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An exhaustive comprehension of the role of herbal medicines in Pre- and Post-COVID manifestations

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ABSTRACT

Ethnopharmacological relevance: The coronavirus disease (COVID-19) has relentlessly spread all over the world even after the advent of vaccines. It demands management, treatment, and prevention as well with utmost safety and effectiveness. It is well researched that herbal medicines or natural products have shown promising outcomes to strengthen immunity with antiviral potential against SARS-COV-2.

Aim of the review: Our objective is to provide a comprehensive insight into the preventive and therapeutic effects of herbal medicines and products (Ayurvedic) for pre-and post-COVID manifestations.

Material and method: The database used in the text is collected and compiled from Scopus, PubMed, Nature, Elsevier, Web of Science, bioRxiv, medRxiv, American Chemical Society, and clinicaltrials.gov up to January 2022. Articles from non-academic sources such as websites and news were also retrieved. Exploration of the studies was executed to recognize supplementary publications of research studies and systematic reviews. The keywords, such as “SARS-COV-2, coronavirus, COVID-19, herbal drugs, immunity, herbal immunomodulators, infection, herbal antiviral drugs, and WHO recommendation” were thoroughly searched. Chemical structures were drawn using the software Chemdraw Professional 15.0.0.160 (PerkinElmer Informatics, Inc.).

Result: A plethora of literature supports that the use of herbal regimens not only strengthen immunity but can also treat SARS-COV-2 infection with minimal side effects. This review summarizes the mechanistic insights into herbal therapy engaging interferons and antibodies to boost the response against SARS-COV-2 infection, several clinical trials, and in silico studies (computational approaches) on selected natural products including, Ashwagandha, Guduchi, Yashtimadhu, Tulsi, etc. as preventive and therapeutic measures against COVID. We have also emphasized the exploitation of herbal medicine-based pharmaceutical products along with perspectives for unseen upcoming alike diseases.

Conclusion: According to the current state of art and cutting-edge research on herbal medicines have showed a significant promise as modern COVID tools. Since vaccination cannot be purported as a long-term cure for viral infections, herbal/natural medicines can only be considered a viable alternative to current remedies, as conceived from our collected data to unroot recurring viral infections.

1. Introduction

The current pandemic of CoV disease is exceptional not just because of its occurrence by a novel coronavirus, but also because of the diverse and unforeseen innate immune responses (Balkrishna, 2020; Jain et al., 2021). The amplitude of the pandemic necessitates an urgent harnessing of all knowledge systems available globally to conquer the disease...
2. Spread of SARS-COV-2

The Ayurveda system is well known for its management to treat various ailments. The medicines which are obtained from a natural source are widely utilized for their efficacy as antiviral, antibacterial, neurostimulation, and for its immune-boosting property, which have potential to fight against foreign pathogens. Viruses are an intracellular parasite that lives in the host cell for their survival. The drug/bioactive interfere with the cellular mechanisms of the virus to hinder its further growth. Therefore, antiviral drugs are vital for the survival of host cells without any adverse effects on the host cell. RDRP is an enzyme that catalyzes RNA replication, and these are essential proteins encoded in the genomes of all RNA-rich viruses without having a DNA stage. RDRP is responsible for the multiplication, growth, and survival of the virus. Hence, RDRP lately arose as a capable target to inhibit viral replication and its high conservation among viral strains (Balkrishna, 2020).

The entrance of SARS-COV-2 into the host cell depends on the interaction with the ACE-2 receptor (Kumar et al., 2020; Seyed et al., 2021). The S protein of the spike attaches with ACE-2; as a result, the virus gets cleaved and is enabled for its annexation into the membrane of the host cell, which is facilitated by the TMPRSS-2 (Hasan et al., 2021; Hoffmann et al., 2020). The clinical assessment of the affected patient with SARS-COV-2 has shown a high level of cytokines and chemokines within the human plasma, which is the responsible factor for the multiplication, growth, and survival of the virus. Hence, RDRP lately arose as a capable target to inhibit viral replication and its high conservation among viral strains (Balkrishna, 2020).

The recommended ayurvedic regimens for the prophylaxis of COVID-19 include the use of Guduchi (giloy) (Tinospora cordifolia) (Wild.) Miers., chyawanprash, golden milk, kadha, nutritional supplement, and the use of warm water, etc. A recent study proposed that the application of Ashwagandha (Withania somnifera) (L.) Dunal), Tulsi (Ocimum sanctum L.), and Guduchi constituents are very effective against COVID-19, owing to their potential to target the ACE-2 receptor. The ACE-2 protein attached to a human immunoglobulin G Fc domain (ACE-2-Fc) of SARS-COV-2 patients may assist traditional neutralizing antibodies, which could allow for the treatment of the infection. ACE-2-Fc might play an imperative role in the treatment of COVID-19 if the function of ACE-2-Fc is inhibited (Adhikari et al., 2021; Gajewski et al., 2021; Vellingiri et al., 2020). For the period of viral infection, host factors provoke an immune response, contrary to the viruses. T cells, specifically CD4+ and CD8+, are crucial for an antiviral role to battle the pathogens and raise the risk of evolving autoimmunity/inflammation. The CD4+ T cells produce viral-specific antibodies by stimulating T cell-dependent B cells. Nevertheless, CD8+ T cells are cytotoxic and kill virus-infected cells. It has been observed that the patients infected with SARS-COV-2 showed CD8+ T cells in the pulmonary interstitium which are 80% of the total inflammatory cells and they play a vital role in eradicating the CoV from infected cells and recovering immune damage. (Cecere et al., 2012; Maloir et al., 2018).

