

# Repurposing of the Herbals as Immune-Boosters in the Prevention and Management of COVID-19: A Review

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## Abstract

Coronavirus disease (COVID) is highly contagious, and negligence of it causes high morbidity and mortality globally. The highly infectious viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was abbreviated as COVID-19 (Coronavirus disease 2019) by World Health Organization first time on February 11, 2020, and later on, WHO declared COVID-19 as a global pandemic on 11/3/2020. Epidemiological studies demonstrated that the SARS CoV-2 infects the overall population, irrespective of age, gender, or ethnic variation, but it was observed in clinical studies that older and compromised immunity population is much more prone to COVID-19. SARS-CoV-2 majorly spread through aeration route in droplet form on sneezing and coughing, or by contact when touching eyes, nose or mouth with the infected hands or any other organs, resulting from mild to severe range of SARS-CoV-2 infection. This literature-based review was done by searching the relevant SCI and SCOPUS papers on the pandemic, SARS-CoV-2 and COVID-19, herbal formulation, and Ayurveda from the databases, Academia, Google Scholar, PubMed, and ResearchGate. The present review attempts to recognize the therapeutic strategies to combat Covid-19 because of the current human risk. Indian system of medicine, including herbals, has immense potential in treating and managing various viral infections and provides evidence to utilize Ayurvedic medication to improve immunity. Cumulative research findings suggest that Ayurvedic formulations and herbal immunomodulators (Tinosporacordifolia, Withania somnifera, Crocus sativus, Zafraan, Allium sativum, Zingiber officinale, Albizia lebbek, Terminalia chebula, Piper longum, Mangifera indica, Ocimum sanctum, Centella asiatica) are promising in the treatment of outrageous viral infections without exerting adverse effects. Considering the ancient wisdom of knowledge, the herbal formulations would compel healthcare policymakers to endorse Ayurveda formulations to control the Covid-19 pandemic significantly.

**Keywords:** Covid-19, Ayurveda, Immunomodulators, Herbals, Viral infections, anti-viral

## INTRODUCTION

Mounting research findings suggest that Covid-19 is primarily a respiratory syndrome chronically affecting whole-body organ; caused by a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], and have affected the quality of life and is a burden on the socio-economic system of the nation. SARS-CoV-2 is a highly fatal ailment, and to date, there is no specific vaccine or drug in the treatment market. Supportive treatment is the only choice for disease management and prevention. Various studies are being performed worldwide, and few selected drugs are in clinical trials but still far from the final goal.

As per the current scenario, only those having strong immunity can survive, fight, and protect themselves from Covid-19. Several herbal medicines as Immunomodulators have been utilized by humankind since time immemorial or ancient period. Although complete scientific validations of these herbs Immunomodulators have not been evaluated, still several trials are

in progress. Fundamentally, the Immune system can differentiate between host proteins/cells and foreign particles or antigens. Further, the body's immune system fights against various infectious diseases/agents after foreign bodies/agents' invasion. Some other infectious agents are also involved in the immunization, including external stimuli. The immune system can be categorized into two broad classes based on function, i.e., one is the innate immune system known as the non-specific immune system, and another one is an adaptive immune system that is commonly known as acquired/specific immune system<sup>1,2</sup>.

Various studies demonstrated that different types of barriers, including microbial, chemical, and physical are innate immunity. Additionally, some other imperative mediators of the defense system instantly distribute defense bio-chemicals like inflammatory markers/immune-proteins and macrophages, monocytes, complement, and neutrophils, collectively recognized as pattern recognition receptors (PRRs). These pattern receptors for host sensors can

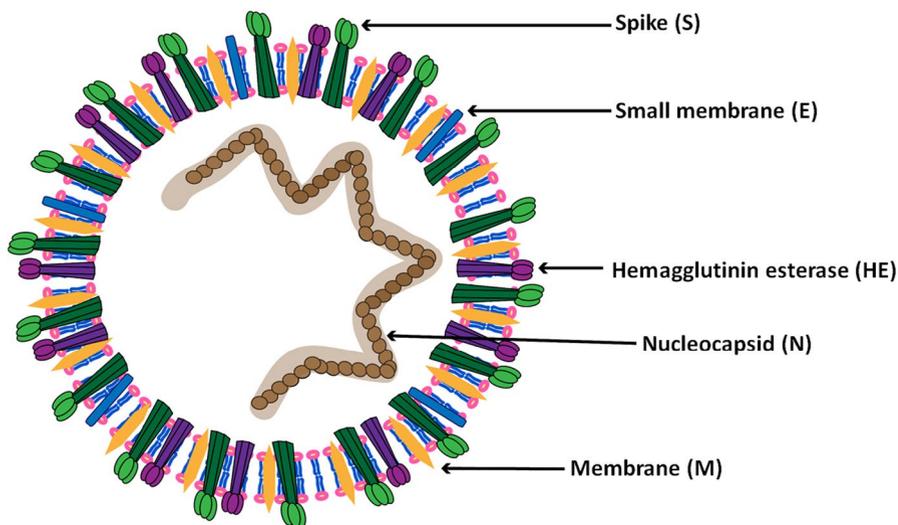
be identified as pathogen-associated molecular patterns [PAMPs]. Furthermore, when pathogens entered the host, they trigger the expression of PAMPs, further release a mixture of immune molecules such as interferons, chemokines, and cytokines, nitric oxide [NO], dendritic cells, and also involved in the establishment of the phagocytosis process. These immune-components are also concerned with the activation of memory B and naive T cells<sup>3,4</sup>.

Globally, the human community faces unprecedented health problems in the form of a novel Corona virus-19(CoVs-19) disease documented as Covid-19. CoV-19 originated from Coronavirus, known as severe acute respiratory syndrome corona virus-2 [SARS-CoV- 2] and is associated with respiratory damages. At this instant, the world health organization (WHO) has declared the Covid-19 pandemic and has realized it as a significant health issue in the world. The first time Cows-19 infected person was identified at Wuhan city, Hubei Province, China, with an outbreak of respiratory sickness or damage. In the beginning, it was reported to the WHO on December 31/2019, which was declared Covid-19 on January 30, 2020, by the WHO. In the current scenario, COVID-19 spread worldwide within very short time duration and was declared a pandemic by the world health organization<sup>1-4</sup>.

