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Antiviral with Immune Booster Therapy: Current concept for clinical care in Covid-19

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ABSTRACT

Objective: Objective of the article is to provide a brief overview of novel corona virus, discussing the role of immunity in the pathogenesis, analyzing the comparative efficacy of anti-viral vs. immune-enhancer medicines and propose a stepwise treatment methodology of both these groups of herbs for prevention as well as management of COVID-19. **Data Source:** Ayurvedic texts including *Brihatatrayi* (*Charaka Samhita, Sushruta Samhita & Astanga Hridayam*), *Laghutrayi, Nighantus*, published article in PubMed, Scopus, Science Direct, Google Scholar, AYUSH Portal, etc., were thoroughly searched for the compilation of information. **Review method:** Narrative and systematic methods for reviewing the literature and related published article was used **Discussion:** There is yet no proven drug for the treatment of COVID-19 and therefore presently medicines having substantial evidences are use for the treatment of COVID-19 on trial basis to assess best possible treatment. In this direction, this article provides a framework of treatment methodology according to *Ayurveda* for the prevention as well as management of COVID-19. **Conclusion:** The article provides details of anti-viral medicines and immune-boosting medicines described in *Ayurveda* and give the logistical approach for their sequential use to manage the disease.

Key words: Immunotherapy, Rasayana, Anti-viral herbs, Kalaja Bala, Cosmic immunity.

INTRODUCTION

What is Novel Corona Virus?

The novel corona virus was first reported from Wuhan city of China in December 2019 (as per WHO record) and is named as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (Corona virus Study Group). Novel corona virus belongs to the family Coronaviridae, suborder Cornidovirineae and order Nidovirales with a total of 39 species. Species of 2019-nCoV is Severe acute respiratory syndrome related

coronavirus (SARS-CoV-2) and its genus is Beta-coronavirus. Although species belonging to the family Coronaviridae are mostly enzootic i.e., affecting animals but COVID-19 is a zoonotic virus that infects humans. Until now, seven human corona viruses are discovered out of which two (NL63 AND 229E) belongs to alpha-coronavirus genus and rest (SARS-CoV, HCoV-HKU₁, SARS-CoV-2, MERS-CoV HCoV-OC43) belongs to beta-genus. The SARS-CoV-2 belongs to large RNA viruses having single stranded enveloped RNA which possess a positive-sense RNA genome with a 5'-cap structure and 3'-poly -A tail. It has four important structure proteins viz. membrane protein (M), envelop protein (E), spike protein (S) and Nucleocapsid protein required for regulating function and structure of SARS-CoV-2.^[1-5]

SARS-CoV-2 and SARRS-CoV shares sequence homology. Despite of this similarity, SARS-CoV-2 has marked difference in diagnostic methods and transmission efficiency. The distinguishing feature is probably due to the nucleotide changes in the spike (S) protein and its receptor-binding domain (RBD).^[6,7]

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Corona viruses are primarily associated with upper respiratory tract mild to moderate infections (URTIs) including common cold. But, SARS-CoV and MERS-CoV are corona viruses that may cause severe pneumonia in humans. Incubation period of COVID-19 is reported to be 2 weeks. During this period the symptoms develop slowly due to replication of virus in the lungs parenchyma forming lesions. Fever, cough, dyspnea, malaise, diarrhea are the common presenting Complaints.^[8,9,10] In few immunocompromised patients it may advanced to fatal complications like acute respiratory distress (ARDS) and severe pneumonia that requires artificial respiratory support (ventilator) to maintain life. New studies have shown that SARS-CoV-2 may even infect organs other than lungs like central nervous system (CNS) to produce neurological disease.^[11] It may even invade peripheral nerves (PN) and enter the CNS via the synaptic route and can destroy medullary neurons. Signs like headache, nausea and vomiting are indicative of possible neuroinvasion. As neuroinvasion in COVID-19 patients causes respiratory failure, management should aim to prevent entry of virus into brain.