Having a healthy immune system is just that abundance of vibrancy, vitality, and health. The developed vaccines and identified medicines are not effective on a long-term basis to prevent COVID-19 from spreading among the population. Moreover, the mutating nature of a virus limits the effectiveness of the developed vaccine against them. During the various waves of this pandemic, most of the countries were suffered severely while the spread was not in abundance in India due to the use of herbal immunity boosters which is protecting our body by magnifying the immunity.

Abbreviations

Antibody-secreting cells ASCs
Angiotensin convertase enzyme 2 ACE-2
Coronavirus CoV
Coronavirus disease of 2019 COVID-19
Cyclooxygenase-2 COX-2
Dendritic Cells DC
Follicular helper T Th
Food and Drug Administration FDA
Herpes simplex virus HSV
Interferon IF
Interleukin IL
Interleukin-1 receptor-associated kinase IRAK
Macrophage inflammatory protein-1-alpha MIP-1-α
Mitogen-activated protein kinases MAPKs
Monocyte chemoattractant protein MCP
Natural killer cells NKc
NF-kB-inducing kinase NIK
Non-structural proteins Nsp
Once in a day O.D.
Oral nutrition supplement ONS
Phospholipase A2 PLA2
Receptor binding domain RBD
Replication/transcription complex RTC
RNA-dependent RNA polymerase RDRP
Severe acute respiratory syndrome coronavirus 2 SARS-COV-2
Tablespoon tbsp
Teaspoon tsp
T-helper th
Three times a day T.I.D.
Tissue necrosis factor TNF
Tool like receptors TLRs
Transmembrane protease, serine TMPRSS
Twice a day B.I.D.
Vascular endothelial growth Factor VEGF
World health organization WHO

efficiently. However, WHO has proposed guidelines to prevent oneself from effecting by social distancing to avoid direct contact of virus, and patient isolation at an early stage, circulating the evidences accurately to the public, and curating the social and financial influence on them. Since the start of the COVID-19 outbreak, traditional herbal therapies have been vigorously used among the people as the home remedies (Mousavi et al., 2021). Ayurveda has shown substantial potential towards prevention and treatment of COVID-19 (Singh et al., 2022; Xu et al., 2020). The involvement of Ayurveda to manage the COVID-19 challenge is not limited but is potentially well known to support health services. SARS-COV-2 infection generally affects people with a weak immune system. So, it is a primary goal to enhance immunity using the Ayurvedic system for the treatment of COVID-19 patients. Ayurveda intrusions become even more pertinent by the fact that there is a broad explanation of the causation and management of the COVID-19 pandemic in Ayurveda. The identification and the use of phytochemicals obtained from medicinal herbs could help to lower the infection rate and successfully have become a new approach for the treatment of viral infections (Mousavi et al., 2021). Ayurveda has shown substantial potential to eradicate the CoV from infected cells and recovering immune damage (Mousavi et al., 2021).
anti-inflammatory molecules. The SARS-COV-2 spike protein has two
domains S1 and S2. S1 is behind the insertion of the virus into the host
cell while S2 mediates the fusion of the host and the viral membrane to
facilitate the viral RNA genome within the host. Thus, these play a
pivotal role in drug design. Many phytochemicals inhibit the entry of
the viral genome to the host. The spikes proteins are also active in modu-
ating the immunity of host cells toward CoVs (Dubey and Dubey, 2022)
and S is a significant antigen on the virus surface (Yuan et al., 2017).
Another Nsp3 protein responsible for CoV is RTC formation. It releases
Nsp1, Nsp2, and interacts with other Nsp and RNA to form RTC
(Hardenbrook and Zhang, 2022; Wu et al., 2022).

