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Ayurvedic Immuno Booster: Is it Myth or Reality in COVID-19 Pandemic

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ABSTRACT

Ayurveda Immune boosters (AIB) are Rasayana drugs which increase the number of white blood cells and train them to fight against microbes causing diseases. Some of them kill microorganisms, increase immunoglobulin, repair of DNA of an inflamed cell, increase Agni, and conditioning the gut to increase the beneficial gut microbiota. This review aimed to generate scientific evidence for Ayurveda Immune boosters (AIB) are effective to prevent and cure COVID-19 infection or it is a myth through Ayurveda and modern literature review. The properties of Rasayan are reviewed from Ayurveda Literature. The immunopharmacology, mechanism of immuno-booster and Rasayana herbs are reviewed from current medical literature for its subclinical and clinical evidence. Ayush kwatha and single herb like Guduchi (500-1000mg) extract, Aswagandha powder (3-5gm), and Haridra milk/gargling recommended as AIB by the Ministry AYUSH are safe and effective for prevention and cure of COVID-19 with sufficient preclinical and some Randomised clinical trials (RCT) evidence. So, the myth of Traditional Ayurveda herbs won't boost our immunity to the virus is not true rather Ayurveda Medication (AIB) can boost our immunity to fight against COVID-19. More RCT evidence is required for clinical practice.

Key Words: Ayurveda Immuno booster (AIB), Rasayana, Ayush kwatha, Guduchi, Aswagandha, Haridra

INTRODUCTION

In the COVID-19 pandemic situation, Immuno -boosting is a matter of dialogue among common citizens and mostly appearing in social, press, and electronic media. Common people want to use it with a high expectation for prevention and cure corona virus1. Therefore, there is an increasing demand for Ayurvedic Immuno-booster (AIB) to strengthening Immuno system to prevent coronavirus infection rather than treating existing diseases. Looking at the demand in India, several initiatives have been taken to utilise the vast potential of Ayurveda in this pandemic.[1,2] The Ministry of AYUSH has released a set of guidelines for boosting immunity and measures for self-care by using Ayurvedic principles. Further, the Indian Prime Minister in his address to the nation also advised using Ayurveda medicines for improving immunity against COVID-19. The demand for the AYUSH system across the country has increased and has also been put on alert for being called anytime to serve the nation.[2] Unfortunately, the idea that Ayurveda pills, preparations, functional foods, or wellness yogic habits can provide a shortcut to a healthy immune system is a myth. Many authors enumerated that the concept of "boosting" your immune system doesn't hold any scientific meaning.[3] But a study on 9,000 US children has shown that the administration of some complementary therapies, including chiro-practice and other shorts of alternative medicine (excluding multivitamins/multi-minerals) is related to a lower uptake of influenza vaccine.[4]

Immunity is a natural protective mechanism to protect from exposed harmful pathogens and environmental pollutants that affect the health status and homeostasis of an organism. This is maintained through a chain of networks of cells, tissues, organs, and biochemical mediators generated to defend the organism against any foreign invaders that threaten the integrity of the organism. One of the key features of immunity is to recognise its cell or tissues (self) and rejection of foreign protein molecule or microbes of the environment[5]. In the past two decades, epidemiological data have provided evidence of an increase in immunological diseases, therefore a new branch of pharmacology i.e Immuno-pharmacology developed, and a new group of molecules in immunotherapy is called Immunomodulators.[5,6] Immuno-modulators are a

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specific group of molecules that suppress the immune response or stimulate the immune cells in immune-mediated disorders and infection. The immunosuppressive drugs are hugely used to inhibit the immune response in many immune-mediated diseases (Organ transplant and Autoimmune diseases) whereas immunostimulatory drugs are used to prevent or cure the infection. The synonyms used for immune stimulants are Immuno booster/buster. Immuno boosters are vitamins, minerals, probiotics, functional food as well as traditional medicines and approaches to stimulate the immune system to prevent and cure diseases.[6,7] However, the concept of Vaccine is a well-recognized and effective way of Immuno booster to prevent infection. On the contrary, Ayurveda is a live traditional system of medicine with an unbreakable practice for 3000 years. Its principles and its approaches including oral administration of preventive drugs, herbs, formulae, decoction, indoor herbal medicine fumigation, etc. were recommended for effective prevention and treatment whenever the emergent of new disease[7]. Rasayana is one of the main branches of eight specialities (Astanga Ayurveda) which can enhance longevity, memory intelligence, freedom from disorder, youthfulness, the excellence of lustre, complexion, and voice, optimum of physique and sense organs, mastery over phonetics, and brilliance. These are health-promoting and rejuvenating procedures to prevent and cure diseases by enhancing physical strength (Bala), energy (Urja), Immunity (Vyadhi khamatwa), and mental power.[8] Immuno boosting study was concluded to be commercially biased without scientific evidence.[9] In this context, new and innovative approaches to Ayurveda Immuno boosters are to be studied for more effective prevention and treatment of infectious diseases special reference to COVID-19 as Ayurveda has vast literature that would represent some inspiration.[8,9]