SARS-CoV-2 and SARS-CoV have similar kind of receptors, receptor binding motif (RBM) and receptor binding domain (RBD). In the SARS infection the receptor binding motif of the structural protein gets attached to the Angiotension-Converting Enzyme 2 (ACE2) in the humans causing severe pneumonia and acute myocardial injury and chronic damage to the cardio-vascular system. The very first step to combat the SARS-CoV-2 infection is to prevent its entrance in the host cells. The point to be consider here is that although the host ACE2 protein does not change but as in HIV in which the capsid protein gp120 has 5 domains and five variable loops; it may possible that the capsid protein of SARS-CoV-2 has multiple domain and variable loop. SARS-CoV-2 has many distinctive features imparting its high virulence like presence of furin like cleavage site in the S protein giving it much higher strength for attachment with host receptor namely ACE-2.^[12] On the basis of its similarity with SARS-CoV it is assumed that SARS-CoV-2 also acquires the same path for getting entrance in the host cell.

Upon binding to the receptor, cellular transmembrane protease serine 2 (TMPRSS2) cleaves the S protein into S1 and S2 domains and induces conformational changes in SARS-CoV-2. This is followed by the insertion of the fusion protein into the membrane and membrane fusion occurs facilitating the entry of the virus into the cell.^[13] Cell entry is facilitated by host type- 2 transmembrane serine protease, TMPRSS2 through S protein. Once the virus enters into the cell, its polyproteins encoded for the replicase-transcriptase complex are starts synthesizing and virus synthesizes RNA via its RNA-dependent RNA polymerase. Structural proteins thus synthesized helps in completion of assembly and release of viral particles. As soon as the virus enters the human host cell, ADAM17 gene cleaved and shed ACE-2 into the extra-membrane space.

With the entrance of virus into the cell the ACE-2 gets cleaved and shed by the ADAM17 gene into the extra membrane space. Loss of ACE2 causes alveoli injury and increase pulmonary vascular permeability.^[14,15]

Role of Immunity in pathogenesis

Available data shows that about 80 % COVID-19 infected patients are having mild or no symptoms, 15% may develops severe illness and only 5% required ventilator and are critically ill.^[16,17,18] This data, clearly reveal that immunity plays important role in the prevention of disease.

Based on the research articles published in the electronic media (searching word: pathogenesis of COVID-19 in Google search, PubMed central, science direct, Elsevier, etc.), it is found that COVID-19 disturb the immune homeostasis.^[19,20,21] Viral protein acts as antigen and provokes uncontrolled immune hypersensitivity response as evidence by “cytokines storm”, dysregulation of Th1/Th2, etc., which in turn causes massive alveolar damage and multi-organ failure.^[22,23] Delayed innate immune response in recognizing the virion causes delayed adaptive immune response in the formation of neutralizing antibodies (IgM & IgG). These cause unchecked viral replication and further worsen the disease. Thus, regulation of immune response is required to eliminate the virus and

to prevent disease progression to severe stage. Modulation of immune responses is known to be useful in reducing disease aggravation and mortality rate. Before we discuss the methods for immune-regulation, it is necessary to have a brief outlook about the possible mechanism for immune dysregulation caused by corona-virus.

A. Breaching of Innate Immunity^[24]: Possible causes

- **Pattern Recognition Receptors:** Epidermal dysfunction through defect in pattern recognition receptors causes malfunctioning of epidermis resulting in inadequate host response to a pathogen or a persistent inflammatory state.
- **Ciliary dysfunction:** Cilia present over gastrointestinal and respiratory mucosa may also have malfunctions resulting in sluggish movement of mucous, thereby trapped virus is not expelled and its retention gives virion ample chance to invade the host cell and provoke immune response.
- **Intraepithelial lymphocytes dysfunction:** Skin and mucosal epithelium have intraepithelial lymphocytes. These lymphocytes are primarily gamma/delta T type lymphocytes (LT- $\gamma\delta$), and are involved in the host defense through cytokine production, phagocyte activation and also in destruction of infected and tumor cells. Along with T lymphocytes, skin and mucosal epithelium also have a subpopulation of B lymphocytes that secretes immunoglobulin M (also known as natural antibodies) as a part of immune system. Failure of this defense system allows the virus to invade host cell.

Immunotherapy

Presently, numbers of asymptomatic COVID-19 cases are increased markedly. This can be taken as positive development as it indicates that immune system has developed enough neutralizing antibodies that neutralize the biological effect of virus. But as the virion (antigen) is present in the circulation the PCR for corona virus detect the genetic material of virus and the individual test positive for COVID-19. Though, the

individual himself acts as latent carrier and spread disease to others. Therefore, therapeutic strategies are requiring targeting pre and post exposure management.

