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# Review on Potential Herbal Remedies to Combat Covid-19

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## ABSTRACT

The present review focuses on the overview of the immune system regarding its protection of the human body against COVID-19 virus; illustrates the immunity boosting activity of herbal plants against SARS-CoV-2 infection. This work also provides information regarding virus structure information, immunopathogensis of virus with human body and role of Ayurveda in coronavirus disease. A number of herbal plants based active principles have been isolated and extracted with potential immunostimulant and immunosuppressant activity that can explain their beneficial use in traditional medicine and form the further research base for the future studies. The goal of this review is to foreground the immunity boosting activity of different herbal plants and its beneficial use in COVID-19 disease. Many plants and their phytochemicals, responsible for immunomodulation mechanism in SARS-CoV-2 infection have been explained. This review shall hopefully encourage researchers to undertake further work on herbal or medicinal plants with potential immunity boosting activity in COVID-19 disease.

**Keywords:** Ayurveda, Coronavirus, COVID-19, Herbal plants, Immunity.

### INTRODUCTION

Corona virus disease 2019 (COVID-19) is defined as illness caused by a novel corona virus (SARS- CoV-2; formerly called 2019-nCoV). COVID-19, is a transmissible disease which was spread from bats to human beings[1,2]. Although COVID-19 originating from animals but it affects human beings. Corona virus transmitted in an identical way to the common cold, via influence with droplets of infected individual's upper respiratory tract secretions that is from coughing and sneezing[2]. Being an unfamiliar virus type, immunopathogenesis of COVID-19 disease causation is not fully recognized and vaccines and medications against corona virus are still in trial. Thus, no effective medications and vaccines have been advised by higher regulatory authority. COVID-19 generally presents with respiratory and systemic manifestations. Individuals infected with corona virus are asymptomatic and can act as a carriers, signs and symptoms are non-specific such as fever (84-90%), cough (65-75%), fatigue (30-40%), sputum production (31-35%) and shortness of breath (15-25%)[2].

Research studies suggest that SARS- CoV-2 virus can form mutants(drug defiant), which downturns the present drug's action and efficacy[1]. High fatality ratio amid immune-compromised people signifies the factors that enhance immunity can prohibit severe manifestations due to COVID-19 viral infection. Bountiful Ayurvedic and herbal formulations are found to have immunomodulatory and antiviral property, so their exploration can be a milestone in the prevention and management of COVID-19 viral disease[1]. Authority of India, Ministry of AYUSH suggests some preventive health measures and immunity boosting agents with special recommendations to respiratory health[2].

Immunity is a biological term that is defined as a state of having ample biological defences to avoid disease or other undesirable biological invasion and infections. The immune system provides protection to the host from pathogens or other foreign material while minimizing damage to own tissue. Immune system is the second line of body defence mechanism against pathogens or foreign material[2].

The linked network of cells, proteins and lymphoid organs which are strategically placed to ensure maximum protection against infection is define as individuals immune system. Immune defence or response categorized into the two ways i.e., 1.innate immune response, 2.adaptive or acquired immune response. Innate immune response provides immediate shelter against an invading pathogen while Adaptive immune response which takes more time to develop but confers long lasting protection exquisite specificity[2].

In ancient science of life i.e., Ayurveda the concept of immunity offers a holistic approach and a potential promise regarding immunotherapy. The main purpose and objectives of Ayurveda is the eradication of

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diseases which are curable and preservation of health in healthy individual[2]. Ayurveda contribute the health of individuals via strengthening of host defences or immunity. In Ayurveda wellness of everyday is termed as "*Vyadhiksamatwa*". The concept provides information for both preventive medicines "*Vyadhibalavirodhitvam*" along with curative treatment "*Vyadyutpadapratibandhakatvam*"[2].

Daily wellness of human beings is depends on "*Vyadhiksamatwa",* for recovery and prevention from diseases, diseases, complications and infections. When human body come in contact with etiological factors or risk factor or any foreign pathogens infection may occurs, and body tries to resist against that disease. In Ayurveda "*Vyadhiksamatwa*" implies a resistance against the loss of the integrity, interrelationship and proportion amongst the individual's *Dhatus* and *Dosas*. Ayurveda classics described The countless useful *dravya*, route of administration, formulations, dosages, mode of immunity enhancement(*Bala* or *Vyadhiksamatwa*)[2].

In North America most COVID-19 vaccine development activity is their, with 36 i.e., about 46% developers of the confirmed corona virus active vaccine candidates compared with Asia (excluding China), China, Australia and in Europe. China done additional vaccine development efforts via conduct of various meets with Chinese Ministry of Science and Technology to confirm their vaccine development status. About 19 countries in world are lead developers of active COVID-19 vaccine candidates. However, in Africa or Latin America, there is currently no information regarding vaccine development to the people of that region, although in this region there is regulatory framework s and manufacturing capacity exist. The differ in geography directly affects change in epidemiology of COVID-19, so that greater coordination with each other is require to effective control on these pandemic[3].

mRNA-1273 from Moderna, the most advanced vaccine candidates have recently moved into clinical study. CanSino Biological's Ad5-nCoV and pathogen-specific aAPC and LV-SMENP-DC from Shenzhen Geno-Immune Medical Institutes. US biotech company Moderna's mRNA-1273, after analysis of its phase III clinical trial showed it was 94.5% effective the UK government has ordered 5 million doses of these vaccine candidates[4]. So far, adjuvanted vaccines against COVID-19 development plans done by at least 10 developers and vaccine developers including Seqirus, GlaxoSmithKline and Dynavax have committed to form licensed adjuvants (MF59, AS03 and CpG 1018 respectively) for novel COVID-19[3].

Serum institute, bharat biotech, zydus cadila, indian immunologicals, panacea biotec, biological E and mynvax are the pharma companies working on the COVID-19 vaccines development in India[5]. "India's COVID-19 vaccination drive would begin form January 2021 and normal life of individual can be expected to return by October 2021 after everyone get vaccinated" the words said by adar poonawalla CEO of Serum institute of India[6].