3. Chemical constituents and properties of selected
phytochemicals

Since the coronavirus outbreak, computer docking models have been
used to screen beneficial constituents from phytochemicals against
coronavirus in vitro and in vivo research. Natural polyphenols such as
Tulsi, Ashwagandha, Amla, Piperine, Guduchi, and others have demonstrated
to be effective against COVID 19 activity in the studies listed above (Ispanio et al., 2021).
Tulsi contains phenolic compounds like apigenin, cirsimaritin,
rosamic acid, isothymusin, cirsilineol, and a substantial amount of
eugenol. The volatile oil content of Tulsi is about 0.7% it comprises
about eugenol (71%) and methyl eugenol (20%); carvacrol and sesqui-
terpene hydrocarbons, caryophyllene, and ursolic acid. Orientin and
vicenin are flavonoids present in Tulsi that display different pharma-
cological activities. Eugenol (phenylpropanoid) is a derivative of
guaiacol with an allyl chain substituted para to the hydroxy group (Orlo et al., 2021). The animal and human experimentation data reveal the
antimicrobial (including antibacterial, antiviral, antimalarial),
anti-diarrheal, anti-oxidant, anti-inflammatory, hepato-protective,
cardio-protective, ren-protective, analgesic, anti-tyreptic, immune-modulatory properties. Ursolic acid is a pentacyclic triterpe-
noid with three terpene units which is constructed by an isoprene unit
with theaferin-A having aneone ring responsible for its biological activity.

Curcumin is a chief phytoc constituent of Piper or kaliyirch (Piper
nigrum L.) comprised of an aromatic ring with a methylenedioxy bridge,
a conjugated diene system, and a pipeirdine ring composed of an
amide bond which provides biological activities (Pal Singh and
Choudhary, 2015). Black pepper is used as medicine to treat digestive
and respiratory tract-related diseases caused by a viral infection such as
acute respiratory infection, asthma, chronic indigestion, and fever.
Pepper is well known to boost antioxidant property, bioavailability
enhancer, enzymatic activity, lipid peroxidation, and immunomodula-
tory effect (Kumar et al., 2021). Garlic (Allium sativum L.) is one of the
well-known immunity boosters that contains 33 sulfur compounds, 17
amino acids, and nutrients such as calcium, copper, germanium, iron,
magnesium, potassium, selenium, zinc, and vitamins A, B1, and C
(Arifah et al., 2021). Out of these germanium, selenium, and zinc are the
major immunostimulators (Ali et al., 2007; Bizinov et al., 2018).
It directly affects cell-mediated immunity, including macrophages and T
cells (Abdullah et al., 1988). The availability of different garlic chemical
constituents are found to be present on their different part (1) fresh
bulbs contain S-allyl-L-cysteine sulfoxide (alliin); (2) powder and dried
garlic contains allin and disulphide; (3) ground garlic (macerates) are
enriched with sulphide family compounds, dithiones, and ajoene com-
ponents; (4) in steam distillation oil sulfoxides are main; (5) ethanolic so-
lution of chpped, slathered and aged garlic contain S-allyl-L-cysteine
and S-allyl mercaptocysteine. Another herbal medicine is ajila (Phyl-
lanthus emblica L.) which contains tannins, alkaloids, and phenols. The
ajila fruit constitutes alkaloids (phyllantine, phyllmebne, phyllanti-
dine); hydrolyzable tannins (emblicin A and B, punigluconin,
pedunculagin, chebulinic acid, chebulagic acid, corilagin, geraniin,
and ellagotannin); phenolic compounds (gallic acid, methyl gallate, elagic
acid, triggylae glucose), amino acids, carbohydrates, organic acids,
flavonoids, and vitamins. The antioxidant activity is due to the presence
of ascorbic acid-containing hydrolyzable tannins. Emblicin A, embli-
cinan B, punigluconin, and pedunculagin are some chief constituents
that accounted for antioxidant activity. Licorice (Glycyrrhiza glabra L.)
is one of the well-known immunomodulator containing flavonoids,
glicosides, cinnamic acid, and courmarin derivatives are among the
phenolic chemicals. Liquiritin, isoliquiritin, glucosides, triterpenoid sa-
ponins such as glycyrrhizin, a potassium and calcium salt of glycy-
rhizinic acid, and others are the primary active components. Compounds
that have been extracted from neem (Azadirachta indica A. Juss.) are
nimbim, nimbimibin, and nimbdbin. The compounds that are isolated from
the aqueous extract of bark are gallic acid, catechin, epicatechin, mar-
ggonolone, polysaccharides (G1A, G1B, G2A, and G3A), and peptido-
glucan. The essential compounds found in the neem leaves are
nimbanene, nimbandiol, nimbin, nimbid, 6-desacetylnimbimbinene,
asorbic acid, nimbidole, amino acid, n-hexacosanol, 7-desacetyl-7-ben-
zyloyledunin, 7-desacetyl-7-benzyolazadiradione, and 17-hydroxyaza-
diradione (Latif et al., 2020). The phytochemicals of neem have
already it directly affects been known for antiviral and antibacterial
activity. Pomegranates (Punica granatum L.) are high in polyphenols
including ellagittannins, which include mainly α and β isomers of PC,
anthocyanins, ellagic acid, gallic acid, glycosylated derivatives (Sharma
et al., 2021; Tito et al., 2021). The chemical structures of chief immu-
nomodulatory phytoconstituents are depicted in Fig. 1.