Recent findings suggested that Covid-19 infection affects the population with weak immune system attacks with the worst outcomes that affect the respiratory system and result in complete organ failure and become lethal in certain cases<sup>5,6</sup>.

In the current scenario, Covid-19 has affected approximately 215 countries and territories around the world, still have reported, with more than 63,228,544 confirmed cases and more than 1,467,830 deaths until December 2, 2020. As per the WHO report, COVID-19 is one reason for causing health issues and ascending wealth problems<sup>1-5,7</sup>. Phylogenetic evolutionary studies have shown resemblance of Covid-19 with other already available coronavirus strains because Covid-19 have shared identical nucleotide with SARS-CoV, bats SARS-CoV and MERS- CoV. Previous studies have reported the structure of Covid-19 as multiple layered spherical structures with crown-like spikes all over the surface, providing well-known crown morphology<sup>1-4,7,8</sup> [figure-1a & b].

The spike protein trimers form the peplomers embedded inside the envelope that provides a down-like shape to the virion. Merely, few members of CoVs, including the hemagglutinin-esterase -HE protein involved in the formation of smaller spikes on the membrane[M]



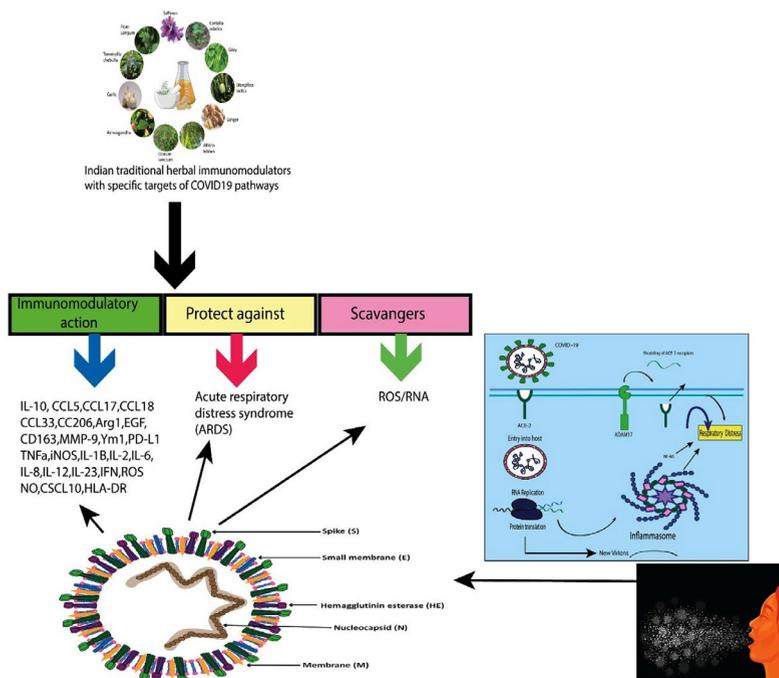
**Fig. 1a.** the structure of Corona virus virion and its genome RNA contain (trans-membrane proteins) the N protein (outward appearance a helical cased within membrane of the viral), hemagglutinin-esterase (HE); spike(S); Small membrane envelope(E); Membrane (M)

with small membrane [E] protein (Minor component of the viral envelope). These are also transmembrane proteins that are associated with CoVs assembly (Fig. 1a & b). According to reports, CoVs have various proteins that perform different tasks, such as the S glycoprotein, which acts as the receptor-binding protein that causes infection and targets neutralizing antibodies. Similarly, the M glycoprotein involves virus gathering at intracellular membranes in the region of the endoplasmic reticulum Golgi complex [ERGIC]<sup>9-14</sup>.

To date, only a few vaccines and anti-viral drugs such as Hydroxychloroquine, Favipir, Ritonavir, Oseltamivir, Lopinavir, Ganciclovir, and Remdesivir are the highly and exclusively effective therapeutic approaches to treat viral disease; whereas, there are no existing viable vaccines to eliminate or suppress Covid-19 infections<sup>15-17</sup>. Based on its previous clinical application, assorted anti-virals in different countries and regions [include Lopinavir/Ritonavir [400/100mg.12hourly], Chloroquine [500 mg 12 hourly] and Hydroxychloroquine [200 mg 12 hourly] and Azithromycin 500mg in 24 hours antibiotic for secondary infection, used to curtail

the Covid 19,19, whereas these drugs have minimal effect; moreover, as per WHO guideline some precaution make to safe from Covid-19 such as social distancing, quarantine, and isolation of suspected or infected person, are the best tools. Also, maintenance of proper hygiene, frequent hand wash with soap or alcohol [ $> 70$  or  $80\%$ ] based sanitizers, and a mask<sup>7,18-21</sup>. Recently, WHO has declared that eight Covid-19 antivirus vaccines enter preclinical and human clinical trials, but these vaccines might require months/years to launch into the market. Simultaneously, to negate the homicide situation until the vaccine approval and launch therapeutic herbal medications must be explored<sup>18-21</sup>.

In Indian ancient Ayurveda methodology, modern scientific study, and our practical knowledge are in the parallel clinical setting and, like other several studies, we have assessed the plan for evaluation of the immunomodulatory activity of herbal medicines. In the current time, Ayurveda is more popular and applicable because of its elaborative description of the root cause and management strategies of several epidemics (Janapadodhwamsa) in the Ayurvedic



**Fig. 1b.** Systematic effect of traditional immunomodulatory on the suppression of different inflammatory marker and protective effect against the scavengers

therapeutic system. Still, maximum research study and development have a target to identify such biochemical, biological moieties or solitary compounds could lead to precise target to withstand and overcome diseases associated with Covid-19, worldwide<sup>19,21</sup>.