First indigenous COVID-19 vaccine of India, COVAXIN, inactivated vaccine, is crossing all phases of human clinical trials across the country. Indian Council of Medical Research-National Institute of Virology and Bharat Biotech have collaboration for these vaccine development[7]. Drug Controller General of India give approval for these candidate to human clinical trials and has reported that it produces strong immunogenicity without any serious side effects and adverse drug reactions. In addition to the ongoing efforts in developing effective vaccines, monoclonal antibodies(immunotherapeutics approach) with a high neutralizing index, with live or inactivated vaccines which supposed to avoid any side effects or adverse events[7,8].

Safe and effective vaccines for COVID-19 will be successfully developed by different countries that cautiously optimistic approach given by the WHO. There is robust pipeline of potential vaccine candidates development and some have already done clinical trials and some in post marketing surveillance. So that, we not only rely on a future vaccine to fight against this pandemic and we must use masks, sanitization procedures, contact tracing, virus testing and physical distancing[9].

**IMMUNOPATHOGENESIS OF COVID-19**

It has been shown that SARS-CoV-2 virus disrupts immune responses of infection patient, leading to an uncontrolled inflammatory responses and impaired immune system in patients with severe COVID-19 infection. These patients possess sign of lymphocyte activation and dysfunction, lymphopenia, granulocyte and monocyte abnormalities, an induction in level of immunoglobulin G (IgG), high cytokine levels, and elevated total antibodies in the patients[10].

Coronavirus virions are enveloped particles with spherical to pleomorphic shaped, envelope contains projecting glycoproteins, and surrounds a core consisting of matrix proteins. The single strand of positive-sense RNA (Mr $6 \times 10^6$) associated with nucleoprotein is enclosed within inner core. For attachment to the host cells, the envelope glycoproteins are plays role and carry the main antigenic epitopes, and this epitopes are perceived by neutralizing antibodies[11].

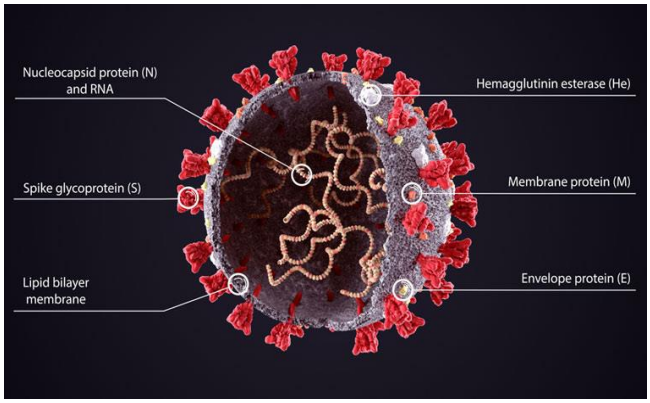


**Figure 1:** Structure of SARS-associated Coronavirus

Virus bounds to ACE 2, the host target cell receptor with the help of 'S' protein[1,12]. Diversified other sites where ACE 2 receptor proteins are found are lungs, stomach, heart, bladder, intestine and kidney. Non-specific symptoms such as fever, headache myalgia and respiratory symptoms shown after active replication and release of the virus in the lung cells[12]. The different tissues ACE 2 receptor distribution may explain the sites of infection and various symptoms of corona virus. For example, the ACE 2 receptor is found on the epithelium of the intestine and blood vessels and endothelial cells in the kidney, which may explain GI symptoms and cardiovascular complications. Postmortem pathology examination of the lung, kidney, heart and liver shows lymphocytic endotheliitis as well as myocardial infarction and liver cell

necrosis in patients who died by infection of covid-19. By above findings one can indicate that the coronavirus directly affects many organs of human body, as was seen in influenza and SARS-CoV-1[12].

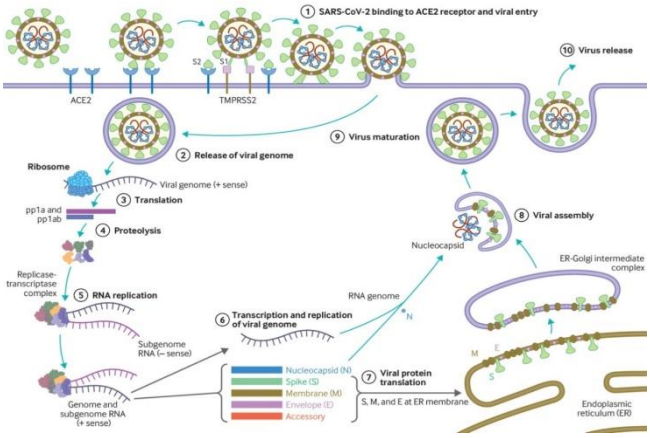


**Figure 2:** Stages of Corona virus immunopathogenesis: (1)SARS-CoV-2 binding to ACE2 receptor and viral entry (2)Release of viral genome (3)Translation (4)Proteolysis (5)RNA replication (6)Transcription and replication of viral genome (7)Viral protein translation (8)Viral assembly (9)Virus maturation (10)Virus release[12]

This coronavirus cause cell destruction mainly by two ways i.e., immune response mediated eradication and direct cytopathic trappings of the virus. Major pathway of cell damage is due to immune-mediated destruction as COVID-19 cannot lyse the host cells directly [1]. The pathogenesis of SARS-CoV-2 virus can be divided into two different stages:

***Non-severe stage***

The corona virus enters in to the host cell through airway epithelium via fuse with the host cell membrane [13]. The virus enter lower airway and alveoli after proliferation inside host cell. In new grown-ups with good cellular and innate humoral immunity virus multiplication can be limited and viral abundance diminished reaching alveoli thus recovery can occur within 2–3 weeks of infection. Prevention of the viruses to penetrate new cells is done via humoral immunity of body while cellular immunity eradicating virus-infected cells. In these stage, a vigorous immune system can be advantageous in prevention of the proliferation of the virus thus reducing the COVID-19 infection severity[1,13].