4. Antiviral and immunomodulatory mechanisms of
recommended bioactive compounds

The Npx15 is a protein that acts as an endoribonuclease and prefer-
entially cleaves 3’ of uridylates through a ribonuclea A (RNase A) like
mechanism and also facilitates viral replication and transcription (Zrieq
et al., 2021). A study predicted that many of the phytochemicals of the
Kadhya have a significant binding affinity with Np3 and Npx15. Green
tea extract also increases the lymphoblast to induce the production of
IL-1α, IL-1β, monocytes, and lymphocytes. The EGCG and EGC may
prevent inflammation; impede proliferation, proinflammation, and activation of NF-κB. These conditions reduce the levels of IL-8 and enhance immunity (Di Lorenzo et al., 2013). Thus, the phytochemicals (berberine, pigenin, curcumin, piperine, quercetin, tinospoide, urosolic acid, withonolide, withaferin, and withanone, etc.) may disrupt the formation of RTC and stop the viral genome replication (Maurya and Sharma, 2020; Zrieq et al., 2021). It is well known that NF-κB is the master regulator for several genes such as COX-2, VEGF, pro-inflammatory cytokines (IL-1, IL-2, IL-6, and TNFα), chemokines (e.g., IL-8, MIP-1α, and MCP-1), adhesion molecules, immunoreceptors, growth factors, and other agents associate in proliferation and invasion. NF-κB activation mediates through two of the redox signaling pathways. One pathway includes NIK/IKK, whereas the second pathway involves MAPKs, and both cause the induction of transcriptional activation of NF-κB. In the non-canonical NF-κB signaling pathway, NIK is a pivotal mediator. The main activity of NF-κB is that its transcription factor acts directly on oxidative stress. Therefore, oxidative stress activates nuclear factor-inducing kinase (NIK)/IκB kinase (IKK) and MAPKs. NIK/IKK and MAPK pathways activate NF-κB and migrate to the nucleus and bind to κ elements on DNA at enhancers and promoter regions. Many herbs suppress inflammatory diseases by controlling the pro-inflammatory pathways by producing pro-inflammatory mediators (Maurya and Sharma, 2020). There is also evidence that phytochemicals found in the Kadha have a significant binding affinity with NIK, which can stop NF-κB mediated downstream events (Fig. 2). Recently, Huang et al. (2020b) showed that the patients infected with SARS-COV-2 had high levels of IL1, IFNγ, IP10, and MCP1, which can mediate cytokine storm-related multi-organ damage. At the same time, SARS-COV-2 infection also initiates the secretion of Th2 cytokines (eg, IL4 and IL10) which suppress inflammation (Huang et al., 2020). The increased secretion of inflammatory mediators was also associated with the moderation of helper T cell responses in COVID-19 patients. In this series, the entire tulsi plant is useful for the immunomodulatory effect. The myricetin and scutellarein found in tulsi potentially inhibited SARS-COV helicase by inhibition of ATPase activity (Islam et al., 2021). Scutellarein is a natural flavonoid obtained from tulsi. The scutellarein docks well into the cavity of the RDRP enzyme (catalyzes RNA replication of SARS-COV) with a docking score of −8.3 kcal/mol. It may perturb Motif B, which is used by the coronavirus for its polymerization (Balkrishna, 2020). Thus, the hang-up of RDRP offers a striking means to control pathogenicity and the spread of COVID-19. Tulsi possibly minimizes the IgG1 level and increases the level of IgG2a to set up a defending immune response. Few phyto-compounds present in tulsi may hit the catalytic cleft of the RDRP (Fig. 2).

Many studies have been conducted showing the significant effect of tulsi in enhancing the immune response. The immune-boosting ability of tulsi assessed in cattle with subclinical mastitis shows improved IL-2 gene expression and IL-2 production in male Wistar rats (Goel et al.,

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Fig. 1. Chemical structures of chief immunomodulatory phytoconstituents.
The possible mechanism for improving immunity is a modulation of the GABA pathway (Goothy et al., 2020). Tulsi enhances immune response by increasing T-helper and NK cells; phagocytic activity and index with the rise in lymphocyte count, neutrophil count, and antibody titer (Gautam et al., 2022). It has been observed that when 3 ml/kg of tulsi oil was administered by the intra-peritoneal route, the rat showed a high augmentation in the anti-sheep red blood cell antibody, and decreased histamine release at the peritoneal mast cell confirmed the humoral immune response (Godhwani et al., 1988). Further, similar dosing of tulsi has shown a potent antiviral effect by avoiding the entry of the virus into the cell. In other research, Paidi et al. (2021) screened the various component of the tulsi leaf. By the Alpha Screen assay, it was observed that the eugenol significantly inhibited the interaction between spike S1 and ACE2. In silico and thermal shift assays reported that the eugenol is associated with spike S1, but it did not have any impact on ACE2. Consequently, eugenol strongly suppressed the entry of pseudo typed SARS-COV-2 and decreased SARS-COV-2 spike S1-induced activation of NF-κB and in the human A549 lung cells, the expression of IL-6, IL-1β, and TNFα was also found to be reduced, confirming its potential for selective targeting of spike S1 of SARS-COV-2 (Paidi et al., 2021).