The properties of Rasayan are reviewed from Ayurveda Literature. The immunopharmacology and Rasayana herbs are reviewed from current medical literature for its subclinical and clinical evidence.

IMMUNO SYSTEM AND ITS RESPONSES

The immune system is the network of cells, tissues, organs, and biochemical mediators that work together to protect the body. The immune cells are phagocytic cells and lymphocytes. Phagocytic cells are large white cells (monocytes, macrophages, mast cells, and neutrophils) are the most prevalent cells that can engulf and digest foreign organisms. The second most abundant cells are lymphocytes which are distinguished as B and T cells. Again, helper T cells are regulating the function of T cells whereas cytotoxic T cells destroy the infected cells or cancer cells. Natural killer cells destroy abnormal cells/cancer cells. The primary lymphoid organs are bone marrow and thymus and secondary lymphoid organs lymph nodes, spleen, tonsil, and payer's patches in the small intestine. Complement is also a series of proteins worked together with antibodies. The chemical messenger of the immune system is a cytokine. The cytokines that release T and B cells are Lymphokines whereas monokines are secreted from monocyte and macrophages. Cytokines encourage cell growth, promote cell activation, destroy target cells. The cytokines are Interferon, Interleukin, chemokines.[10]

Immuno response is traditionally classified as innate and adaptive immunity. Innate immunity is a short-term response that includes phagocytic cells, complement system, and receptors (TLRs, PPPs), whereas adaptive immunity is long term response that includes antigen-specific system mediated through memory cells and their specialised receptors. It is also known to be acquired as a specific antigen strategically used to create an immune response. Innate immunity recognises the infection and alerts the adoptive system through antigen, MHC, and cytokine. The total immune response worked through well recognised humoral and cell-mediated immune components. The moral response or antibody-mediated response starts from phagocytosis to the huge production of an antibody by plasma cells to memorize the specific antigen for quick mobilization of the system in later life. The cell-mediated immune response started with the recognition of antigen, secretion of lymphokine to stimulate T & B cell growth, enhance the macrophages to engulf and destroy the microbes.[11,12]

Immuno system does remarkable work to defend against diseases causing microbes, but sometimes it fails due to age, poor nutrition, environmental pollutants, organ damage/ dysfunction, and unhealthy lifestyle.[13]

IMMUNO RESPONSE AGAINST COVID-19

The invasion of coronavirus and immunopathology of COVID-19 are associated with host immunity. The spike of glycol protein (S Protein) on the virus envelops binds to its receptor, angiotensin-converting enzyme 2 (ACE2), on the surface of human cells. Innate immunity is the first line of defence against virus invasion. The identification of pathogen-associated molecular patterns, such as RNA & uncapped m RNA results in subsequent cytolytic immune responses, mainly through the type I interferons (IFN) and natural killer cells. Adaptive immunity also plays a crucial role in viral clearance via activated cytotoxic T cells that destroy virus-infected cells and antibody-producing B cells that focus on virus-specific antigens. Patients with COVID-19, especially those with severe pneumonia are reported to possess significantly lower lymphocyte counts and higher levels of plasma concentrations of a variety of inflammatory cytokines like IL-6 and tumour necrosis factor (TNF). Another study reported that CD4+ T cells, CD8+ T cells, and natural killer cells were reduced in severely ill patients compared with