***Severe stage***

Once the immune system is intruded, viral multiplication is their and reaches the alveoli and lower respiratory tract. Then the virus can permeate alveoli and reaches systemic circulation provoke "viremia". After that organs with ACE2 receptor proteins virus attaches there[1]. During this stage, immunity particularly cellular immunity, becomes sturdy and starts releasing various pro-inflammatory cytokines (IFN-α, IFN-γ, IL-6, IL-1B, IL-12, IL-33, IL-18, TNF-α, etc.) and chemokines (CCL2, 3, 5, CXCL8, 9, 10, etc.) inducing damage to multiple organs called as "Cytokine storm"[14]. So, for recovery to these stage we require to abolish the inflammation or lower down cytokines levels[1].

Anti-inflammatory interleukin (IL-10) and IL-6 receptor inhibitor (Tocilizumab) are exhibited therapeutic and beneficial role in the minimization of severity and lethality of COVID-19. As there is increased risk of thromboembolic phenomena with COVID-19, prophylactic antithrombotic medications are advised during this stage, [1,15].

**IMMUNITY CONCEPT IN AYURVEDA**

Protection to diseases or immune system against diseases is of two different ways i.e. the one which avoid the manifestation of diseases and other that is attenuate the manifested disease[16]. According to Ayurveda immunity of individual mainly depends on Ojas, stable state of Kapha and Vata. In Ayurveda there are two phrasing used to discuss about the theory of Vyadhiksamatwa (immunity) namely Ojas and Bala. Diseases of immune system emerge due to interruption in Ojas, Kapha, Bala and Vata.

Charaka has provided the term "*Vyadhikshamatwa"* and proposed that during certain conditions, all unhealthy regimen are not equally toxic, all persons are not capable of defending diseases, even unhealthy food does not cause disease promptly. This proposed that the in disease progression body's immune system plays a vital role[17]. The "*Swasthya"*, is stable state of "*Dhatu"*[17]. Thus, in Ayurveda immunity is defined as *Vyadhikshamatwa* and *Ojas,* which leans on the condition of *Agni, Dhatu and Dosha.*

There are three elements *Aahara, Brahmacharya* and *Swapna* (diet, celibacy and sound sleep respectively) that hold the individuals life by which the body will be with strength and development for lifetime[1,17]. "*Bala"* (strength/immunity) is of three categories- congenital, acquired and time affected. Congenital is that which is evolved naturally in the body and mind of person; Acquired is proper pertinence of exercise and diet; due to infrequent variation and age factor is time affected. Thus, carrying out yoga or exercises with proper practice as "*Rasayana* therapy" will raise acquired strength when person is on proper diet[17]. "*Ojas"* is also known as *Bala*; is the main core of all "*Sapta Dhatu"*, located in *Hridaya*, merges with *Rasa* and delivered through *Dhamani* and performs *Prinanam* or *Tarpana* of the whole body[1].

The nutrition and its conveyance in the body for generating excellent *Rasadi Dhatu*s referred as "*Rasayana* (*Rasa* + *ayana*)"; which leads to improved longevity, health, freedom from disorders, optimum strength of sense organs and physique. *Rasayana* promotes nutrition by especially enriching the nutritional value of *Rasa* by intensifying *Agni*, i.e., absorption, digestion and metabolism (by *Srotashodhana*). Consequently, any medication improves the health of all body tissues via enhancing *Rasa's* consistency[1,17].

**ROLE OF AYURVEDA IN TRADITIONAL MEDICINE**

Every society or culture has its own individual medical system and this medical system is strongly rooted in its society and guided by its life's philosophy. Ayurveda, Traditional Chinese medicine (TCM), Sowa Rigpa, Ancient Egyptian medicine etc. medicinal system of drugs remain the ancient yet living traditions in South East Asia, Eastern Mediterranean, Western Pacific, Africa regions. Some Asian and African countries (up to 80%) depend upon traditional medicines for primary health care needs[18]. Being culturally diversified countries, they developed several sorts of traditional or herbal medications via

practices, lore supported beliefs, theories, skills, experiences and concepts to different cultures[1]. For the prevention and management of different communicable and non-communicable diseases and infections for thousands of years made possible by the above described medicinal systems that is Ayurveda and other traditional medicine systems. Experiences regarding herbal remedies passed from generation to generation and culture to culture, which resulted in population counting on herbal remedies. For common diseases few simple home remedies are often used by illiterate citizens of nation. The self-medication or self care with home remedies using various herbs or home spices is the most common remedy for India, Bhutan, Nepal and China for different flu, sneezing, common cold, diabetes, fever, skin infections, GI disorders, etc. Prevalence between the per million population COVID-19 cases and therefore the spices supply(gm) per capita per day is clearly interrelated observed by one research study. More COVID-19 cases per million population reported in nations with lower spice intake per capita[19]. Although, with the invention of new medicines, many historically used herbal remedies became modern medicines. Few notable examples include digoxin, morphine, colchicine and artemisinin. As many herbal drugs are found to possess antiviral, immunosuppression and immunostimulation role, Antiviral treatments targeted towards coronavirus also reported in Ayurveda and Traditional Chinese Medicines regarding immunomodulation and role of immunity in COVID-19 disease[1].

The interaction between the individual's immune system and corona virus is the vital factor for COVID-19 to occur and evolve. As medicinal plants antagonize activated transcription factor 2 (ATF-2), increases NK cell activity, down-regulate Th17-related cytokines including transcription factor IL-17A, RORγt and Th2-related cytokines including IL-5,-13,-6; suppresses GATA3, IL-4, -1β, RORγt, TNF-α, IL-17A expression and upsurge the secretions of INF-γ, IL-10 etc., it shows that natural herbs have potent immune-suppresive and immune-boosting activities which will be supportive during the innate immune reaction to diseases[20,21].

Traditional medicinal systems of India - Ayurveda, Unani and Siddha. The ancient *Vedas* and other ancient literatures also possess information of above mentioned medicinal system. In India Ayurvedic concept appeared and developed between 2500 and 500 BC [22]. The literal meaning of Ayurveda is "science of life". It has been pointed out that the metabolically well-balanced human beings means positive health. Ayurveda provides complete system to live a long healthy life so called as "science of longevity". Ayurveda provides disease management to cure many common diseases or complications such as food allergies, flu, fever, cough. However, Ayurvedic nutrition requires the full participation of the patient to succeed as it is not a "magic bullet" system. Ayurveda is a system for empowerment, a system of freedom and positivity, healthy and long life[23].