The ashwagandha significantly increases the cell-mediated immune response in normal mice. The root extract of ashwagandha raises the level of IF-γ, IL-2, and granulocyte-macrophage colony-stimulating factors in mice, the raised level indicates that it is capable of augmenting immunity and myelo-protective effects. Ashwagandha potentially increases the nitric oxide synthetase activity of the macrophages, which in response enhances the microbial assassination potential of these immune cells (Iuvone et al., 2003; Tiwari et al., 2014, 2018). Withanone is a natural phytochemical of ashwagandha that acts on viral RBD and the host’s ACE-2 receptor complex. It was disclosed in docking to the binding edge of the AEC-2-RBD complex which moved slightly towards the interface center on simulation (Varshney et al., 2020). Withanone noticeably reduced the electrostatic constituent of binding free energies of the ACE-2-RBD complex (Fig. 2). Such types of disruptions may potentially block COVID-19 entrance or deteriorate and prevent subsequent infectivity (Varshney et al., 2020). Withaferin-A bound with the DNA polymerase of the HSV and inhibited it to evident the antiviral mechanism of withaferin A (Grover et al., 2011). In the context of COVID-19, withanone showed interaction with the highly conserved protease of CoVs. The molecular simulation study for the N3 inhibitor showed the potential to inhibit the functional activity of SARS-COV-2 protease (Balkrishna, 2020). Moreover, the activity of withanone and withaferin-A was investigated against TMPRSS2. The TMPRSS2 helps to invade the virus and target the host cell. In this, the molecular modeling revealed that both compounds significantly bind and steadily intermingle at the catalytic site of TMPRSS2. At the TMPRSS2 catalytic site, withanone interacted potentially compared to withaferin-A and induce
changes at the allosteric site (Kumar et al., 2020). Two constituents from Ashwagandha with glycowithanoloid i.e. sitoindoside IX and sitoindoside X assessed for immunomodulatory activity (Khare and Naharwar, 2020). By this evidence, we can say that ashwagandha is a major natural compound for improving immunity and antiviral efficacy. Past evidence of the use of Withania with other herbal medicines may play a pivotal role to boost immunity and bring enormous changes to the asymptomatic people of the community.

The aqueous extract of black pepper causes an increment in splenocyte proliferation in a dose-dependent synergistic manner. The rise in Th1 cytokine release by splenocytes and suppression of Th2 cytokine release by splenocytes strongly endorses black pepper for the immunomodulatory effect (Majdalawieh and Carr, 2010). Pepper showed anti-release by splenocytes strongly endorses black pepper for the immune-of the use of Withania with other herbal medicines may play a pivotal role to boost immunity and bring enormous changes to the asymptomatic people of the community.

Studies also confirm the amla’s property of boosting immunity where it inhibits chromium induced free radical and restored the antioxidant property by resolving DNA fragmentation and apoptosis. It also showed the immunosuppressive effect of chromium on lymphocyte proliferation and even restored the IL-2 and IFNγ production (Ram et al., 2002). Mechanisms of action of some herbal immunomodulators are summarized in Table 1.

