxic T cells to kill virus infected cells. Moreover, IL17 are secreted by neutrophils, granulocytes which further stimulate other interleukins and cell stimulating factors [10]. It has been seen that excessive secretion of IL-17 can also worsen the disease condition. All these responses work together to eliminate the viral progression inside the host.

The pathology of COVID-19 has become more complex as the virus is evolving to have defense pathways to evade the immune response of the body. If the virus particles are able to tolerate the immune response in early 7-14 days, it is highly likely that the disease can take form of severe respiratory problems. Then, the body's immune system will act as an enemy worsening the conditions of the disease. The virus is capable of deregulating the host immune system which further helps the pathogen to evade the immune attack [9]. The severe form of T cells stimulation can result in cytokine storm and exhaustion of T cells, making the defense system of the body relatively weaker and puts the patient in dangerous pathological symptoms [11]. Thus it is necessary to boost the immune systems in early infection days to stop viral replication, before they hamper the body's immune regulation.

## 2. MEDICINAL PLANTS FOR IMMUNOMODULATION

Traditional research has shown the role of plants their medicinal products in treating complex diseases caused by bacteria, fungi and viruses. The plant products have shown their mechanism of action to be of similar form as conventional drugs. Though, some plant products can elicit cytotoxicity effect but, the effect can be avoided by concentrating the required product from the crude extract. Medicinal plants have been famous for as pain killer and antipyretics such as willow tree bark which is rich in metabolite of aspirin i.e. salicylic acid [12]. Several drugs including aspirin, diagoxin, quinine and opium have been derived from plant sources. Currently, the researchers have been focusing on finding our potent compounds which are capable of modulating the complex immune system. As the disease scale is increasing the complexity of pathogen survival has made it essential to have compounds which can be used to strengthen the body's self defense mechanism.

There have been studies which show the capability of herbal compounds to regulate sevra cytokines. Cytokines are a group of soluble glycoproteins in the form of interleukins, interferons, chemokines etc., which are essential for innate and acquired immunity. The role of cytokines is evident in prevalent cardiovascular diseases involving liver, heart, vesels and adipose tissues. Several complex diseases such as rheumatoid arthritis, Alzheimer's disease, schizophrenia have been associated with cytokine inhibition as potential target for treatment strategies. The side effects of conventional protocols have made researchers to examine phytotherapy in regulating the expression of cytokines. According to a study conducted by Denzler et al., root and seed products of Chinese plants have been useful in lowering IL-6 concentration [13]. Moreover, garlic has also been found efficiently reducing IL-1 and IL-6, helping in anti-inflammation effect, along with angiotensin- conversion enzyme inhibition [14]. Similarly, several studies have shown potential effect of medicinal plants and their parts in modulating the immune response through cytokine regulation.

Various herbal medicines have been found to modulate innate and acquired immune systems. According to a study conducted by Halwani R et al., *Ganoderma lucidum*, *Glycyrrhiza uralensis*, and *S. flavescens* can reduce infiltration of eosinophils and prevent hyper-response of IgE and cytokines IL-4, IL-4 and IL-13 [15]. Ethanolic extracts of common fig has shown stimulation of humoral and cell mediated immunity *in-vivo* animal models [16]. Such immunomodulatory therapies are useful in situations where host defense system has to be activated under impaired situations or where immunosuppression is required such as in case of autoimmune disorders, transplantations and inflammatory diseases. These therapies provide an alternative to conventional drug based therapies, also eliminating the risk of side effects.

Table 1: Medicinal plants as immunomodulators. The immunomodulation plants have been utilized in up-regulation of immune response as well as downregulation of hyper responsive immune system [17].

Medicinal Plant	Disorders	Effects on immune system
<i>Astragalus membranaceus</i>	Spleen disorders	lower IL-6, inflammatory and impending deterioration marker
<i>Allium sativum</i>	Alzheimer's disease, Bowel's syndrome	lower IL-1 and IL-6, acting as anti-inflammatory, hypocholesterolemic, antioxidant, angiotensin-converting enzyme inhibitor IL-10 modulation in Alzheimer's disease