There are several ways by which immunity can be used to treat disease. Immunotherapy can be used to stimulate or amplify the immune response and is known as activation immunotherapies.^[24] Plant metabolites like saponin may act as immunologic adjuvant having the ability to stimulate, augment and potentiate the cell mediated immune system as well as enhance antibody production and have the advantage that only a low dose is needed. There may be several ways in which the plant products act as immunomodulators like – (1) potentiate the immune response (2) increasing the immunogenicity of weak antigens (3) stimulating cell mediated immunity (4) modulating antibody avidity, specificity, isotype or subclass distribution (5) promoting the induction of mucosal immunity (6) enhancing immune responses in immunologically immature or senescent individuals. Plant products may act as adjuvants that influence the duration, titer, isotype, and avidity of antibody, and affect the properties of cell-mediated immunity.^[25]

Concept of Immunity in Ayurveda

Ayurveda defines immunity as a power to resist disease and is outcome of biological homeostasis of all *Dhatus* (building material of the body i.e., various types of cells in multicellular organism). There are three words to be understood in context of immunity in *Ayurveda*-

- **Vyadhikshamatva:** In broader sense it is similar to the word immunity of concurrent medical science.
- **Oja:** *Vyadhikshamatva* depends upon *Oja*.^[26]
- **Bala:** Physical entity for assessment of *Vyadhikshamatva*.

According to *Ayurveda*, there are three types of *Bala* viz. (1) *Sahaja* (innate immunity) (2) *Kalaja* (cosmic immunity) and (3) *Yuktikrita* (adaptive immunity).

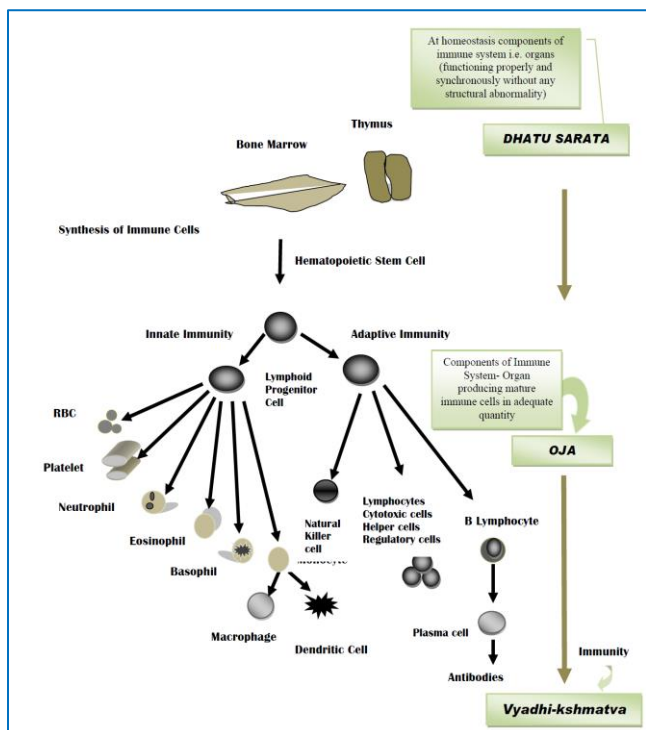
A. Sahaja Bala - It is an inherent strength of an individual that depends upon the strength of particular species or family. This is non-specific type of immunity

and is same for each individual within species. It depends upon the memory coded in the genes based on the nature and lethality of threat encountered during evaluation. This component of immunity can't be modified or it remains unchanged. Its function is to resist invasion of any unwanted biological entity in biological multicellular organism and is responsible for allergic and autoimmune diseases.

B. Kalaja Bala - It is depends upon season and age. At particular time viz. in first half of year it may be declining whereas in second half it may be increases and is most vulnerable during the transmission period between two seasons. This can be fortified with sun-exposure in exponential way (not evidenced with research studies). Its function is to prevent change in the internal environment of multicellular organism caused by change in cosmos. Diminution in this type of immunity is responsible for outbreaks of epidemics.

C. Yuktikrita - This is acquired immunity that can be enhances, modulate or even suppress by using medicines, modulating diet and life style. This component of immunity is specified for fighting against infection. Its diminution causes immunosuppressive diseases such as HIV, tuberculosis, etc.