those with mild disease symptoms. Moreover, a significant reduction of CD4+ T cell and CD8+ T cell counts in the peripheral blood was also observed in a patient who died in Covid 19 infection. The pro-inflammatory subsets of T cells, including IL-17-producing CCR4+ CCR6+ CD4+ (T-helper 17 or Th17) cells and perforin and granulysin-expressing cytotoxic T cells were remarkably increased, which could be quite responsible for the severe immune injuries in the lungs of this patient.[13,16] Antiviral immune response is vital for the elimination of virus by overproduction of inflammatory cytokines which damaged the host tissues and aberrant immune-activation is called a cytokine storm. Cytokine storm is found in COVID-19 which is a serious explanation of disease progression and eventual death. They also found that increased plasma concentrations of both Th1 (e.g., IL-1β and IFNγ) and Th2 (eg. IL-10) cytokines. Patients admitted to the intensive medical unit (ICU) had higher plasma concentrations of IL-2, IL-7, IL-10, granulocyte-colony stimulating factor, IFNγ-induced protein-10 (IP-10), macrophage chemoattractant protein-1, macrophage inflammatory protein 1α, and TNF compared to those not admitted to ICU. Secondary haemophagocytic lymphohistiocytosis (sHLH) might be related to severe COVID-19 cases.[17] HLH is a disease condition manifested by an uncontrolled cytokine storm and expansion of tissue macrophages or histiocytes that exhibit haemophagocytic activity. HLH can result from genetic defects in cytolytic pathways (familial or primary HLH) or other diseases like infection, malignancy, and rheumatic disease (sHLH). The proposed laboratory tests include serum ferritin, total lymphocyte or leukocyte counts, platelet counts, erythrocyte counts, and sedimentation rates that could be used to screen patients to exclude the high risk of hyper inflammation in small setup.[14]

MECHANISM OF IMMUNO BOOSTER

The impact of Rasayana drugs as Immuno boosters in the COVID-19 situation can be studied from the vast pharmacopoeia of Ayurveda which is also a matter of research. The mechanism of immune-boosting properties of Rasayana drugs is not established. Rasayana drugs have a profound effect on the body system so Immuno booster properties can be discussed as,

Rasayana drugs increase digestive power (Agni)

Rasayana drugs increased the enzymatic reaction to increasing digestion and assimilation, and clear the microchannels to provide adequate and appropriate nutrition for cellular function including immune cells. Further, the immune system is activated during infection which requires more nutrients for a good immunological outcome. Diminished digestive power (Agni) leads to the production of ama (undigested food) which can create a subclinical situation for the onset of infection or sopha (Chronic infection).[15]

Rasayana drugs conditioning the gut

Maximum immune cells in the human body are found within gut-associated lymphoid tissue (GALT), reflecting the crucial role of these immune tissues in maintaining host health. Several microbes with massive antigenic stimulation are present in ingested food, that provide us with strong protective immunity against invasive pathogen and tolerating various food proteins. GALT can produce a variety of sensing and effector immune functions to combat those foreign insults. Dendritic cells and M cells within the gut content, while plasma B cells within the lamina propria produce IgA, protecting pathogenic organisms. Peyer's patches are rich in immune cells, allow for communication networks between immune cells residing within the GALT, propagation of signals to the wider systemic immune response, and the recruitment or efflux of immune cells[16]. The gut microbiota will give a signal to produce antigen to interact with the systemic immune system. The human gut microbiome will provide antigens and signals with the potential to interact with resident and systemic immune cells within the gut lumen itself. Several Rasayana drug interventions have demonstrated the capacity to improve gut health or to reduce gut inflammation. Polyphenols in Rasayana drugs modulate the human gut microbiome and thereby promote the growth of beneficial Bifidobacteria and Lactobacillus while inhibiting the growth of undesirable gut microbes. The bioactive compounds of *Triphala* are elicited by gut microbiota to generate a variety of anti-inflammatory compounds.[17,18] Again, there are more ammonia generated bacteria and lactobacillus bacterial are less in constipated patients.[18] Most of the Rasayana drugs have bowel clear property.[19,20]