<i>Aloe barbadensis miller (Aloe vera)</i>	Newcastle disease virus and Bursal disease virus	anti-inflammatory, reduce TNF- $\alpha$ and IL-6
<i>Ganoderma lucidum, Glycyrrhiza uralensis, and S. flavescens.</i>	Allergic reactions	inhibition of hyper responsiveness - level of IgE and associated cytokines IL-5, IL-4, and IL-13
<i>Chlorophytum borivilianum</i>	Immunological disorders	immunomodulator, potentiates non-specific immune response - improves humoral as well as cell-mediated immunity
<i>Picrorhiza kurroa</i>	Infection conditions	Improved immunity – stimulation of humoral response by antibody production

### 3. HERBAL COMPOUNDS AS IMMUNODRUG – RASAYANS AND NON-RASAYANS

According to WHO, 75% of the population is relying on herbs as remedies for primary health care. Herbs have gained significant importance in health care as therapeutics aiding in diseased conditions, to maintain healthy state of the body. Ethnopharmacology and traditional medicine have gained access to international pharmacopoeia by making significant contributions in herbal formulations. The growing importance of natural drugs has made the move from herbalists to research laboratories showing a blend of pharmaceuticals and ayurvedic sciences. This has helped herbal industries' expansion at 20% every year [18]. The herbs have proved their significance in numerous disorders including cancer, neurodegenerative disorders, inflammations and immunodeficiency disorders [19].

#### 3.1 The Ayurvedic concept

The ancient traditional concept of Ayurveda has always proved its root in philosophical as well as experimental domains. The concept of immunity in Ayurveda is known as "Vyadhikshamatwa". The most crucial therapeutic strategy in Ayurveda is focused on enhancing the body's overall natural mechanism to fight against the disease caused pathogens and neutralizing the pathogenic effect to enhance immune response. The section of "Vyadhirodhak Chamata" aims at building body's capacity to resist the disease progression [20]. Ayurvedic concept has been a source of vast number of medicinal herbal compounds derived from plants having potential for anti-ageing, neurostimulation, antiviral and adaptogenic properties. The pharmacological activities in ayurvedic concept have been grouped into *Rasayans* and *Non-rasayans*. These groups independently or in combination can help in providing immunomodulatory compounds for enhancing immune system effect on pathogenic invasion.

##### 3.1.1 The Rasayans

The word 'rasayana' is a combination of elixir/ nutrition (*rasa*) transported through the body (*ayana*). It is beneficial in improving immune protection and required at degenerative phase of the immune system. It has been proved that plants rich in glycosides, flavanoids, coumarins, thiosulfinates pose efficient immunomodulation properties. These herbs have

proved themselves in epidemic situations, showing ethnopharmacological potential [21]. Thus, ayurvedic rasyana can help in COVID-19 at three different stages of life. Firstly, the herbal formulations can help in prevention of viral particles affinity for binding to immune cells, inhibiting the immune dysregulation and prevention of disease. At the second stage, when the person has acquired the infection, the ayurvedic rasayana can help in fighting with the invaded pathogen which is naturally possible as around 83% of people who got the infection, have been cured at initial stage by their natural immune mechanism [22]. At the third stage, when the person is recovering from the infection, ayurvedic rasayana can help in restoring the holistic health and prevent long term problems.

### 3.1.2. The non-rasayans

The non rasayan herbs have shown comparatively similar potential in immunomodulation. The concept is based on herbs possessing ‘ama’ which is an immunologically active compound naturally produced in intestine as defense mechanism against the situation when there is indigestion of food [19]. Several herbs have been reported for immunomodulatory effect and the concept has a huge reservoir to be explored. These herbs have been utilized as anti-allergic compounds for up regulation of T-suppressor cells [23]. According to a study conducted on *Piccorrhiza kurrora*, the compound is found to be affecting sensitivity to histamine and sympathomimetic amines preventing bronchial obstruction induced by platelet activating factor [24]. In the present situation of pandemic, non-rasayanic herbs can be used in variety of forms. The homes, shelters and living areas can be fumigated by ayurvedic herbs eg. Garlic peels, turmeric powder, carom seeds, loban can be used as disinfectants.