Fig. 1: Concept of Immunity in Ayurveda



In the present context, it is *Kalaja* and *Yuktikrita Bala* which are compromised and produces COVID-19 pandemic. As both these types of immunity can be enhanced with the help of medicines, diet and life-style therefore it is necessary to get knowledge about these simple remedies to improve the immunity. Medicines which are used for the enhancement of immunity are known as *Rasayana* drugs. Following is the description of few *Rasayana* herbs and polyherbal compounds along with their pharmacodynamic properties that can be used for improving immunity against corona virus infection-

Table 1: Description of Rasayana Herbs

Name of the herb	Pharmacodynamic Properties
<i>Giloy</i> (<i>Tinospora cordifolia</i>)	<p>Immunomodulatory activity^{[27],[28]}:</p> <ul style="list-style-type: none"> Anti-tumor effects: TC stimulates splenocytes and macrophages enhance nitric oxide (NO) production, production of reactive oxygen species (ROS) and increases phagocytic activity of macrophages. Effect on immune cells: up-regulates IL-6 cytokines, activates T cells and B cells proliferation^[29], influences cytokines productions, activates immune effector cells and thereby modulates mitogenicity. <p>Anti-toxic effect:</p> <ul style="list-style-type: none"> TC is having potential anti-oxidant activity due to which it acts as anti-toxin. It exhibit excellent free radical scavenging property against aflatoxin- B1induced nephrotoxicity. Its antioxidant property is also documented

against lead nitrate induced liver toxicity, it is also found to be beneficial in combating cyclophosphamide induced toxicities.^[30]

Anti-viral activity:

- Anti- HIV activity: TC inhibits HIV protease, it interferes with gp120/CD4 interaction and inhibits HIV reverse transcriptase.^[31]
- TC aqueous extract also found to be effective in inhibiting infectious bursal disease of chicks caused by infectious bursal disease virus due to its immunomodular activity.^[32]
- Berberine (B₁) an isoquinoline alkaloid present in TC is reported to inhibits release of inflammatory mediators in viral pneumonia and have anti-viral activity against influenza virus.^[33] Berberine is also reported for having antimalarial, antiprotozoal and antimicrobial activities.^[34]
- And it is reported for having antibacterial, antipyretic, antitumour and activities.^[33] Berberine is reported for having antiviral effects on the influenza virus. It inhibits viral pneumonia by repressing inflammatory substances release.^[34]

Antimicrobial activity: TC shows broad spectrum antimicrobial activity against gram-positive bacteria like *Salmonella typhi*, *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus vulgaris*,

Staphylococcus aureus, *Salmonella paratyphi*, *Shigella flexneri*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, *Enterobacter aerogene*, and *Serratia marcescens*.^[35] TC also helps in bacterial clearance by improving phagocytic activity and intracellular bactericidal capacities of neutrophils.^[36]

Amalaki (Phyllanthus emblica)

Immunomodulator activity: Amalaki is an excellent source of vitamin C (ascorbate), which account for its immunomodulator activities by promoting free radical scavenging. It enhances natural killer (NK) cell activity (approx. 2 fold increase in splenic NK cell activity) and antibody dependent cellular cytotoxicity.^[37]

Anti-viral activity: *P. emblica* is reported to inhibit herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) infection in-vitro by directly inactivating HSV-1 particles entry at the earlier phase via viral attachment and penetration. It is also found to suppress the intracellular growth of HSV-1 within a long period post-infection.^[38] Chemical constituents isolated from the root of *P.emblica* showed strong anti-coxsackie virus activity in in-vitro study.^[39] The sesquiterpenoid glycoside isolated from the *P. emblica* exhibit potential anti-hepatitis B virus (HBV) activities, especially towards the HBV surface antigen (HBsAg) and HBV excreted antigen (HBeAg) secretion.^[40] Beside these viruses *P.emblica* also showed anti-viral activity against H3N2 and EV71.^[41]