5. Application potential of recommended treatment to fight SARS-COV-2

5.1. Liquorice (Mulethi)

Liquorice (Glycyrrhiza glabra Linn) is also known as “Yashitimadhu” and “Mulethi” in India (Sharma and Agrawal, 2013). Liquorice root powder is an effective expectorant that is used in Ayurvedic medicine for the treatment of upper respiratory tract and throat infections since prehistoric times. The active compound, glycyrrhizinic acid has shown antiviral activity (van de Sand et al., 2021). It has also been used to inhibit the replication of SARS-COV. This active compound can immobilize the virus due to its potent immunomodulatory activity. The polysaccharide fraction of liquorice stimulates the macrophages. It also elevates and assists immune stimulation (Wagner and Juricic, 2002). N-acetylmuramoyl is a glycyrrhizin analog that has shown the potential for in vitro immune stimulation (Dissayake et al., 2020). In a study, Cinatl et al. (2003) compared the antiviral efficacy of 6-azauridine, glycyrrhizinic acid, mycophenolic acid, pyrazofurin, and ribavirin, on SARS-COV. The experimental results showed that glycyrrhizinic acid has a better antiviral activity as compared to the other four drugs in viral adsorption and penetration (Cinatl et al., 2003). It was found that glycyrrhizin possesses the ability to stimulate endogenous defense mechanisms (Arora et al., 2011). Another study suggested that neutrophils’ alcoholic extract of Glycyrrhiza glabra enhances phagocytic activity (Ali-Snafi, 2018). A different study has indicated that SARS-COV-2, as well as SARS-COV, have the same receptor ACE-2. Glycyrrhizinic acid can potentially bind to this receptor and may produce a therapeutic effect on SARS-COV-2 (Zheng et al., 2021). Molecular docking of glycyrrhizic acid revealed its antiviral potency on SARS-COV-2 with potential interaction with ACE-2. The binding energy of glycyrrhizinic acid and ACE-2 used in molecular docking was −7.0 kcal/mol (Huang, F. et al., 2020). The intake of Glycyrrhiza glabra root powder (0.1, 0.2, 0.3, and 0.4 mg) with warm water, may produce a lucrative effect on COVID-19 infection. Factor Xa (FXa) inhibitors effectively block the coagulation cascade and have evolved as a crucial part of the prevention and treatment of thromboembolic diseases and in therapeutic protocols involved in many clinical trials in COVID-19. Ibrahim et al. (2021) performed in-silico studies. When examined in-vitro, licorice flavonoids were found to have significant inhibitory action on coagulation factor Xa. The compounds of liquorice, i.e., liquiritin, nar-ingenin 5-O-glucoside, 3,3′,4,4′-tetrahydro-2-methoxychalcone, and 7-hydroxy-4′-methoxyisoroflavone identified as hopeful anticoagulant agents for the design of FXa inhibitors. These drugs have high oral bioavailability and can be regarded as possible candidates for building orally active direct FXa inhibitors, according to in silico ADMET predictions. Most of the substances examined had superior oral absorption predictions and fewer metabolic interactions compared to that of synthetic drug “Endoxaben”. Gabridin and 7-hydroxy-4′-methoxyisoroflavone showed significant oral absorption (100%) (Ibrahim et al., 2021). Vanzara et al. (2021) evaluated liquiritin and compared with dexamethasone,

Table 1

| Mechanisms of action of selected herbal immunomodulators. |
|----------------------------------------------------------|
| Drug           | Reported mechanisms                                      | References               |
|----------------|----------------------------------------------------------|--------------------------|
| Garlic extract | - Boost the IFNγ and IL-4 production                      | Ota et al. (2012)        |
|                | - Decrease the IL-2 production in Peyer’s patches of mice |                          |
| Allicin        | - The inhibitory effect on NF-κB activation.              | Bruck et al. (2005)      |
| Glycyrrhizin   | - It induces the level of TNF-α and IL-1β in the case of   | (Xie, Y.-C. et al., 2009) |
|                |  |  |  |
| Cinnamon       | - Suppresses IL-1β, IL-6, and TNF-α in LPS-activated       | Kim et al. (2018)        |
| (Cinnamomum    | macrophages, in MAFK dependent pathways, and bleomycin-induced |  |
| verum J. Preel) |  |  |  |
| Long pepper (Piper longum L.) | - Inhibits allergic inflammation by inhibiting Th2/Th17 responses and mast cell activation. | Bui et al. (2017)        |
|                | - Regulate the balance of cytokine production from Th1, Th2, Th17, and Treg cells. |  |
|                | - Inhibits GATA3, IL-4, IL-6, IL-1β, ROHr, IL-17A, TNF-α expression |  |
|                | - It increases the secretions of IL-10, INF-γ. |  |
| n-Gingerol and 6-gengerol | - Prevents Th2-mediated immune responses | Abui et al., 2008; Tripathi et al., 2007 |
| Guduchi        | - A D-glucan noncytotoxic immune-stimulatory poly- | Nair et al. (2008) |
|                |  |  |  |
remdesivir, hydroxychloroquine, and azithromycin. The In-Silico evaluation was carried out by Autodock 4.2.6. The liquiritin showed $-6.62$ kcal/mol binding energy. Liquiritin showed binding formation with six active residues viz. THR26, GLY143, CYS145, HIS 164, GLU166 and GLN189 (Fig. 3E). out of these four, three, four and two residues were similar to that of the dexamethasone, remdesivir, hydroxychloroquine and azithromycin, respectively. Liquiritin, a naturally active chemical, demonstrated the presence of a typical hydrogen bond with THR26, GLY143 (Fig. 3C). Liquiritin also possesses hydrophobic (Fig. 3D) and electrostatic interaction. Liquiritin and the synthetic medication dexamethasone have similar drug abilities, according to an ADMET analysis (Vanzara et al., 2021).

### 5.2. Tulsi

Tulsi is also known as “The Queen of Herbs” and contains Flavones and flavonoids in their extract. Tulsi contains a flavone called scutellarein (Chaudhary et al., 2020). Tulsi is useful for various therapeutic benefits like antiviral, antifungal, hepatoprotective, anti-diarrheal, antioxidant, analgesics, antipyretics, anti-inflammatory, anti-asthmatic, anti-allergic, and produce immuno-modulatory effects (Palai and Giri, 2021). Tulsi drop is a well-regarded substance that has been shown to improve immunity (Jamshidi and Cohen, 2017). It assists in different infections such as fever, cold, sore throat, and cough and helps in building new blood cells. The efficacy of tulsi drop in the prophylactic treatment of SARS-COV-2 can be enhanced by combining it with other immunity-boosting extracts such as Guduchi, turmeric, ginger (Zingiber officinale Roscoe), etc. For this purpose, a proper guideline should be followed for testing the efficacy in different concentration of combined formulation. Three to four washed tulsi leaves should be used with tea or any sort of kwath, according to the AyUSH ministry (Palai and Giri, 2021). The dose of each herb is mentioned in API (The Ayurvedic Pharmacopoeia of India) as 2–3 g powder of Tulsi leaves, 1–3 g powder of cinnamon bark, 250 mg–1 g powder form of black pepper, and 1–2 g powder of ginger.