Research and development should be focused on herbal or natural source/molecules with high selectivity and potency. Low toxicity for targeted molecular or cellular targets and potency of the drug to overcome the Covid-19 situation must also be considered part of the study. After much consent, several studies have been designed to develop herbal medicine as alternative medicine, gaining global interest. In this consideration, researchers and scientists have recommended immune-enhancing herbs like *Phyllanthus Emblica*, *Azadirachta indica*, *Tino sporacordifolia*, *Withania somnifera*, *Crocus sativus*, *Zafran*, and *Swertia chirata* that would

be helpful for the improvement of body defense mechanism to fight Covid-19 infection / to inhibit its replication inside the host cells<sup>18-21</sup>. Several herbal formulations have been reported in the Ayurveda history or ancient cargo-space for the hindrance and management of Covid-19.

In traditional medicinal science, various parts of different plants or herbs were used as an herbal drug against several clinical ailments. Some such bioactive molecules - vinblastine, vincristine and its semi-synthetic offshoots isolated from the *Madagascar periwinkle (Catharan thusroseus)*, *capsaicin* from *chili peppers (Capsicum species)*, *paclitaxel* from *Pacific yew (Taxusbrevifolia)*, and *galantamine* from the *Caucasian snowdrop (Galanthus caucasicus)* are examples of herbal medicines molecules<sup>1-3,7,19,22,23</sup>.

We believe this review will provide details about plants based medicine, which adds up to boost the immune system, act as Immunomodulators, and their essential features that might express potent anti-viral activity.

#### MATERIALS AND METHODS

For extensive pandemic information, SARS-CoV-2, Coronavirus, its structure and pathology, its prevalence, occurrence, traditional medicine, herbal formulation *Tino sporacordifolia*, *Withania somnifera*, *Crocus sativus*, *Zafran*, *Allium sativum*, *Zingiber officinale*, *Albizia lebbek*, *Terminalia chebula*, *Piper longum*, *Mangifera indica*, *Ocimum sanctum*, *Centella asiatica*, and its mechanism, anti-COVID drug, all authors equally, searched for the most recent information about this pandemic using several search engines such as Science Direct & Scopus, PubMed, Springer Link, Research Gate, Wiley Online Library, and Google



Fig. 2. Giloy [Gilu]

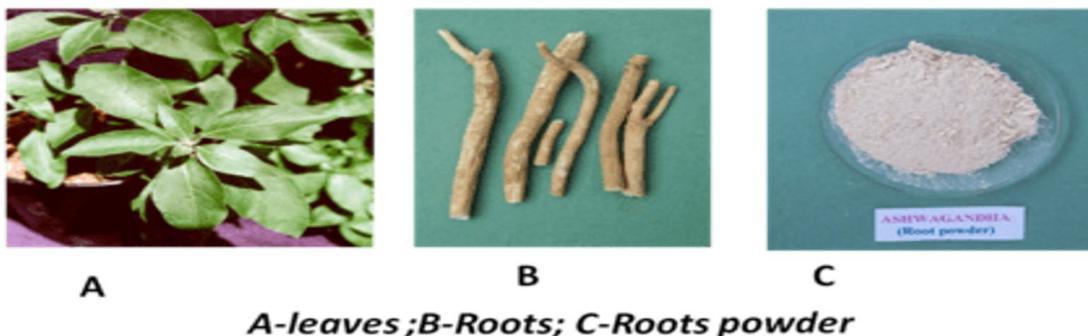


Fig. 3. Asvagandha

**Table 1.** Showing most important and sub groups of natural products present in different parts of *Tinospora cordifolia* and their biological activities

Plant Part	Chemical molecules (Active Component Compound)	Biological activity	Ref.
Stem, Root	<b>Alkaloids</b> (Berberine, Magnoflorine, Tetrahydropalmatine, Choline, Tembetarine, Tinosporin, Palmetine, Isocolumbin, Aporphine alkaloids, Jatrorrhizine.)	Neurological, immunomodulatory, psychiatric conditions Anti-viral infections, Anticancer, anti-diabetes, inflammation,	(32-36)
Whole Plant	<b>Diterpenoid Lactones</b> (Columbin, Furanolactone, Clerodane derivatives [(5R,10R)-4R-8Rdihydroxy-2S-3R:15,16- diepoxy-cleroda-13 [16], 14-dieno-17,12S:18,15dialactone], Tinosporon, Tinosporides, Jateorine)	Induce apoptosis in leukemia by activating caspase-3and bax, inhibits bcl-2Anti-inflammatory, anti-microbial, antihypertensive, anti-viral.	(37-41)
Stem	<b>Glycosides</b> (Palmatosides, Tinocordiside, 18-norclerodane glucoside, Furanoid diterpene glucoside, Tinocordifolioside, Cordioside, Cordifolioside Syringin, Syringinapiosylglycoside, Pregnane glycoside, Cordifolioside A, B, C, D and E)	Parkinsons, Dementia, Immunomodulator Anticancer activities.	(42-51)
Shoot	<b>Sesquiterpenoid</b> (TinocordifolinAliphatic compoundOctacosanol, Heptacosanol Nonacosan-15-one dichloromethane)	Antiseptic, Anti-nociceptive and anti-inflammatory	(52-53)
Root, Whole Plant	<b>Steroids</b> ( $\beta$ -sitosterol, $\delta$ -sitosterol, 20 $\beta$ -hydroxyecdysone, Ecdysterone, Makisterone A, Giloinsterol ) <b>Others</b> (3-[ $\alpha$ ,4-di hydroxy-3- methoxy-benzyl]-4-[4- compounds hydroxy-3- methoxy-benzyl]- tetrahydrofuran, Jatrorrhizine, Tinosporidine, Cordifol, Cordifellone, Giloinin, Giloin, N-transferuloyltyramine as diacetate, Tinosporic acid)	Immunomodulator and For neurodegenerative disorder IgA neuropathy, Anti-viral infections, Anticancer, Anti-inflammatory Protease inhibitors for HIV and drug resistant HIV	(54-57)

Scholar databases and Elsevier. Between May and December 2020, the current review search was performed, and cited literature was screened from various SCI and Scopus index papers. Further treatment and management of Covid-19 by using herbal formulation was the current study that met this review's purpose.