<p><i>Mulethi (Glycyrrhiza glabra)</i></p>	<p>Immunomodulatory effect</p> <ul style="list-style-type: none"> ▪ <i>Glycyrrhiza glabra</i> have Glycyrrhizin as its main chemical constituent that is having potential to up-regulates the expression of CD40, CD86 and MHC-II maturation markers on dendritic cells and also can enhances the production of IL-12 by these cells, thereby it modulates the expression of dendritic cells and thus acts as immunomodulator. In addition to this, it is also found to increases production of IFN-γ and IL-10 and reduces IL-4 production.^[40] <i>G. glabra</i> is also potent anti-oxidant activity.^[43] <p>Anti-viral activity</p> <ul style="list-style-type: none"> ▪ Against SARS-CoV- Glycyrrhizin inhibits SARS-coronavirus (SARS-CoV) replication in vitro.^[44] ▪ Herpes Simplex virus (HSV-1): In-vitro studies have shown that Glycyrrhizic acid of <i>G. glabra</i> can inhibit the growth of DNA and RNA viruses and inactivates Herpes simplex virus (HSV-1).^[45] ▪ Japanese encephalitis virus: Glycyrrhizin and licorice from <i>G. glabra</i> were found to inhibit plaque formation in three strain of Japanese encephalitis virus and reported to have antiviral activity against all three strains.^[46] ▪ Hepatitis B virus (HBV) & HIV-1: <i>G. glabra</i> is found to reduce sialylation and membrane 	<p><i>Haritaki (Terminalia chebula)</i></p>	<p>transportation of hepatitis B virus surface antigen. It inhibits fusion of viral membrane (HIV-1) with the cell by reducing the membrane fluidity of reduces membrane. <i>G. glabra</i> reduces viral latency.^[47]</p> <p>Anti-viral activity:</p> <ul style="list-style-type: none"> ▪ Herpes simplex virus-2 (HSV-2): Chebulinic acids and chebulagic acid from <i>T. chebula</i> extract are found to inhibit virus (HSV-2) attachment and penetration to the host cells more effectively than acyclovir. However, acyclovir is more potent to inhibit post-infection virus replication.^[48] ▪ Herpes simplex virus-2 (HSV-2): Chebulagic acid and punicalagin two hydrolyzable tannins isolated from the dried fruits of <i>T. chebula</i>, inhibit HSV-1 entry in A549 human lung cells. Both chemical compounds inactivated HSV-1 viral particles and prevents binding, penetration, and cell-to-cell spread, as well as secondary infection.^[49] ▪ Influenza A virus (IAV): Chebulagic acid and chebulinic acid are identified as novel inhibitors against IAV replication via neuraminidase. Moreover, these compounds are found to inhibit the viral release even in oseltamivir-resistance mutation of neuraminidase.^[50] ▪ SARS-CoV-2: Two Siddha preparations having <i>Haritaki</i> were analyzed by in vitro study
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using in Silico, molecular docking with two potential targets, PDB id: 6LU7 SARS CoV-2 spike protein and PDB id: 6LZG spike protein complexes with human Angiotensin-converting enzyme 2 (ACE2) receptor using Autodock Vina. Results showed that Chebulagic acid (isolated from *T. chebula*) has a high binding affinity with COVID19 protease in both its free and ACE2 complexed form. Suggesting a possible mechanism of protease inhibition of SARS-CoV2.^[50]

Immunomodulator activity: *T. chebula* extract is found to increase humoral antibody titer and also delayed-type hypersensitivity in mice.^[51]

Polyherbal Rasayana Drug

1. ***Chywanprasha Avleha***^[52]: *Chywanprash* (CP) is an *Ayurvedic* proprietary medicine use as *Rasayana* (general health booster mainly for lung health promoter). It is one among best rejuvenating medicines of *Ayurveda* that gives strength, vitality and stamina in daily life. It is a perfect blend of 50 medicinal herbs including the prime ingredient, *Amla* (richest source of Vit C) that's give it ability to acts as anti-oxidant, adaptogenic and immune-booster. It can be use both as prophylactic for maintaining the normal lung functions as well as curative in chronic respiratory diseases like interstitial lung disease, bronchiectasis, etc. to regenerate lung parenchyma and restoring their normal functioning. As *Chywanprashavleha* is an *Ayurvedic* propriety medicine not much work has been done on it overseas. In India a randomized clinical trial on 627 children by Gupta A. *et.al*^[53] showed that regular use of *Chywanprashavleha* reduces the incidence of immunity related illness more than half as compared to the control. *Chywanprashavleha* also showed better