About 60% of traditional medicines are used by the world's population. These medicines are not only used by the rural masses of developing countries for their primary health care but are also used by developed countries where modern medicines are dominantly used. The huge depository of herbal and medicinal plants that are used in traditional medical therapy is provided by the different indian subcontinents[23,24]. The alternative medicines are derived from herbs, plants, minerals and organic matters while medicinal plants are used to formulate herbal drugs. In India use of plants as a medicine has an ancient practice and is an important part of the health care system. About, 70% of rural population of India depends on the Ayurvedic system of medicine. Most ayurvedic practitioners prepare formulations by their own individual recipes and dispense to the patients according to age, sex, etc. Approximately 40% people of Western countries are using the herbal medicine for the management and prevention of various diseases manifestation. This traditional medicines interest is growing rapidly due to the increased side effects, serious events, adverse drug reactions, and cost factor of the modern formulations[23]. People who do not use or cannot be helped by conventional medicinal system are being use Alternative medicines of traditional medicine systems [24].

**HERBAL IMMUNOMODUPATOR PLANTS**

***Ashwagandha*** (*Withania somnifera*) – *Withania somnifera* commonly called as Aswagandha or Indian ginseng contains withaferin A, withanone, withasomnine as major chemical constituents[2,25]. It has antiinflammatory, antidepressant, antioxidant and immunomodulatory activity. Among the multiple withanolides from *Withania somnifera*, withanolide-D, -G, -M, and -Q were predicted as a lead hit based on drug likeness score, modulated proteins, and docking score to boost immune system and inhibit the COVID-19 infection[26].

***Tulsi*** (*Ocimum sanctum*) - Commonly known as Tulasi or Holy basil which contain eugenol, limonene, camphene, cadinene, bornyl acetate as major chemical constituents. It mainly shows antibacterial, antifungal, adaptogenic, antiviral and immunomodulatory activities[1,2]. Phenolic compounds and antioxidant properties of *Ocimum sanctum* were reported to contribute its therapeutic effects. Tulsi consumption increases the anti-oxidant molecules and enzymes in the body and protects the cells and its membrane from being damaged by the toxic substances. Tulsi acts as immunity booster for the body and helps to defense the threatening virus and bacteria or any foreign particles. Improvement in humoral and cell-mediated immunity was observed in *in vivo* studies after treatment with tulsi oil. The possible mechanism for improving immunity is a modulation of the GABA pathway. Tulsi is being used in the management of fever, cough, pain and diarrhea which are the common symptoms of COVID-19 infection[27,28].

***Ginseng*** (*Panax ginseng*) - Ginseng is the root of plants in the genus *Panax*, such as Korean ginseng (*P. ginseng*), South China ginseng (*P. notoginseng*), and American ginseng (*P. quinquefolius*), typically characterized by the presence of chemical constituents such as ginsenosides and gintonin[29]. Ginseng have activity like treating immunity-related disorders and boosting immunity. Among all herbal supplements, ginseng is the widely studied, demonstrating promising potential action with lower toxic or side effects and beneficial adaptogenic effects on the immunity. However, most immunomodulatory studies are limited to *in vitro* or *in vivo* models, and few have examined the impact of *Panax ginseng* in clinical studies. Ginseng enhance host immunity both actively and passively, and possible uses as a vaccine adjuvant against different disease infections, autoimmune conditions, and bacterial or viral diseases. Ginseng have role as a promising immunomodulatory agent, and further resources should be devoted to studying the impact of ginseng on the immune system of human beings[29,30].

***Chirata*** (*Swertia chirata)* - *Swertia chirata* Buch Ham (*Gentianaceae*) is a perennial herb[31]. Significant decrease in delayed type hypersensitivity shown with use of methanolic extract of Chirata and also beneficially prohibit the production of lymphocytes (CD3) intracellular cytokines (IL-2 and IFN-γ). So, further research require to explore Chirata to develop an immunosuppressive agent which will be effective and having no or minor side effect[31,32]. Phytochemical screening shows the presence of phenolic compound like flavonoids, alkaloids and tannins which may have role in the immunomodulatory activity. Chirata shows proven therapeutic potentials like anti-viral, immunomodulatory and antiinflammatory activities and it will be beneficial to acquire immunity against Covid-19 attack[33].

***Turmeric*** (*Curcuma longa)* - Turmeric is a flowering plant, *Curcuma longa* of the ginger family, *Zingiberaceae*[2], the roots of which are used in cooking. Turmeric aids in making our immunity stronger, the main life-saving ingredient in turmeric is about 3-5% of Curcumin; a phyto-derivative, which contains healing properties. Turmeric helps the body naturally cleanse the respiratory tract. Hot milk is given with turmeric because it helps respiratory system to stay healthy Curcumin has potential effects on number of disease conditions in human beings as well as in animal systems. The end stage of viral diseases is the onset of a cytokine storm, the large or overproduction of cytokines by the immune system of individuals[34]. The cytokine release suppression by Curcumin correlates with improvement in experimental models of disease conditions where a cytokine storm plays a potential role in mortality. Curcumin regulates various inflammatory cytokines such as IL-1, IL-6, IL-12, TNF-alpha, IFN gamma and associated JAK-STAT and NF-kappa signaling pathways in cells of immune system.[35].

***Ginger*** (*Zingiber officinale*) - Commonly called as Sunthi or Ginger which contain α- and β- zingiberenes, zingiberol, methyl-6-shogaol, nevirapine, 6-gingediol, zingerone, α- curcumene, β-sitosterol, 6-gingerol, α-linalool, gingerdion, etc. are well-known to cause inhibition of viral multiplication; among these phytochemicals the most potent inhibitor of reverse transcriptase (RT) enzyme is β-sitosterol, which is anticipated to be used as non-nucleoside reverse transcriptase (NNRTIs) HIV-1 inhibitors[1]. It has anti-inflammatory, anticholinergic, antihistaminic, antioxidant activities and it also has bioavailability enhancer property[3]. An increase in the immunological status of mice with elevated phagocytosis by macrophages shown with alcoholic concentrate of ginger whereas raw extract was also shows increase humoral and cellular or cell-mediated immune responses[1].