**Herbals medicines and COVID-19**

A literature search was performed using a search engine like Science Direct & Scopus, PubMed, SpringerLink, Wiley Online Library, and Google Scholar databases to identify

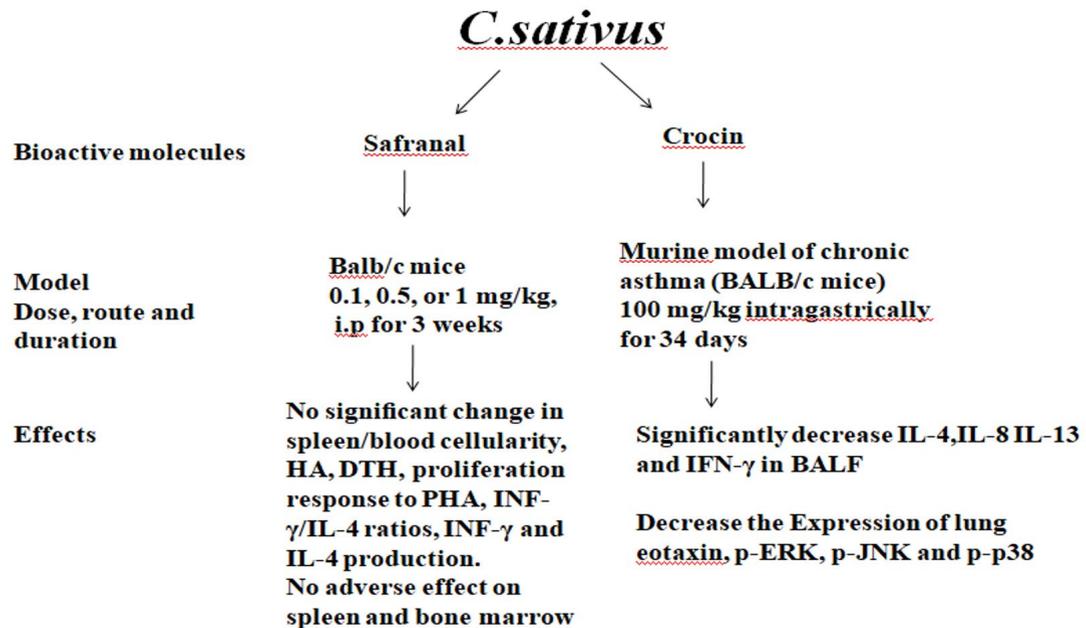
immunomodulatory effects of *Tinosporacordifolia*, *Withania somnifera*, *Crocus sativus* Zafran, *Allium sativum*, *Zingiber officinale* Albiia lebbek, *Terminalia chebula*, *Piper longum*, *Mangifera indica*, *Ocimum sanctum*, *Centella asiatica* and their active constituents with experimental evidence of involvement in the immune system and also using keywords like Coronavirus, pandemic, its pathogenesis, clinical features and structure of COVID 19, Ayurveda, mechanism of various anti-viral plants, and medicinal plants, herbal Immunomodulators and its mechanism. The present review search was conducted between August and October 2020, and obtained cited literature from different SCI and Scopus index journals were screened. The present study that met this review's aim was further screened and examined the herbal Immunomodulators against Covid-19<sup>11</sup>.

The author should mention the term (keywords), database, and search engine used for the manuscript's literature survey.

Natural immunomodulatory products or their extracts (containing bioactive compounds) with immunomodulatory potential may significantly impact infection management with Covid-19 and may establish a novel immunomodulatory agent.



**Fig. 4a.** Saffron (Zafran)



**Fig. 4b.** The potential mechanism of bioactive (safranal and crocin from C.Sativus) molecules against infectious agents through immune response.

**Table 2.** Herbal immune-modulator with their source and mechanism with proven evidence

No.	Plants name	Bioactive molecules	Immunomodulatory Mechanism	Ref.
1.	<i>Coptis chinensis</i> Franch	[Immunomodulators] Alkaloids Berberine	Down-regulate T-helper cells cytokines [Th1 (TNF- $\alpha$ , IL-2), and Th2 (IL-4)] production	104
2.	<i>Chelidonium majus</i> L.	Chelerythrine	Inhibit PGE2 release by regulating cyclooxygenase-2 activity	105
3.	<i>Piper longum</i> Linn	Piperine	Reduce level of pro inflammatory cytokines IL-1 $\beta$ , IL-6, and TNF- $\alpha$ . Down regulate expression of COX-2, NOS-2, and NF-kB.	106-107
4.	<i>Picea crassifolia</i>	Chrysin	Inhibit eicosanoid generation by inhibiting phospholipase A2 and TXA2 synthase activity. Inhibited production of pro-inflammatory cytokine (TNF $\alpha$ , IL-1 $\beta$ , and IL-6). By modulation of intracellular calcium reduce histamine release from mast cells.	108-109
5.	<i>Lithospermum erythrorhizon</i> Sieb. et Zucc.	Shikonin	Inhibit NF-kB activity, inhibit Th1 cytokines expression and induce Th2 cytokines	110
6.	<i>Nigella sativa</i> L.	Thymoquinone	Inhibited LPS-induced fibroblast proliferation and H2O2-induced 4-hydroxynonenal generation. Inhibit IL-1 $\beta$ , TNF- $\alpha$ , MMP-13, COX-2, and PGE2 while blocking phosphorylation of MAPK p38, ERK1/2, and NF-kBp65.	111
7.	<i>Andrographis paniculata</i>	Terpenoid 14-deoxyandrographolide	Enhanced proliferation of lymphocytes. Enhanced IL-2 induction in lymphocytes.	112
8.	<i>Tripterygium wilfordii</i>	Demethylzelasteral	Inhibits proliferation of vascular endothelial cells.	111
9.	<i>Luffa cylindrica</i>	Echinocystic acid	Enhance phagocytic index of macrophages in humoral and cell-mediated immune responses	112
10.	<i>Tripterygium wilfordii</i>	Demethylzelastera	Inhibits proliferation of vascular endothelial cells	113
11.	<i>Luffa cylindrica</i> , Phytolacca americana	Oleanolic acid	Reduce level of IL-1 $\alpha$ , IL-6, and TNF- $\alpha$ , as well as their effect on complement pathway through the inhibition of C3 convertase. Inhibits adenosine deaminase activity	114
12.	<i>Panax ginseng</i>	Ginsang	Enhances the production of cytokines and reactive oxygen species by macrophages. Stimulates the phagocytic activity of macrophages.	115
13.	<i>Tripterygium wilfordii</i>	Triptolide	Inhibits lymphocyte activation and pro-inflammatory cytokines gene expression (IL-2, iNOS, TNF- $\alpha$ , COX-2, and IFN- $\gamma$ ). It also inhibits activation of transcription factors such as NF-kB, NFAT, and STAT3.	116
14.	<i>Tripterygium wilfordii</i>	Celastrol	Inhibit expression of pro-inflammatory cytokines, adhesion molecules, proteasome activity, and topoisomerase II.	117