percentage improvement in strength, stamina, energy levels, physical fitness, and quality of life in children. The authors concluded that regular consumption of *Chywanprash Avleha* for a period of six months could significantly improve immunity, energy levels, physical fitness, strength, stamina and quality of life in school going healthy children. Evaluating the efficacy of *Chywanprash Avleha* in oral premalignant cancer in a cytogenetic study revealed that due to its antioxidant property it reduces the genetic damage in betel quid chewing oral precancerous patients.^[54] The authors suggested requirement of extended clinical trial to evaluate the long-term effectiveness of *Chywanprash Avleha*. Clinical study by S.S.Pandey. *et.al.* on 128 healthy college students concluded that CP is helpful in improving the cognition, wellbeing and academic performance in college students and authors recommended its use in college going students for improving their academic performance.^[55] Dabur pharmaceutical company conducted mega research trial to evaluate the efficacy of Dabur *Chywanprashavleha* in various ailments.^[56] This includes its effect on seasonal influenza, nasal allergies and infections, as an adjuvant with tubercular drugs, immunomodulator effect, etc., and found highly significant results.

2. ***Agastya Rasayana***^[57]: *Agastya Haritaki Rasayana* is also an *Ayurvedic* proprietary medicine use as lung tonic to potentiate lung functions and to prevent respiratory diseases like dyspnea, cough, common cold, allergic rhinitis, etc. Its contents like *Dashmula*, *Atmagupta*, *Sati*, *Bharangi*, *Citrakamula*, etc. gives it characteristic pharmacodynamic properties like anti-tussive, mucolytic, antioxidant, anti-allergic, anti-inflammatory and mild laxative. *Agastya Rasayanam* is also very useful in chronic respiratory problems.

Anti-Viral Herbs

Herbs having specific phytochemicals can act as potent anti-viral agent. There are lots of research have been done on searching the efficacy of herbs in the

management of viral diseases. Following is the description of few herbs along with their pharmacodynamic properties, which are commonly use in Ayurveda for the management of various types of infections-

Table 2: Description of Anti-Viral Herbs

Name of the Herbs	Pharmacodynamic Properties
Tulsi (<i>Ocimum tenuiflorum</i>) (<i>sanctum</i>)	<ol style="list-style-type: none"> Antiviral activity^[58,59]: In-vitro studies have shown that <i>Tulsi</i> (Holi Basil) is having potential anti-viral activity. Terpenoid isolated from the leaves of <i>Tulsi</i> has anti-viral activities against H9N2 virus. It shows mild to moderated anti-viral activities against veterinary viruses like paramyxovirus and orthomyxovirus, bovine herpes virus-1 in different solvents. Immuno-stimulatory effect^[60,61]: Plant extract of <i>Ocimum sanctum</i> is found to have potent immune-stimulant activity. Both aqueous and alcoholic extract are found to have immunomodulatory effects. In human trial its alcoholic extract is found to significantly increase the level of interferon- γ, IL-4, T helper cells and natural killer cells (NK). Antitoxin Effect^[62]: Protects the cells from the damage caused by chemical injury by increasing anti-oxidants production like glutathione and anti-oxidant enzymes. <p>Phytochemical constituents of <i>Tulsi</i> are oleanolic acid, ursolic acid, rosmarinic acid, eugenol, carvacrol, linalool, β-caryophyllene (about 8%).</p> <ul style="list-style-type: none"> In- vitro as well as clinical studies based evidences. Antiviral and innate immunity stimulant are important pharmacodynamic properties in particular context.
Bilva (<i>Aegle marmelos</i> L.)	<ul style="list-style-type: none"> Virucidal activity^[63]: In vitro studies have shown that the chemical constituent marmelide has potent virucidal effect. It interferes at the early stages of virus replicative cycle involving its adsorption, penetration against coxsackievirus B3.