***Giloy*** (*Tinospora cordifolia)* - Guduchi or Amrita contain chemical constituents tinosporin, cordifolide and tinosporide. It has phagocytic activities, antioxidant, antipyretic action as well as immune system alteration properties[2,36]. It is also mentioned as Medhya Rasayana in Charaka Samhita[2]. This plant is renowned for its immunomodulatory activity. Plant active chemical constituents 11- hydroxymustakone, N-methyl-2- pyrrolidone, cordifolioside A, magnoflorine, N-formypannonain, tinocordiside and syringin shows beneficial immunomodulatory and cytotoxic effects. Clerodane furano diterpenoid glycosides such as cordioside, cordifolioside A and cordiol plays an important role in specific and non specific immune responses followed by their macrophage activation. Study shows the immunomodulatory activity of *Tinospora cordifolia* ethanolic extract of stem (100mg/kg) by altering the concentration of the antioxidant enzymes, raise the level of antibody, T and B cells which have potential role in immunity, which further elevates the melatonin level in pineal gland and increasing the range of cytokines like IL, particularly IL-2, 10 and TNFα, which plays a influential role in immunity[36,37,42].

***Amla*** (*Emblica officinalis)* - Amalaki or Indian gooseberry rich source of Vitamin-C[38]. It contain low molecular weight hydrolysable tannins. It also contain ellagic acid, linolic acid etc. as chemical constituents showing activities against carcinogenesis, it also shows cytoprotective, anti-inflammatory, antimicrobial, antioxidant and immunomodulatory activities[3]. *Emblica officinalis* or *Phyllanthus emblica*, is probably the foremost important herbal plant within the Indian traditional system of medicines, the Ayurveda. Most important part of plant is the fruit, along with that diferent parts of the plant are wont to treat a number of diseases. Many complications of diseases are treated by the amla fruit which is used either alone or along with other herbal plants. These include diuretic, laxative, cold and fever, as a liver tonic, restorative, anti-inflammatory, hair tonic, as a digestive, to stop peptic ulceration. *Emblica officinalis* possesses so many pharmacological activities like analgesic, antipyretic, antitussive, antiatherogenic, gastroprotective, cardioprotective, antidiarrheal, antihypercholesterolemic, antiatherosclerotic, hepatoprotective, nephroprotective properties as demonstrated in numerous preclinical studies[2,39,40].

Study reported that Immunomodulatory role of *Emblica officinalis* in mice with in-vivo animal model i.e., arsenic induced oxidative damage and apoptosis in thymocytes. The conclusion of the above study shows that arsenic induced apoptosis and oxidative stress significantly inhibited by treatment with *Emblica officinalis* that could be due to its strong potentiality as an antioxidant[40].

***Aloe Vera*** (*Aloe vera*) - *Aloe vera* (*Aloe barbadensis*), is a perennial plant of Liliacea family, commonly known as Ghritakumari[38]. On dry drug basis, aloe gel consists of polysaccharides, minerals, sugar, proteins, lipids and phenolic compounds. The curative potential of plant credited to polysaccharides present in the inner leaf parenchymatous tissue of leaf extracts. Various range of effective secondary metabolites possessed by plant that includes tricyclic aromatic quinine structure with anthraquinone base. Aloe-emodin and chrysophanol are main naturally-developing anthraquinone compounds from aloe vera. Two types of exudates are secreted by aloe leaves, one is transparent and resembles colorless gelatin and another that is bitter reddish yellow juice due to the presence of aloe-emodin, aloin and related compounds. Aloe vera possess wound healing, antiinflammatory, anticancer, antidiabetic, antiulcer, antihyperlipidemic activity, antioxidant effects and Immunomodulatory activity. Immunomodulatory properties of extracts of Amla and its interaction with Aloe vera in immuno-compromised states[40].

***Liquorice*** (*Glycyrrhiza glabra*) - Yashtimadhu or Liquorice which contain glycyrrhizin, glycyrrhizic acid, glycyrrhetic acid and glabrine etc. as major chemical constituents. Natural triterpenoid saponin derived from the root of liquorice (*Glycyrrhiza glabra*) that is Glycyrrhizin has shows numerous pharmacologic actions, including antiinflammatory, antibacterial, antioxidant, antitumor, antiviral and immunomodulatory activities[2]. Stimulation of IL-12 and suppression of IL-10 production and NO production from macrophages, up regulation of costimulatory molecules on dendritic cells, augmentation of NK cell activity, increase in T cell proliferation and Th1 directed immune response, are the most

known immunomodulatory activities possess by glycyrrhizin. *Glycyrrhiza glabra* mentioned in Ayurveda as "*Rasayana*"[41].

***Brahmi*** (*Centella asiatica*) - Mandukaparni or Gotukola contain asiatic acid, centic acid, centellic acid, carotene etc. as major chemical constituents. It possess *Rasayana* (anabolic), immunomodulatory and analgesic properties. In Ayurvedic classics Brahmi has been mentioned as *Medhya Rasayana*[2].

In one research study, fresh concentrate of Brahmi and Giloy (juice) was assessed for the first time for their antioxidant and immunomodulatory activity. Fresh juice extracts of both plant shows high immunomodulatory as well as antioxidant activities. The fresh juice extracts used as dietary herb or as nutraceutical in clinical applications[42].