World Health Organization has currently permitted a few herbal-based immunomodulator medicines undergoing preclinical trial and clinical trials<sup>1-3, 18,19,21,24</sup>. Concurrently, In India, the Ministry of AYUSH has also recommended using herbal medicine as preventive healthcare services and enhancing immunity with particular reference to respiratory health or Covid-19.

### Rasayana Chikitsa

*Ayurveda*, or ancient science of life, dealt with immunity as a holistic approach and a potentially promising immunotherapy approach. *Ayurveda*, deal defense of health as a healthy character and also suppress/cure the diseases. Specifically, *Ayurveda* emphasizes promoting and improving health by boosting the strengthened power of host defenses and acting as a resistive force against day-to-day physiological extremes and opportunistic maladies<sup>22</sup>.

In *Ayurveda*, human beings' daily literature wellness, known as "*Vyadhiksamatwa*," means fighting against a specific infectious disease. The terms protective medicine and curative aspects are management terms as the self-explanatory "*Vyadhibalavirodhitvam*" and "*Vyadyutpadapratibandhakatvam*" - resistance against the loss of the integrity, proportion, and interrelationship amongst the individual's *Dosas* and *Dhatus*<sup>22</sup>. Several useful *dravya* or liquid, preparation or formulations, the mechanism involved in enhancing immunity (*Balaor Vyadhiksamatwa*) [classical *Ayurveda*]<sup>22</sup>.

In *Ayurveda*, epidemics or pandemics were already described as "*Janapadodhvansa*"<sup>25</sup> or "*Marak*"<sup>22,26</sup>. *Rasayana Chikitsa* is known to *proRasa*, *Rakta*, *Mamsa*, *Medha*, *Asthi*, *Majja*, and *Sukra* [essential seven vital



Fig. 5. Garlic



Fig. 6. Ginger



Fig. 7. *Albizia lebbek*



Fig. 8. *Terminalia chebula*

tissues] and *Ayana* [the path or channel]. In *Rasayan* therapy, there was some point described for a healthy life or boost up of immunity [the *Ojas*] [*Vyadhiksamatwa*] such as *Satmya Ahara*, *Nidra* rejuvenate the physiology of the body and produce resistance against infection at both physically and mentally- bring about proper uptake, growth, and improvement of essential Saptadhatus] along with Swasthavritta Paripalana [Dinacharya and Ritucharya] and that collectively called Rasayana therapy. *Rasayana* [*Rasa* and *Ayana*] [*Rasa* means Saptadhatue (proper sleep), *Yogic Asanas*, and *Brahmacharya*<sup>22,25,26</sup>. According to *Acharya Charaka*, a person undergoing *Rasayana* therapy achieves long life, memory, mental power, freedom from infection<sup>25</sup>. Some studies have also suggested *Rasayana* therapy will provide better treatment by boosting immunity power in this pandemic time or safe from Covid-19 infection<sup>22,25,27,28</sup>. The mode of action of *Rasayan* therapy can be performed through different actions like nutrition, immunomodulatory agent, an antioxidant, anti-aging, and neuroprotective. Some medicinal plants play an essential role in enhancing the Immune described below.

#### ***Guduchi (Giloy, Gilu, Tinosporacordifolia)***

In Unani, *Guduchi* is famous as Gilu (figure-2), while in Ayurveda's medicine system has shown remarkable medicinal properties like antioxidant, phagocytic activities, and anti-sedative antipyretic action as well as immunomodulatory properties<sup>27</sup>. *Rasayana Chikitsa* uses fevers (different form) and acts as a blood purifier, immune enhancer, including analgesic effect. Also, provide anti-inflammatory benefits and chronic cough or respiratory relief. In Unani medicine system use in the treatment of tuberculosis, leprosy, syphilis, and gonorrhoea. It contains (as shown in table-1) bioactive *Rasayana* constituents tinosporin, tinosporide, and cordifolide. It has antioxidant, phagocytic activities, antipyretic action as well as immunomodulatory properties<sup>25,27</sup>.

Few studies support the evidence for activation of macrophages like NF- $\kappa$ B translocation and cytokine synthesis followed by activation of the immune system in HIV positive patients and Infectious bursal disease in young chicks were also get relief by its effect<sup>29–31</sup>. The studies have supported that it is involved to

activate macrophages like NF- $\kappa$ B translocation and inflammatory synthesis, even though, ultimately, activates the immune system and Human immunodeficiency virus (HIV) positive patients and Infectious bursal disease in young chicks were also get relief by its effect<sup>29–31</sup>.