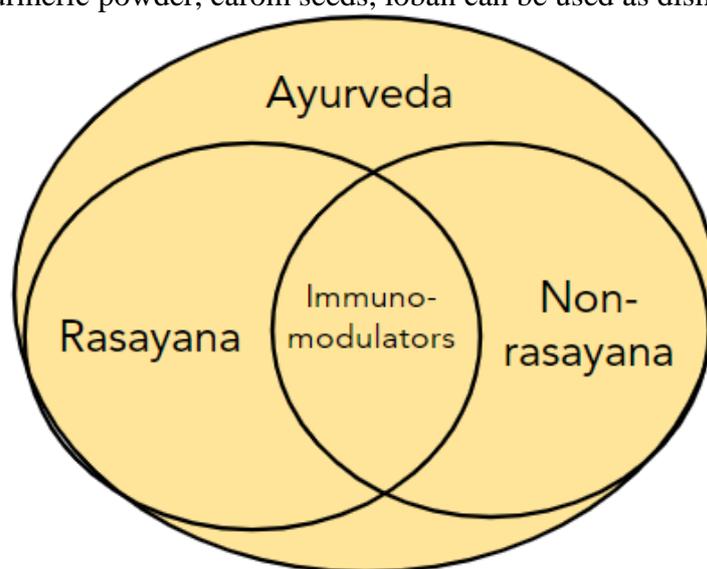


Figure 1: The ayurvedic concept for immunomodulation. The ayurvedic concept has two groups of Rasayans and Non-rasayans which contain herbal compounds as immuno drugs. The immuno drugs can upregulate or downregulate expression of immune system key players.

## 4. IMMUNOMODULATION AGAINST COVID-19

Currently, drugs used in complex viral infection such as HIV are being repurposed for providing symptomatic relief to the COVID-19 patients. According to the clinical reports, people with weak immune systems are highly susceptible to the infection and its worst possible outcomes. Hence it is important to understand the immune system robustness as an important factor to prevent the disease along with antiviral effects. The ayurvedic herbal compounds can be a reservoir for screening immunomodulating compounds in synergy with antiviral properties. Considering the fact that, some people are recovering the infection within

7-14 days without any drug prediction, describes host's potential to fight against pathogenic species. According to studies, immunomodulating herbs exist which have antiviral properties and can be helpful in enhancing the immune system of the body. Table 2 describes potential immunomodulating herbs that can be used in curtailing COVID-19 infection.

Table 2: Immune system modulating herbs. The herbal compounds are capable of modulating immune system as well as viral pathogen clearance by antiviral properties [25].

<b>Immunomodulating herbs</b>	<b>Bioactive compounds</b>	<b>Function</b>	<b>Action on immune system and viruses</b>
<b>Giloy</b> ( <i>Gilu</i> ) ( <i>Tinospora cordifolia</i> )	Polysaccharides, phenolics, diterpenoids, steroids, sesquiterpenoids	Blood purification, immunity booster, analgesic, anti-inflammatory	Reduces histamine induced broncho-spasm, activate macrophages, NF- $\kappa$ B translocation and cytokine production (immune system activation)
<b>Saffron</b> ( <i>Zafran</i> ) ( <i>Crocus sativus</i> )	Safranol, crocin, picrocrocin	Anti-inflammatory, expectorant, brain tonic, cardiogenic, antiviral, anti-asthmatic	Enhance humoral and cellular immunity
<b>Black cumin</b> ( <i>Kalonji</i> ) ( <i>Nigella sativa</i> )	Thymoquinone, dithymoquinone, p-cymene, alfa-pinene, thymohydroquinone, sesquiterpene, carvacrol, pentacyclic triterpene, terpineol, and saponins	anti-inflammatory, analgesic, antioxidant, anti-cancer, antidiabetic, antiasthmatic, bronchodilator, hepatoprotective, gastroprotective, nephroprotective activities	Antiviral activity against herpes simplex virus, hepatitis C virus
<b>Indian goose berry</b> ( <i>Amla</i> ) ( <i>Emblica Officinalis Gaertn.</i> )	gallic acid, ellagic acid, norsesquiterpenoids, gearaniin, prodelphinidins	antioxidant, anti-inflammatory, free radical scavenger, antipyretic, hepatoprotective, neuroprotective and anticancer	Immunity enhancer, antiviral for influenza virus
<b>Turmeric</b> ( <i>Chob zard</i> ) ( <i>Curcuma longa</i> )	antioxidant, anti-inflammatory, antimicrobial, anticancer activities	Curcumin, dihydrocurcumin, hexahydrocurcumin, effective in acute respiratory distress syndrome, acute lung injury, pulmonary fibrosis	Suppression of TNF- $\alpha$ , inhibition of NF- $\kappa$ B, antiviral against H1N1, H6N1, respiratory syncytial virus