***Ajowan*** (*Trachyspermum ammi*) – *Trachyspermum ammi* commonly known as Ajwain and Ajmo. Medicinally, it has been confirm that ajwain possess various pharmacological activities like antioxidant, antifungal, immunomodulatory, antimicrobial, hypolipidemic, cytotoxic, antihypertensive, antilithiasis, antispasmodic, broncho-dilating actions, antifilarial, diuretic, antitussive and anthelmintic. Studies reveal the presence of various phytochemical constituents mainly glycosides, carbohydrates, phenolic compounds, saponins, volatile oil (para-cymene, thymol, γ-terpinene, and α- and β-pinene), fiber, protein and mineral matter containing iron, calcium, phosphorous and nicotinic acid[43].

Many arabinogalactans isolated from medicinal herbs were reported to induce phagocytic activity of macrophages and polymorphonuclear leukocytes. Arabinogalactan protein from *Trachyspermum ammi*(Ajowan) displays significant immunomodulatory activity, at 1 µg/mL activated macrophages in releasing NO and significantly promoted phagocytosis. The carbohydrate fraction contains 45.7% galactose, 34.5% arabinose, 7% glucose, 5% mannose and 4% xylose. Whereas deproteinized AGP or deglycosylated AGP showed compromised efficiency. Therefore, the structural complexity protein-glycan plays a crucial role in activating the immune response that mainly functions on the molecular pattern recognition mechanism. These polysaccharide fractions stimulated macrophages for an enhanced NO production via induction of nitric oxide synthase, and induced macrophages to secrete both inflammatory and anti-inflammatory cytokines[44].

***Shatavari*** (*Asparagus racemosus*) - Commonly known as satavar, shatavari and shatamull having a place in the family *Asparagaceae*. Traditionally it was used as galactagogue, aphrodisiac, Rasayana, antiepileptic, adaptogenic, general health tonic and in numerous female reproductive system problems[45]. Punarnava contains specific steroids, flavonoids, phenolic compounds and glycosides as chemical constituents. Extract of different parts of the plant has been approved for its both in vitro and in vivo activities. Shatavari has a potent immunomodulatory property by altering the function of macrophages It has immunomodulatory, antidiabetic, antioxidant, anticancer, hepatic, and neuroprotective effect, antimicrobial, antiurolithiatic, aphrodisiac, memory enhancing the property, antitussive effect, etc[46,47].

***Punarnava*** (*Boerhaavia diffusa*) - Punarnava has immunomodulatory effects due to its immunosuppressive and immunostimulatory activity[48]. Administration of Punarnava consequently decrease down the enhanced level of pro-inflammatory cytokines such as TNFα, IL-1 β, and IL-6 in experimental animals. These outcome point out the immunomodulatory action of Punarnava[49]. Extracts of *B. diffusa* roots have anti-inflammatory activity by inhibiting natural killer (NK) cell, cytotoxicity, production of nitric oxide in human and very high antiviral activity[49].

***Pippali*** (*Piper longum*) - Commonly called as Pippali or Long pepper which contain piperine, piplartine, pellitorine, caryophyllene etc. as major chemical constituents. In atharvaveda, Pippali is mentioned as rasayana. Acharya Charaka and Susruta also mention Pippali as rasayana[2]. It has anti-inflammatory, antispasmodic and immunomodulatory properties. Pippali *Rasayana*, a famous Ayurvedic preparation, reported having significantly activated macrophages in an experimental study on mice. Immunomodulatory action of Pippali fruits (via modulation of both specific and non-specific immune response) has been reported by using haem agglutination titre (HA), macrophage migration index (MMI) and phagocytic index (PI) in mice. The effect was more prominent at a lower dose (225 mg/kg) and was marginally reduced when the dose was increased[47,50].

***Cinnamon*** (*Cinnamomum zeylanicum*) – Cinnamon is a potent immunity booster and it used in different manifestations like indigestion, flu, cough, edema, etc. Cinnamon bark contains cinnamaldehyde, cuminaldehyde, benzaldehyde and terpenes[1]. In one study, cinnamon shows immune-stimulant activity at high dose about 100 mg/kg, as it significantly raise the phagocytic index antibody titer, serum immunoglobulin levels and declined the %reductions in neutrophil count. Cinnamon elevates serum immunoglobulin levels only at lower dose that is 10mg/kg. This shows that low dose shows effect only on humoral immunity while high dose increases both cell mediated and humoral immunity[51].

***Black Pepper*** (*Pipper nigrum*) - Black pepper(marich) contains principal monoterpene compounds in the pericarp were α-pinene (9.2%), 2-β-pinene (14.3%), δ-3-carene (21.5%) and DL-limonene (18.8%), and the primary sesquiterpenes were α-copaene (5.1%) and caryophyllene (17.2%). Drug shows immune-modulatory, analgesic, antiplatelets, antioxidant, antihypertensive, anti-asthmatic, antipyretic, anticancer, antiinflammatory, antidiarrheal, anxiolytic, antidepressants, antispasmodic, antifungal, antiulcer, anti-metastatic, antiapoptic, antibacterial and anti-amoebic properties. The concentrate of drug and its phytochemicals like piperine, control the balance of the cytokines generation of Th1, Th2, Th17, and Treg cells, downturn the aggregation of inflammatory cells, blocks the expressions of GATA3, IL-4 and 6, IL-1b, IL-17A and TNFα, increase INF-gamma and IL-10 secretions in Broncho-alveolar lavage fluid and upsurge macrophage activation and B and T cell propagation[1,52].

***Neem*** (*Azadirachta indica*) - Commonly called as Neem or margosa tree contain azadirachtin, nimbin, nimbidin, azadirachtol and arachidic acid etc. as major chemical constituents[2,53]. It shows anti-inflammatory, antimicrobial and immunostimulant activity[53,54]. The aqueous extract of neem bark and leaf also possesses anticomplement and

immunostimulant activity. Plant selectively activating the cell-mediated immune mechanisms when used as "Neem oil"[55].

***Garlic*** (*Allium sativum*) - Lahasun or Garlic contain alliin, vitamins (folic acid, niacin, riboflavin, thiamine, vit.c), allicin, allisatin etc. as major chemical constituents. It is mentioned as Rasayana in ayurvedic classics and it's indicated for Shwasa, Kasa etc[2]. Higher concentration of sulfur compounds of garlic which are answerable for its medicinal effects. Garlic has been scientifically observed to have its antiinflammatory, antioxidant, antiviral, antifungal, antibacterial, antistress, anticancer, cardiovascular disease, antidiabetic property, immunity booster and antimicrobial effects etc[56,57].