#### ***Ashwagandha- Withania somnifera (W.S.)***

*Ashwagandha* (figure-3) is well-known as *Withania somnifera* (W.S.), which means 'Smell of Horse,' which may be because of two main reasons 1) the root itself smells like a horse, 2) the root is supposed to imbibe with the strength and virility of a horse. It brings into being Kamashakti as like horse in human and its plant bears smell like a horse. Except for this use, various traditional reports have supported that W.S is very useful in treating several diseases like inflammation, cancer, stress, fatigue, diabetes, and cardiovascular complications. W.S includes an analgesic, astringent, antispasmodic, and immune-stimulant compound, with particular emphasis on a stress-related suppression in immunity. Some studies have shown that its adaptogenic usage is emphasized for stress-insomnia, incapacity, and nervous fatigue<sup>58</sup>.

In the Indian medicinal or therapeutic system, *Withania somnifera* is a beneficial medicinal plant used to treat various ailments but is mainly concerned with neuro-related diseases such as stress or insomnia, depression, anxiety, neurodegenerative<sup>58</sup>. W.S is also supportive medicine for age-related disease; for better improvement of the immune-system, historically, it involves detoxification when consumed its root extract with food<sup>58–60</sup>.

#### ***Kumkum (Crocus sativus Zafran) Saffron***

In India, *Kumkum Saffron (Crocus sativus)* (figure-4) is a valuable or exclusive, expensive species<sup>61</sup>. Iranian medical books have major descriptions of Saffron (the dried and dark red stigma) of *Crocus sativus Zafran*. *Crocus sativus Zafran* is a famous medicinal plant globally and cultured in many countries like Central Asia, Europe, India, Turkey, and China. It contains bioactive molecules safranol, crocin, and picrocrocin include 63 percent sugar, 12 percent proteins, 5 percent fat, 5 percent minerals, 10 percent water, few fibers, and including anthocyanins, glycosides, alkaloids, and some flavonoids, including quercetin<sup>61–62</sup>. *In vitro* & *In vivo* studies have shown its potent

anti-aging<sup>62</sup>, anti-inflammatory<sup>63</sup>, antioxidant<sup>64</sup>, antimicrobial<sup>17,65</sup> anti-asthmatic, anti-viral, and free radical scavenging effect. Additionally, it acts as a cardio-protective, neuro-protective nephron-protective, and hepatoprotective herbal remedy<sup>62-65</sup>. It acts as a potent immune booster on humoral and cellular immunity<sup>65</sup>. Several studies suggested that *crocin and crocetin (major bioactive components of Saffron) are affecting the natural killer cell (NK-cell) activity or could increase NK-cell activity in the elderly; through this mechanism, both are involved in modulating the immune response*<sup>65</sup>. On the other hand, different *in vivo* and *in vitro* supportive findings explained its immunoregulatory (figure-4b) properties and constituents. Therefore, compounds with immunoregulatory properties may help prevent and treat such communicable diseases and affect Covid-19 treatment.

#### **Rasona[*Allium sativum*]Garlic**

*Rasona* or Garlic is known as *Lehsun* (figure-5), (tunicate bulb belongs to Lillaceae family, is hot and dry in temperament as per the Greco-Arab system of medicine<sup>66</sup>. From ancient times due to blistering **properties, lehsun** helps recover from respiratory damage, cough problem, arthritis, and constipation. It protects from epidemic diseases<sup>69</sup>because of its active chemical ingredients -alliin, allicin, ajoene, vinylidithin, S-allylcysteine, and diallyl sulfides<sup>67</sup>.

Multiple studies have documented its biological effects: antioxidant, anti-inflammatory,

immunomodulatory, antibiotic, bacteriostatic, antifungal, anti-viral, antihelminthic, antithrombic, hypotensive, hypoglycemic, and hypercholesterolemic, as well as anti-influenza B, herpes simplex, and coxsackievirus anti-viral activity<sup>69-70</sup>. Some studies reported that Garlic molecules could modulate cytokine expression in lipopolysaccharide-activated human blood and inhibit NF- $\kappa$ B from which show its immunomodulatory effect is evident<sup>71</sup>.

It is also involved in activating macrophages, promoting immunoglobulins<sup>71</sup>, and reducing polymorphonuclear cells' migration through endothelial cell layers<sup>72</sup>. Some studies have observed that it involved inhibiting the fabrication of NO and prostaglandin-E2, suppresses inducible form of NO synthase and COX-2 expression, decreases the production of inflammatory cytokines like TNF- $\alpha$ , interleukin 6, and interferon  $\alpha$ <sup>70-72</sup>. Some other finding has supported that involved to improve lung function in smokers,<sup>73</sup> and reduce tracheal exudates in horses<sup>73</sup>.

On the other hand, in the case of Covid-19, proinflammatory cytokines ( Tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interferon-gamma (IFN- $\gamma$ ) and leptin) are among those exhibiting an increasing tendency. In contrast, Garlic contains countless compounds that have the potential to influence immunity, and alternately, are involved in the modulation of cytokine secretion, which may provide a mechanism of



**Fig. 9.** *Piper longum*



**Fig. 10.** *Mangifera indica*

action for many of its therapeutic effects and other infectious disease treatment<sup>73</sup>. Therefore, Garlic has beneficial effects immunological and hormonal, causes significant increases in CD4 + and CD8 + cells, and stimulates NK. Additionally, cells decreased leptin, leptin receptor, peroxisome proliferator-activated receptor-gamma (PPAR- $\alpha$ ), and IL-6 concentrations<sup>73</sup>. Through this beneficial effect of Garlic play an essential role in the treatment of patients with Covid-19 infection.

#### **Shunthi[Adraka, Zingiberofficinale]Ginger**

According to the Greco-Arab medicine system, ginger or *adrak*(figure-6) is a rhizome, [brown color and bitter taste] has the hot and dry temperament and is commonly used as an appetizer and general tonic. It has been used to treat anorexia, flatulence, high blood pressure, arthritis, and the common cold from the ancient period. It contains many bioactive molecules that act as immunomodulators like zingiberine, gingerol, gingerdione, shogaol, paradol, hexahydrocurcumin, and gingerenone A<sup>74</sup>.