### 5.3. Ashwagandha

The immunomodulatory effect of the root extract of Ashwagandha was evaluated in the three myelosuppression models in mice such as azathioprine, cyclophosphamide, or prednisolone. The study revealed that the Ashwagandha increased the red blood cells, white blood cells, platelet count, and body weight in mice as compared to untreated control mice. The estimated dose found in rats 200 mg/kg/day. The histopathology of the liver, stomach, kidney, spleen, and lungs was observed normal after the treatment at this dose (Yan et al., 2018). Another study also investigates the production of IL-1 and TNF-α after the administration of Ashwagandha to mice treated for carcinogenic ochratoxin A (Mishra et al., 2000). Ashwagandha showed immuno-modulatory effects at doses of 150 and 300 mg/kg in IgE-mediated anaphylaxis as a reduction of ovalbumin-induced paw edema in comparison to the drug disodium cromoglycate (Agarwal et al., 1999).

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Fig. 3. Docking analysis of SARS-CoV-2 Mpro binding with Liquiritin (A) hydrophobicity surface 3D representation (B) 3D representation of Liquiritin-SARS-CoV-2 Mpro interaction (C) Interactions of Liquiritin through H-bond in a pocket site of SARS-CoV-2 Mpro (D) Interactions of Liquiritin through hydrophobic bond in a pocket site of SARS-CoV-2 Mpro (E) 2D representation of Liquiritin in the active site of SARS-CoV-2 Mpro (CC BY NC ND 4.0 License) (Vanzara et al., 2021).
Ashwagandha produces toxicological effects in our body in overdose condition. A recent study has reported a strategy that blocks or weakens the COVID-19 viral infections. Ashwagandha most potential phytochemical for controlling COVID-19 infection by disrupting the spike protein’s electrostatic interaction and lowering the binding free energy between the viral RBD and its ACE-2 receptor. This was proved by a disease where phyto compound withanone was screened by molecular docking and showed a distinct effect on RBD and ACE-2 receptor complex. It was observed from the study that withanone significantly reduces the electrostatic component of binding free energies between viral RBD and its ACE-2 receptor. These disruptions of the electrostatic interaction results in interference of viral protein entry and other manifestations via the ACE-2 receptor (Varshney et al., 2020). Two salt bridges were also occupied at the interface. When withanone incorporated, it subverted salt bridges and reduced their possessions. This study focused on the most applicable option for controlling CoV entry into host cells. Thus, we can say, these studies provide an alternative and attractive means for the successful treatment of COVID-19 infection (Varshney et al., 2020). Ashwagandha is available in various forms like powder, capsules, and extract (liquid). The standardized extract dose of ashwagandha is 100–200 mg twice per day. We can also take the dried powder of ashwagandha (1–2 g) daily one to three-time for therapeutic effect in COVID-19 (Shah and Krishnamurthy, 2013).

5.4. Garlic

Garlic is also called Lahsan (Hindi) belonging to the family Alliaceae (Yasmin et al., 2020). They show beneficial effects on various diseases like viral, fungal, parasitic, and anti-inflammatory properties. A key advantage of garlic for COVID-19 patients is that it protects against various inflammatory diseases like allergic-airway inflammation, inflammatory bowel disease, and many more (Moutia et al., 2018). Garlic preparation may be liquid (aqueous, oil, or solvent) or solid (dried power and fresh cataplasm). Garlic is efficient in maintaining the homeostasis of the immune system and prevents immune dysfunction. The garlic boosts the function of the immune system by provoking the cells, such as lymphocytes, macrophages, NKc, DC, and eosinophils. It works by modulation of immunoglobulin production, cytokinin secretion, macrophage activation, and phagocytosis (Arreola et al., 2015). Several studies reported the immunomodulatory and antiviral effects of garlic and its components (Prajapati et al., 2021; Vathsala and Murthy, 2020). Some researchers used the molecular docking method and investigated that alliin may be a functional inhibitor of SARS-COV-2 as compared to remdesivir, chloroquine, and ritonavir (Cheng and Li, 2020). If garlic and its active constituents are used in proportionate quantities, then it may produce beneficial effects against COVID-19. Suitable dosing and dosage form can be achieved by employing drug delivery advances in nanotechnology.