Rasayana drugs reduce chronic systemic inflammation

Chronic systemic inflammation is the key underlying feature of a wide range of chronic non-communicable disease conditions such as cardiovascular disease, stroke, and autoimmune disorders. This chronic inflammation is positively correlated with ageing. immunotolerance and reduced immune response, and other co-morbidities (e.g., obesity, cardiovascular disease, insulin resistance) which is related to bad outcomes of any infection and sepsis. A study in healthy adult found that risk factor of chronic systemic inflammation is increased with increased age irrespective other risk factors such as obesity, hypertension and blood lipids[21]. Histamine, bradykinin, neuropeptides, prostaglandins, thromboxane, leukotrienes, and platelet-activating factor stand out among the non-cytokine/chemokine mediators that are involved in the inflammatory response. Chronic inflammation involves the progressive changes in inflammatory cells as well as in

tissue destruction and repair due to the on-going inflammatory process and loss of immune response due to the failure of h toll-like receptors (TLRs) of innate immunity.[22] The active components from some of Rasayana plants that can modify inflammatory pathways are linked to chronic inflammatory diseases.[23]

Rasayana drugs can produce immune cells and Cytokine

Rasayana drugs are inherently non-specific as they enhance the body's resistance to infection. It acts through innate as well as adaptive immune response.[24] Some of the Rasayana drugs improve phagocytic function by increasing PMN count, T helper cells, and NK cells.[25,26] It also increased immunoglobulin proteins in the intestinal tract to combat foreign invaders. Rasayana also modulation of mono-amine function and reduction of stress, anxiety, and depression which increase the cytokines through psycho-neuro-Immuno mechanism.[27]

Rasayana drugs can target COVID-19 directly

Rasayana drugs can damage the coronavirus structure by binding the spike protein, E protein, and N protein. It can act by inhibiting virulence by binding Nsp1, Nsp 3c, and ORF7 protein. Most of the Rasayana drugs act through inhibiting RNA synthesis and replication by binding the active site of COVID-19 proteases.[28,29]

Potential Immuno booster from Rasayana drugs

Scientists realised the need for Ayurveda which mentioned epidemic management and defines immunity as the ability to preventing and arresting the progression of the disease to maintain homeostasis. The Ayurveda has emphasized building strength in the mind and body to cope with various environmental and biological stressors, including infection. Similar to innate and acquired immunity, the Ayurveda concept of immunity (Bala or strength) is classified as natural (Sahaja), chronobiologic (Kalaja), and acquired (*Yuktikrut*). Several treatment options are available in Ayurveda for enhancing immunity against respiratory illnesses, these include certain immuno-stimulant(Rasayana), local and systemic interventions.[29] The Ministry of AYUSH, Government of India with an interest in health promotion in the COVID-19 outbreak situation recommended *Ayush kwatha* which consists of holy basil leaf, cinnamon bark, ginger rhizome, black pepper mostly used in Indian kitchen.[30-32] Guduchi (500-1000mg) extract, Aswagandha powder (3-5gm), and Haridra milk/gargling are also recommended as single drug immuno-booter by Ministry AYUSH.[33,34] *Makardwaja* is gold-containing mercurial preparation used for vigour and vitality.[35] The mechanism of action of different potent Ayurveda drugs is described in Table 1.

Table 1: Potential Rasayana drugs having Immuno boosting properties and its mechanism

Name of Rasayana	Latin Name	Mechanism of Immuno boosting
Tulsi	Ocimum sanctum	Inhibit replication of COVID-19 supported with its immune-modulatory feature and ACE II blocking properties. Ocimum sanctum containing, Tulsinol (A, B, C, D, E, F, G) and dihydrodieuginol-B inhibit SARS Coronavirus Main Protease and Papain-like Protease[34]
Dalchini	Cinnamomum zellenicum	act as a strong regulator of monocyte/macrophage-mediated immune responses, possibly by the induction of thiolation at cysteine residues in the target enzyme (PDK1 or PI3K)[36]
Sunthi	Zingiber officinale Roxb	The rhizome of Ginger and its main components like gingerols, schools, etc inhibit prostaglandin and leukotriene biosynthesis, inhibit cyclooxygenase and lipoxygenase activities, inhibits the synthesis of pro-inflammatory cytokines such as IL-1, TNF-α, and IL-8 without any significant effect in IL-6 levels[37]
Maricha	Piper nigrum Linn	The extract of Maricha and its constituents like piperine, regulate the balance of the cytokines production of Th1, Th2, Th17, and Treg cells, reduce the accumulation of inflammatory cells, inhibit the expressions of GATA3, IL-4, IL-6, IL-1β, RORγt, IL-17A and TNF-α, increase INF-γ and IL-10 secretions in BALF (Broncho-alveolar lavage fluid) and increase macrophage activation and T and B cell proliferation[38]
Guduchi	Tinospora Cordifolia	phagocytic activity of macrophages, production of reactive oxygen species (ROS) in human neutrophil cells[39] 2 It increased of proinflammatory cytokines such as IL-1β, IL-6, TNF-α, granulocyte monocyte-colony stimulating factor (GM-CSF)[40,41]