	<p>Main chemical constituent having virucidal activity is marmelide</p> <ul style="list-style-type: none"> In-vitro studies based evidences.
Neem (<i>Azadirachta indica</i>)	<ol style="list-style-type: none"> Antiviral activity^[64]: <ul style="list-style-type: none"> Polio Virus (PV)^[65] - Polysaccharides obtained from <i>Azadirachta indica</i> act against polio virus by inhibiting the initial stage of viral replication. Dengue virus -2 (DV)^[66] - In vitro and in vivo inhibitory potential of crude aqueous extract of <i>Neem</i> leaves and pure <i>Neem</i> compound (Azadirachtin) on the replication of Dengue virus type-2 showed that aqueous extract of leaves are able to inhibit the replication of dengue virus as evidenced by absence of dengue symptoms whereas no inhibition of virus was obtained by Azadirachtin. Antibacterial, antifungal, antiplasmodial and antitrypanosomal activity: <i>Neem</i> possess potent antimicrobial activities against wide range of pathogens including Gram positive, Gram negative bacteria, fungi and protozoan's. <p>The most important of bioactive constituents of plant are alkaloids, tannins, flavonoids and phenolic compounds.</p> <ul style="list-style-type: none"> In vitro as well as clinical studies based evidences.
Rasona (<i>Allium Sativum</i>)	<ul style="list-style-type: none"> Antiviral activity (virucidal)^[67,68]: Using polar diffraction pattern the chemical constituents responsible for the virucidal activity of <i>A. sativum</i> are isolated. Ajoene found in the oil-macerated fraction (absent in fresh garlic extract) was found to have maximum virucidal activity followed by allicin (isolated from fresh garlic extract). Assessing the antiviral activity of <i>A. sativum</i> on influenza virus by Mehrbod P. <i>et.al.</i> showed that the <i>A. sativum</i> extract has inhibitory effect on the virus penetration and proliferation and they suggested it as potent antiseptic agent. Antimicrobial Activity^[69,70,71,72]: Allicin found in raw garlic is a characteristic hydrophobic sulfur-containing compound and exhibits antimicrobial activity against both Gram-positive and Gram-negative

bacteria. Additionally, it is found to inhibit the biofilm formation of bacteria which is a major cause of bacterial resistance to the antibiotic treatment.

- **Immunomodulator activity**^[73,74]: *A. sativum* is found to improve the functioning of immune system by activating the immune cells like lymphocytes, macrophages, eosinophils cells, dendritic cells, and natural killer (NK) cells, by modulating cytokine secretion, immunoglobulin production and phagocytosis. *Allium* is capable of generating an anti-inflammatory gene expression thereby suppress inflammatory signals and prevented the increase in expression of proinflammatory cytokines IL-6 and MCP-1. Garlic oil enhances the shifts toward Th1-type response at low doses. It promotes an anti-inflammatory environment at high doses by shifting Th1-Th2 balance toward the Th2 type.

Phytochemical analysis of *Allium sativum* aqueous and ethanol extracts shows presence of Alkaloid, flavonoids, terpenoids, phenol, steroid, Anthraquinones, saponin, tannin and glycoside. Among these alkaloids are most abundant about 7.2% followed by Tannin and saponin constituting 4.8% and 4.3% respectively.

- Mostly in-vitro studies based evidences.

DISCUSSION

Corona virus related disease (COVID-19) requires sequential treatment for complete elimination of disease. It means that any single treatment modality or herb or herbo-mineral preparation is not sufficient enough for proper management of disease. Herbs having specific phytochemicals (e.g., berberine a phytochemical present in several plants having anti-malarial, anti-inflammatory, antipyretic properties) and proteins act as natural neutralizing antibodies and provide passive immunity against viral infections. Therefore, herbs having anti-viral potential can be use at the first stage of infection (i.e., at the time of appearance of signs and symptoms). Anti-viral herbs are safe, cost-effective, and easy for consumption, widely available, can be given to any age group patients

just by modulating doses and most importantly having no toxic side effects. Once the disease get cure as indicated by subsidence of sign and symptoms, then immune-modulator (IM) herbs should be use for rejuvenation of immune cells and repair of wear and tear by scavenging free radicals and reactive oxygen species (ROS). IM herbs are rich in anti-oxidants and have ability to potentiate the immune system by various mechanisms. IM herbs can also be used for prophylaxis to prevent the disease. As it is reported that IM medicines stimulate innate immunity (activate natural killer cells (NKs), phagocytes, neutrophils, etc.). Thus, it is suggested that sequential use of anti-viral and IM medicines is useful in preventing (for prophylaxis) as well as managing the COVID-19.

CONCLUSION

As presently, we don't have any treatment / medicine that claim to have definite efficacy in managing COVID-19 and moreover medicines which are using for the treatment of the COVID-19, are all documented for having toxic side effects. Therefore, it is recommended that instead of endangering life of COVID-19 suffers by using unproven treatment modality; it is judicious to use non-toxic and effective treatment modalities. The article discusses simple herbs that acts as anti-viral and immunomodulators; keeping in focus that these herbs are available easily in different countries, can be easily identify and can be consume as medicine to prevent as well as cure COVID-19 pandemic in a general interest to serve humanity.

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