Some studies have supported that its extract is involved in reducing oxidative stress and inhibit superoxide production; it also affects anti-inflammatory and analgesic activities<sup>58</sup>. Recently a report has observed that its effect against swine flu [H1N1] and human respiratory syncytial virus in human respiratory tract cell lines<sup>75-77</sup> and

including bronchodilator effect ameliorates allergic asthma<sup>74-79</sup>.

Numerous studies have suggested that gingerols showed anti-viral properties against the human respiratory syncytial virus on HEp2 and A549 cell line and participate in promoting bronchodilation (relieving fluid in the lungs, preventing lung fibrosis, naso or trachea/pharyngeal clogging, alleviating cough, and also relieving chest pain, and make easy to breathing). Thus, its active molecules play a promising role against the novel Covid-19 for blocking receptor binding and viral phagocytotic internalization of the SARS-CoV-2 (the binding of the S- (spike) protein to the angiotensin-converting enzyme 2 (ACE-2) receptors) and significantly relieving to Covid-19 patients<sup>79</sup>.

#### **Shirisa (Albizialebbek)**

Generally known as *Shirishor Siris* (figure-7) contain Albigenian, albiziagenin, lebbecacidin, myricitrin as major chemical constituents, and bioactive molecules, its effect as an anti-inflammatory, antihistamine, antioxidant, and anticancer activities<sup>27,80-83</sup>.

Both *in vivo* and *in vitro* studies have shown the immunomodulatory effect (on the humoral and cell-mediated immune responses) of the bark of *Albizzia lebbek* (Sirisha). Numerous studies have shown that hyperinflammatory response (cytokine storm) sign of Covid-19; therefore, reducing inflammatory markers could be considered a potential therapeutic target against Covid-19. Thus, *Albizzia lebbek* is involved to decrease the level of pro-cytokines - leptin,



**Fig.11.** *Ocimum Sanctum*



**Fig. 12.** *Centella asiatica*

leptin receptor, peroxisome proliferator-activated receptor-gamma (PPAR- $\alpha$ ), and IL-6. On the other hand, the extract of sirisha increased the serum antibody titer, several plasma cells in the spleen with a concomitant decrease in DTH response, MPO enzyme activity in the spleen, and serum level of TNF-alpha, IFN-g, and IL-6 in rodent studies<sup>81-83</sup>.

#### **Haritaki [*Terminalia chebula*]**

It is known as Haritaki or *Harad* (King of medicine' in Tibet) (figure-8) and is mentioned in Ayurvedic literature, *Rasayana*, *Tridoshahara* indicated for *Swasa* and *Kasa*. Various studies isolated some essential bioactive ingredients such as chebulinic acid, anthraquinone, arachidic acid, etc., along with other phytoconstituents such as polyphenols, terpenes, anthocyanins, flavonoids, alkaloids, and glycosides. They play a significant role as antibacterial, antispasmodic, antioxidant, and immunomodulatory activities<sup>25,84-88</sup>. The previous finding supported that its fruits hold various active chemical compounds responsible for different health benefits like geriatric diseases and improve memory and brain function. It is useful to treat various clinical diseases like cancer, cardiovascular diseases, paralysis, leprosy, ulcers, gout, arthritis, epilepsy, cough, fever, diarrhea, gastroenteritis, skin disorders, urinary tract infection, and wound infections<sup>84-86</sup>. Therefore, its extract contains various active compounds involved in the treatment of diabetes, bacterial and fungal infections, immunodeficiency diseases, hyperlipidemia, and possess other pharmacological beneficial effects<sup>87-88</sup>, so that its supplement might be responsible for fights against Covid-19

#### **Pippali [*Piper longum*]**

*Pippali* (figure-9) is locally famous as Long pepper, and with a long history, it is mentioned in *Atharvaveda*, *Pippali* mentioned as *Rasayana*. *Acharya Charaka* and *Susruta*. Numerous finding has supported that it acts as anti-inflammatory, antispasmodic and also showed immunomodulatory properties. Its chemical profile contains various significant active molecules like Piperine, Piperine, piperitone, caryophyllene, etc., as major chemical constituents<sup>27,89-91</sup>. The extract of *P. longum* was significantly involved in improving the immune system through activating macrophages in vitro study. In another

in vitro study, its extract caused an increase in the total WBC count, Bone marrow cellularity, along with  $\alpha$ -esterase positive cells. Some other findings supported its immunomodulatory property and were proven by using the macrophage migration index (MMI), haem-agglutination titre (H.A.), and phagocytic index (P.I.) in mice<sup>90-91</sup>. Numerous studies have proven that SARS-CoV-2 mainly damages the immune system and induces oxidative stress, cause damage to airway epithelial cells.

Additionally, an increased cytokine level causes damages to tissue damage of the lungs, kidney, and heart and leads to severe complications like respiratory failure, etc<sup>91</sup>. Other findings supported that the extract of *P. longum* as a supplement acts as anti-viral activity against different viruses, reduced stress, anti-inflammatory effect, and reduced the level of cytokines<sup>89</sup>. Therefore, the previous finding supported that it might take responsibility to inhibit the replication of SARS-CoV-2 RNA (Covid-19) in the host cells to benefit Covid-19 prevention.

#### **Amra [*Mangifera indica*]**

*Mangifera Indica* or *Amra* or Mango (figure-10) contain mangiferin, quercetin, gallic acid as chemical constituents and show anti-viral and anti-influenza activities<sup>27,92-97</sup>. However, numerous studies have explained its inhibitory activity against other than Covid-19, infectious disease, causing viruses viz., Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV) (C) Hepatitis B Virus (HBV), Epstein-Barr Virus (EBV), Foot and Mouth Disease Virus (FMDV), Newcastle disease virus (NDV) etc<sup>92</sup>. Another finding also supported that its bioactive molecules have been shown to inhibit cyclophosphamide bone marrow suppressive effect and phagocytic activity in rodents and thus possess as herbal immunomodulatory. It could be responsible for inhibiting SARS-Coronavirus replication<sup>97</sup>.