***Shankhpushpi*** (*Evolvulus alsinoides*) - The whole plant of shankhpushpi, used in ayurvedic practices as a brain tonic, febrifuge and as a antiphlogistic to treat scrofula and nervous debility[58]. Though many therapeutic action of shankhpushpi, there is lack of information on the immunoalternative effects of phytoconstituents of plant as anti-inflammatory agents[58,59].

***Tamal Patra*** (*Cinnamomum tamala*) - Indian bay leaf, also known as tezapatta, Malabar leaf, rich in monoterpenes (65.6%) containing (Z)-b-ocimene, trans-sabinene hydrate, α-pinene, myrcene, β-sabinene and sesquiterpenes (32.9%) containing eugenol, germacrene A and a-gurjunene as major constituents and flavones such as quercetin and its derivatives[60].

The leaves of *Cinnamomum tamala* clinically used as diuretic and antidiabetic, but no reports are available towards immunomodulating property[60]. Plants hexane extract was given to rats via oral route for 10 days and delayed type of hypersensitivity, antibody production against sheep red blood cells (SRBCs) and concanavalin A mediated proliferation of lymphocytes were evaluated[61]. Further on 30 days treatment, change in body weight, thymus weight, spleen weight, bone marrow cellularity and changes in hematological parameters were observed. Further studies reported its effect on lymphocyte functions with reference to cell mediated and humoral immunity[61].

**Table 1:** Brief description of herbal plants mentioned above:

| Name | Biological source | Phyto-constituents | Uses | Reference |
|---|---|---|---|---|
| Ashwagandha | Ashwagandha consists of the dried stem bases and roots of *Withania somnifera,* belongs to *Solanaceae* family. | Withaferin A, withanone, withasomnine, triterpene lactones – withanolides, withaferinA steroidal lactones, tropine, and cuscohygrine | Antistress, neuroprotective, antitumor, anti-arthritic, analgesic and anti-inflammatory, immunomodulator | [2,25,26] |
| Tulsi | Tulsi consists of fresh as well as dried leaves of *Ocimum sanctum*, from family *Labiatae*. | Oleanolic acid, rosmarinic acid, ursolic acid, eugenol, linalool, carvacrol, β- elemene, β caryophyllene, germacrene | Antibacterial, antifungal, adaptogenic, antiviral and immunomodulation activities | [1,2,27,28] |
| Ginseng | Ginseng consists of dried roots of *Panax ginseng* and other species of *Panax*, from the family *Araliaceae*. | Ginsenosides, alkaloids, polysaccharides, glucosides, phenolic acid | Antioxidation, antiinflammatory, vasorelaxation, antiallergic, antidiabetic, and anticancer | [29,30] |
| Chirata | Consist of entire herb of chirata, *Swertia chirata*, belonging to family *Gentianaceae*. | Sawertiamarine, xanthones, mangeferin, amarogenitine, balanophonin, oleanolic acid, maslinic acid, and sumaresinolic acid, swerilactones | Used for fever, constipation, immunomodulatory agent, upset stomach, loss of appetite, intestinal worms, skin diseases, and cancer | [31,32,33] |
| Turmeric | Turmeric consists of the dried rhizomes of *Curcuma longa*, belonging to family: *Zinziberaceae*. | Curcuminoids, curcumin, demethoxycurcumin, bisdemethoxycurcumin, turmerone, germacrone, atlantone, zingiberene | Prevent heart disease, Alzheimer's and cancer, anti-inflammatory and antioxidant, improve symptoms of depression and arthritis and immunomodulator | [2,34,35] |
| Ginger | Dried rhizomes of the *Zingiber officinale*, belonging to family *Zingiberaceae*. | Zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, α-curcumene, gingerol, paradols, shogaol | Anti-inflammatory, anticholinergic, immunity booster activity, antihistaminic, antioxidant activities | [1] |
| Giloy | Herbaceous vine of the *Tinospora cordifolia*, belongs to family *Menispermaceae*. | Alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds | Immunomodulatory activity, antioxidant, antidiabetic, Jaundice, rheumatism, urinary disorder, skin diseases, diabetes, inflammation, radioprotective properties, | [2,36,37,42] |
| Amla | Amla consists of dried and fresh fruits of the plant *Emblica officinalis, Euphorbiaceae* famliy. | Gallic acid, ellagic acid, emblicanin A & B, ascorbic acid and quercitin | Diuretic, laxative, hair tonic, to prevent peptic ulcer, analgesic, antitussive, antiatherogenic, cardioprotective, gastroprotective, antianemic, antihypercholesterolemic, hepatoprotective, antidiarrheal and neuroprotective property | [3,38,39,40] |
| Aloe vera | Aloe is dried juice from the bases of the leaves collected by incision, of various species like *Aloe perryi*, *Aloe vera* or *Aloe barbadensis* and *Aloe ferox*, from family *Liliaceae*. | Anthraquinone glycoside derivatives, phenylpyrone derivatives, flavonoids, phenylpropanoids, coumarins, phytosterols, naphthalene analogs, lipids, and vitamins | Wound healing, antiinflammatory, anticancer, antidiabetic, antiulcer, antihyperlipidemic activity, antioxidant, immunomodulatory action | [40] |
| Liquorice | Liquorice consists of subterranean peeled and unpeeled stolons, roots | Glycyrrhizine,liquiritic acid, glycyrretol, liquiritin, isoliquiritin,asparagin, traces of | Antibacterial, antitussive, antiinflammatory, antioxidant, antiviral, antitumor, | [2,41] |