<b>Licorice</b> ( <i>Mulethi</i> ) ( <i>Glycyrrhiza glabra</i> )	expectorant, mucolytic, phlegmagogue, detoxicant, anti-pyretic, diuretic, nerve stimulant	glycyrrhizin, glabridin, 18-beta-glycyrrhetic acid, liquiritigenin, licochalcone A, licochalcone E	Immunity booster, anti-inflammatory, antiviral against hepatitis C virus, H5N1 influenza A virus
<b>Hedge mustard</b> ( <i>Khaksi</i> ) ( <i>Sisymbrium officinale</i> )	symptomatic relief from cough, fever	isopropyl-isothiocyanate, butyl-isothiocyanate, phenylethyl alcohol, eugenol	Immunity booster, antiviral
<b>Neem</b> ( <i>Azadirachta indica</i> )	antiseptic, blood purifier, antimicrobial, analgesic, antipyretic anti-inflammatory	nimbin, nimbidin, nimbolide, limonoids, $\beta$ -sistosterol, quercetin	Anti-inflammatory, immunomodulatory,
<b>Ginger</b> ( <i>Adrak</i> ) ( <i>Zingiber officinale</i> )	treatment of anorexia, flatulence, high blood pressure, arthritis and common cold	gingerol, zingiberine, shogaol, gingerdione, hexahydrocurcumin, paradol gingerenone A	Anti-inflammatory, anti-rhinoviral, bronchodilatory
<b>Cinnamon</b> ( <i>Darchini</i> ) ( <i>Cinnamomum zeylanicum</i> )	antiseptic, cardiogenic, aphrodisiac, phlegmagogue actions	cinnamic acid, cinnamaldehyde, cinnamate, essential oils like eugenol, trans-cinnamaldehyde, cinnamyl acetate,	Immuno-enhancer, antiviral
<b>Pepper Mint</b> ( <i>Pudina</i> ) ( <i>Mentha piperita</i> )	antioxidant, antitumor, analgesic	Flavanoids, menthol, menthanone	Immunomodulatory, antiallergic and antiviral
<b>Garlic</b> ( <i>Lehsun</i> ) ( <i>Allium sativum</i> )	antihelminthic, antithrombic, hypotensive, hypoglycemic, hypocholesterolemic properties	alliin, allicin, ajoene, vinylidithin, S-allylcysteine, diallyl sulphides	anti-inflammatory, antiviral, immunomodulator
<b>Winter cherry</b> ( <i>Asgandh</i> ) ( <i>Withania somnifera</i> )	body tonic, nerve tonic, antiarthritic and antivenom medicine	ashwagandhine, isopelletierine, cuseohygrine, anaferine	anti-inflammatory, immunity booster, antiviral for H1N1
<b>Cinchona bark</b> ( <i>Chal-i-konain</i> )	used for common cold, influenza, leg	cinchonine, quinine, cinchonidine, quinidine	Inhibition of SARS-CoV[26]

<i>(Cinchona officinalis)</i>	cramps		
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## 5. CONCLUSION

COVID-19 is a fatal disease which has major effects on immune system deregulation as the pathogen has affinity binding with the cell receptors which mediate excessive immune response. The pathological characteristics of the disease include “cytokine storm” which accounts for disease severity. No specific medicine or vaccine has been accounted for the disease till date. Several studies suggest that weak immune system in early days of the infection causes the pathogen to hijack the immune system regulation, which is worsened in the subsequent days of illness. Thus a strong immune system will not only provide prevention from the pathogen but also help in pathogen clearance and recovery if infection has occurred. There exists a scope of immunomodulation in COVID-19. Several medicinal plants, herbs have been known for immunomodulatory properties. The ayurvedic concept provides rasayanic and non-rasayanic compounds as immunomodulators. The reservoir of traditional therapeutics holds the potential to be explored for strategies to curtail COVID-19. These herbal strategies have been beneficial in improving the immune system, helping in eliminating the disease by host’s self defense system even in the past viral epidemics. Moreover, these compounds have potential antiviral, anti-inflammatory, cold, cough, fever relieving properties to help in relieving symptoms and targeting the pathogen. Hence, it is need of the hour to adopt herbal therapeutics for fighting the global pandemic.

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