#### **Tulsi [*Ocimum sanctum*]**

Locally famous name as *Tulsi* or Holy basil (figure-11) contains bornyl acetate, cadinene, camphene, eugenol, and limonene as major chemical constituents. Previous scientific studies have shown that *Tulsi* is antimicrobial, hypoglycemic, hypolipidemic, hepatoprotective, immunomodulatory, antioxidant, anticarcinogenic,

analgesic, wound healing, anti-inflammatory, antipyretic, antidiarrheal, anti-asthmatic, anti-ulcerogenic and adaptogenic.<sup>98-100.</sup>

The most active components are eugenol and eugenol epoxide and may prevent HIV-1 replication with two different mechanisms (increase in IL-4, IgE, PLA2, and T.P. levels, all pathological lung indices as well as a significant decrease in IFN- $\alpha$ /IL-4 ratio) was seen in the asthmatic compared to the control rats. The most active components are eugenol and eugenol epoxide and may prevent HIV-1 replication with two different mechanisms (increase in IL-4, IgE, PLA2, and T.P. levels, all pathological lung indices as well as a significant decrease in IFN- $\alpha$ /IL-4 ratio) was seen in the asthmatic compared to the control rats. Its extract causes decreased IL-4, IgE, PLA2, and T.P. levels, whereas increased IFN- $\alpha$ /IL-4 ratio in vivo study. Higher concentrations of the extract were significantly more than those of dexamethasone. Its extract causes pathological changes, immunological and inflammatory markers, and acts as a potent anti-viral activity against hepatitis B virus, adenoviruses, African swine fever virus, and some RNA viruses *in vitro* study<sup>100</sup>. Therefore, its active phytochemicals are predicted to have the potential to be repurposed as anti-Covid-19 herbal immunomodulatory or ayurvedic therapeutics.

#### **Mandukaparni [Centellaasiatica]**

It is commonly known as *Mandukaparnior Gotukola* (figure-12); contains Asiatic acid, centric acid, centellic acid, carotene, betulinic acid, thankunic acid, and isothankunic acid, etc. as major chemical constituents. Furthermore, there are some other triterpenes like brahmnic acid, centellin, centellicin, asiaticin, bayogenin, terminolic acid, 3<sup>2</sup>,6<sup>2</sup>,23-trihydroxyolean-12-en-28-oic acid, 3<sup>2</sup>,6<sup>2</sup>,23-trihydroxyurs-12-en-28-oic acid, 3-O-[ $\pm$ -L-arabinofuranosyl] 2 $\pm$ ,3<sup>2</sup>,6<sup>2</sup>,23- $\pm$  tetrahydroxyurs-12-en-28-oic acid, centellasapogenol A, centellasaponins A-D, ursolic acid, pomolic acid, 3-epimaslinic acid, 23-O-acetylmadecassoside, and 23-O-acetylasiatoside B101

Various studies suggested that *Centella asiatica* displayed antioxidative, anti-inflammatory, and effective drug for neurodegenerative disease induced by glutamate- or  $\beta$ -amyloid<sup>102</sup>. Its inhibitory activities against fibroproliferative

disorders (Keloids) through blocking the TGF- $\beta$ /Smad pathway and major active molecules suppress HIV-1 LTR transcription and viral replication (vital function to inhibit herpes simplex virus)<sup>103</sup>. On the previous anti-viral effect, it might be responsible for inhibiting the replication of Covid-19. It has established *Rasayana* [anabolic], analgesic, and immunomodulatory properties. It has been mentioned as *MedhyaRasayanain* Ayurvedic classics<sup>101</sup>.

Additionally, the potential use as immunomodulatory agents, modes of action, and plant origin important a plant-based compound has also been comprehensively target point for curtail of Covid-19. Several previous finding has supported that some compounds, other than phytochemicals including essential oils, steroids, terpenoids, phenolics, pigments, flavonoids, and alkaloids, etc. have exhibited immunomodulatory effect. Plant-derived compounds showing promising potential as immunomodulatory agents against Covid-19 are listed in table-2.

#### **CONCLUSION**

Despite the few vaccines against Covid-19 available in the market; still, a psychological stigma against Covid-19 remains the same. To date, there are no satisfactory remedial measures against Covid-19 treatment, early diagnostic tools, and efficient treatment modalities in the modern health system warrants extensive research. Further, the pharmaceutical industries face serious challenges towards the drug discovery/vaccine development against highly versatile Covid-19. There is an urgent need to develop new drugs and Immunomodulators in combination with traditional knowledge validated through modern science against the treatment and management of Covid-19. These herbal immune-modulators drugs show a promising approach to promote the immune system and healthy living. However, necessary to use herbal medicinal products to alleviate Covid-19's burden and promote healthy living. These traditional medicines are regarded as new and promising sources of potential anti-viral drugs. These encouraging preclinical and clinical trials suggested that the traditional medicines are promising drug candidates in the treatment and management of Covid-19. In a nutshell, to obtain

better therapeutic benefits, less expensive, and minor adverse reactions, search for alternative medicine from the natural source, i.e., herbal remedies, used traditionally, now documented with the safety profile. It is high time to validate herbal medicines as primary or adjuvant therapy to prevent and manage Covid-19 infection.

Further, extensive research is required to validate herbal Immunomodulators and their molecular mechanisms in *in-silico*, preclinical, and well-designed clinical trials. It would be interesting to design future therapeutic approaches for immunomodulatory pathways with a synergistic combination of natural herbal drugs.

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#### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

#### AUTHORS' CONTRIBUTION

This review was carried out in collaboration with all the authors, and they have fully contributed to the literature review planed, preparation, and editing of the manuscript.

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#### ETHICS STATEMENT

Not applicable.

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