| | | | | |
|---|---|---|---|---|
| | and subterranean stems of *Glycyrrhiza glabra*, belonging to family *Leguminosae*. | tanin. | hepatoprotective, and immunomodulatory activities | |
| Brahmi | Brahmi is the whole fresh or dried herb of *Centella asiatica*, belonging to *Umbelliferae* family. | Hersaponin, D-mannitol, apigenin, monnierasides I, II, III, plantainoside B, cucurbitacin, brahmine, nicotine, herpestine | Antiinflammatory, antidepressant, antimicrobial, brain tonic, memory enhancer, hepatoprotective, antioxidant, immune system boosting agent | [2,42] |
| Ajowan | Ajmo is the dried ripe seeds of *Trachyspermum ammi*, from *Apiaceae* family. | Thymol, p-cymene, γ-terpinene, carvacrol, α-pinene, β-pinene, dipentene | Antifungal, antioxidant, immunomodulator, ntifungal, antiviral, antinociceptive, hypolipidemic, antihypertensive, antispasmodic, broncho-dilating actions, antilithiasis, abortifacient, antitussive effects | [43,44] |
| Shatavari | Shatavari is derived from dried roots and tuberous roots of *Asparagus racemosus*, from family *Liliaceae*. | Steroidal saponins, isoflavones, asparagamine, racemosol, polysaccharides | Immunomodulatory, antidiabetic, antioxidant, anticancer, hepatic, and neuroprotective effect, antimicrobial, antiurolithiatic, aphrodisiac, memory enhancing the property, antitussive effect | [45,46,47] |
| Punarnava | It consist of whole herb/roots of *Boerhavia diffusa*, belonging to family *Nyctaginaceae*. | β-Sitosterol, sitosterol, palmitic acid, tetracosanoic, hexacosonoic, arachidic acid, urosilic acid, hentriacontane, triacontan-ol | Treatment of cancer, jaundice, immunity enhancer, antiinflammatiory, ophthalmic, enlargement of spleen, abdominal pain and as an antistress agent | [48,49] |
| Pippali | Pippali is the dried ripe fruits and roots of *Piper longum,* belonging to family *Piperaceae.* | Piperine**,** starch, protein and alkaloids, volatile oils, saponins, carbohydrates, amygdalin | Anti-irritant, immunomodulatory action, analgesic, anti-asthma and bronchitis | [2,47,50] |
| Cinnamon | Cinnamon is dried inner bark of coppiced shoots of *Cinnamomum zeylanicum*, from *Lauraceae* family. | Cinnamaldehyde, cinnamate, cinnamic acid, and numerous essential oils, eugenol | Antioxidant, antiinflammatory, antidiabetic, immunomodulator, antimicrobial, anticancer, lipid-lowering, and cardiovascular-disease and in neurological diseases | [1,51] |
| Black pepper | Fruits of *Piper nigrum*, also known as black pepper is the member of *Piperaceae* family. | Pipercide, N-trans-feruloytyramine, Methylenedioxcycinnamic, Piperettine, Ascorbic acid Trichostachine, Citronellol, Serine, Cryptone, Piperonal, Camphene, Pipecolic acid, Cryptone, Piperonal, Threonine, Carotene, Piperine | Immunomodulatory, anti-oxidant, antiplatelets, antihypertensive, anti-asthmatic, antipyretic, analgesic, anticancer, antiinflammatory, antidiarrheal, antispasmodic, antidepressants, hepatoprotective, antiapoptotic, anti-metastatic, antimutagenic, antibacterial action | [1,52] |
| Neem | Neem consists of the fresh or dried leaves and seed oil of *Azadirachta indica*, belonging to the family *Meliaceae*. | Nimbolinin, azadirachtin, nimbin, nimbidol, nimbidin, sodium nimbinate, quercetin, gedunin, salannin | Used in leprosy, eye disorders, bloody nose, intestinal worms, stomach upset, loss of appetite, skin ulcers, cardiovascular disease, fever, diabetes, antiinflammatory, antimicrobial, antifungal, immunostimulant activity | [2,53,54,55] |
| Garlic | *Allium sativum,* is the ripe bulb of Lahsun belonging to family *Liliaceae*. | Organosulfur compounds, such as allicin, diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), E/Z-ajoene, S-allyl-cysteine sulfoxide (alliin), S-allyl-cysteine (SAC) | Antioxidant, antiinflammatory, anticancer, treatment for cardiovascular diseases, immunity booster, antimicrobial effects and antidiabetic activity | [2,56,57] |
| Shankhpushpi | It consists of the whole plant of Convolvulus pluricaulis, belonging to Convulvulaceae family. | Shankhapushpine, convolamine, convoline, convolidine, convolvine, confoline, convosine | Febrifuge, as a brain tonic to treat nervous debility, immunomodulatory and antiinflammatory activities | [58,59] |
| Tamal patra | Tamala patra consists of dried mature leaves of *Cinnamomum tamala*, belonging to family *Lauraceae.* | Eugenol, cinnamaldehyde, linalool, trans sabinene hydrate, β-ocimene | Cold, cough, allergy, headache, scalp infection, asthma, other respiratory problems, abdominal pains and discomfort, heart diseases, immunity enhancer, arthritis, gout, antiinflammatory activity | [60,61] |

**CONCLUSION**

This review on immune system boosting with the help of herbal plants is a potential resource for the treatment of COVID-19 diseased patients. Since, SARS-CoV-2 has a high rate of mutagenesis rate, so it has a big challenge for the researchers to find a solution for this deadly pandemic. These SARS-CoV-2 virus mainly damage immune system homeostasis and alters immune regulatory mechanisms. So, Ayurveda

recommends prophylaxis measures for respiratory diseases that may have potential role in COVID-19 disease prevention. Various secondary metabolites(alkaloids, glycosides, saponins, coumarines, flavonoids, sterols, etc.) of above herbal plants exhibits antiviral, immunomodulatory, antioxidant, antiinflammatory, antiatherosclerotic as pharmacological properties, pretend to be efficient in immunity regulation for the avoidance and minimization of COVID-19 viral disease complications. As there is inadequacy of enough indications on definite benefits of the above herbal plants in coronavirus disease, there is possible requirement to prove the effectiveness of these potential drugs with considerable pharmacological, toxicological, biotechnological and clinical research.

**Conflict of Interest**

None declared.

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