Table 1: ***(Continued)***

Name of Rasayana	Latin Name	Mechanism of Immuno boosting
Ashwagandha	Withania Somnifera	Aswagandha stimulated cell-mediated immunity, IgM and IgG titers reaching peak value with 30 mg/kg b.wt. Flow cytometric analysis of lymphocyte surface markers of T cells (CD_3(+), CD_4(+) and CD8(+)) and B cells (CD_{19}(+)) indicated prominent enhancement in proliferation and differentiation of lymphocytes. The extract selectively, induced type 1 immunity because it guided enhanced expression of T helper cells (Th)1 cytokine interferon (IFN)-gamma and interleukin (IL)-2 while Th2 cytokine IL-4 observed a moderate decline. Aswagandha useful applications against the intracellular pathogens and in the management of immune-suppressed diseases[42,43,44].
Haridra	Curcuma longa	Curcumin is an Ayurvedic plant extract with high safety and low toxicity such that people take it as a diet supplement, and growing evidence from preclinical studies demonstrates that it effectively inhibits viral infection, alleviates the severity of lung injury through offsetting the cytokine storm, inhibits subsequent fibrosis, and increases survival rates[45].
Makardwaja	Gold-containing Cinnamon	Makaradwja is gold-containing mercurial preparation can increase phagocytosis and cytokine production[46].

DISCUSSION

Ayurveda describes many drugs as *Rasayana* and *Ojovardhak*, which ae claimed to possess' immuno-stimulatory effect. Some of the Rasayans which have been subjected to scientific studies are found to possess immunomodulatory and anti-inflammatory effects. If our immune system is working properly then it protected from all dangers caused by microbes. If not, we suffer sickness and disease.[36,37] It is possible to intervene in this natural protective process to make our immune system stronger using immune boosters. Immune boosters work in many dimensions such as Ayurveda Immuno Booster can increase the number of white blood cells in the immune system, train them to fight against microbes causing diseases.[38,39] Some of them are killed microorganism, increase immunoglobulin, repair of DNA of inflamed cell.[40,41] The RCT's investigation showed the potential clinical improvement of herbal medication for COVID-19 in terms of Symptom score, WBC count, Lymphocyte count and CRP.[47] *Ayush Kwatha* and the other single herbs as advised by Ministry of AYUSH have excellent preclinical pieces of evidence (Table no-1). More research studies of Ayurveda formulations are registered for clinical trials.[48] The presenting herbs and their phytochemicals, flavonoids act directly in the priming of SARS-CoV-2 attachment proteins by the host and viral enzymes, and the release of HMGB1 by host immune cells.[46] The small observational study of Guduchi and Aswagandha have a good preventive effect on COVID-19. One of the therapeutic targets of anti-COVID-19 drugs is angiotensin-converting enzyme 2 (ACE2). ACE2 is the main functional receptor for CoV associated with COVID-19. Ashwagandha binds ACE2 effectively and the spike protein of CoV, thus enabling the virus to infect the epithelial cells of the host. The natural flavonoids have potential efficacy against COVID-19 through ACE2 receptor inhibition.[42-45] Herbal medicines as immuno-booster can be used in the battle of COVID-19 pandemic before the inoculation of vaccine. So the myth of Traditional Ayurveda herbs won't boost your immunity to the virus is not true rather Ayurveda Medication can boost your immunity to fight against COVID-19. *Ayush kwatha* which is consisting of holy basil leaf, cinnamon bark, ginger rhizome, black pepper and single herb like Guduchi (500-1000mg) extract, Aswagandha powder (3-5gm) and Haridra milk /gargling recommended as immuno-booter by the Ministry AYUSH are safe and effective for prevention and cure of COVID-19.

CONCLUSION

Ayush kwatha and single herb like Guduchi (500-1000mg) extract, Aswagandha powder (3-5gm) and Haridra milk /gargling are recommended as immuno-booter by the Ministry AYUSH are safe and effective for prevention and cure of COVID-19. More RCT pieces of evidence are required for common clinical practices.

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