5.5. Neem

Neem is a tree belonging to the family Meliaceae. Neem possesses immunomodulatory as well as anti-inflammatory, antioxidant, antiviral, antibacterial, and anti-tumor activity. Each part of the neem plant is useful in developing strong immunity (Alzohairy, 2016). One such study suggested that neem oil potentially induced the production of IFNγ by Y-lymphocytes. It activates the macrophages to enhance phagocytic ability. Neem oil is efficient in antigen uptake and cellular activation (Upadhyay et al., 1992). The research study investigated the immunomodulatory and growth-promoting effects of neem leaves. 50 mL/L of fresh neem leaves infusion on broiler chicks showed that neem infusion successfully improved antibody titer, growth performance, and gross return water (Durrani et al., 2008). In another study, broilers, and dry leaves powder of neem showed humoral as well as cell-mediated immune responses. It was observed that neem (2 g/kg) significantly enhances the antibody titers against the new castle disease virus (NCDV) antigen (Alzohairy, 2016; Sadekar et al., 1998). Application of neem oil on the body or intake of 1 gm neem powder daily with lukewarm water enhances the immunity power and produces a beneficial effect on fighting SARS-COV.

5.6. Ashwagandha

Ashwagandha is a shrub belonging to the family Menispermaceae, and shows immunomodulatory effects against several microbial infections. Commonly it is known as Amrita, Ashwagdhi, Gurach, Tinospora. This plant mainly constitutes choline, berberine, tinosporic acid, tinosporine, tincordifolioside, tinosporon, tinosporaside, and trembeterine (Sarangi and Soni, 2013). These active phytochemicals help Ashwagandha to fight against various diseases such as jaundice, gout, urinary disorder, asthma, inflammation, urinary infections, and pyrexia. It is an anti-allergic that provides substantial relaxation from nasal pruritus, nasal discharge, and sneezing (Badar et al., 2005). A study revealed that G1-4A is a type of polysaccharides having a molecular weight of $2.2 \times 10^6$ Da obtained from Ashwagandha, which modulates the levels of pro-inflammatory cytokines such as TNF-$\alpha$, IL-$\beta$, IL-6, IL-12, IFN-$\gamma$. The result indicates that G1-4A is a potent therapeutic agent that inhibits Mycobacterium tuberculosis through the immunomodulatory effect both in-vivo and in-vitro (Gupta et al., 2016). Ashwagandha is also used against several viral diseases such as herpes HIV, etc. it is suggested to be a potent agent in monitoring COVID-19 due to its immunomodulatory and antiviral nature.

6. Pharmaceutical product developments for immunity-boosting against COVID-19

Researchers from all over the world are seeking to find a cure for COVID-19. Health experts have recommended promoting the body’s immune system with ayurvedic herbs which may help to minimize viral load and speed up the recovery from the disease. For this, there are various marketed preparations available in different forms to promote immunity.

6.1. Nanoparticles

Nanoparticles (NPs) have emerged as a novel vehicle for the targeted delivery of drugs, vaccines, bioimaging, and enhanced bioavailability. Because of its unique features of water solubility, biocompatibility, cost-effective manufacturing, and low toxicity, NPs are the preferred carrier (Dheyab et al., 2021; Mohammadzadeh et al., 2022; Prajapati et al., 2019). Due to their structural similarities, synthetic NPs can precisely imitate the virus and interface extensively with its proteins. As a result, NP-based techniques for combating this virus possess a good prospect. Earlier, NPs had been proven to be successful against a variety of viruses, particularly those belonging to the Coronaviridae family (Medhi et al., 2020; Mosselhy et al., 2021). Recently, NPs are emerging as a carrier for drug delivery in the treatment of COVID-19. Zhao et al. (2021) synthesized glycyrrhizic acid NPs (GANPs) to inhibit the proliferation of the murine coronavirus MHV-A59 and reduce proinflammatory cytokine production caused by MHV-A59 or the N protein of SARS-COV-2. GANPs revealed their targeting efficiency in the severe inflammation area such as the lung and had antiviral and anti-inflammatory impacts, reducing organ failure and providing a substantial survival benefit to diseased mice (Zhao et al., 2021).

6.2. Tablets

Recently, the Coronil tablet has received certification from AYUSH Ministry as per the WHO certification scheme. The company (Patanjali Ayurved Limited) claimed that it is the first evidence-based medicine to fight Covid-19. Coronil tablet is the combination of several herbal ingredients including Ashwagandha, Konch Shuddha (Mucuna pruriens (L.)
DC.), Satavar (Asparagus racemosus Willd.), Safed Musli (Chlorophytum arundinaceum Baker), Javitri (Myristica dalctyloides Gaertn.), Jaiphal (Myristica fragrans Houtt.), Shuddhkuclha (Strychnos nux-vomica L.), Akarkara (Anacculus pyrethrum (L.) Lag.), Jundbedaster (Castorium), Swarn Bhasma (Incinerated oxide of gold), Praval Pishiti (Coral), Vang Bhasma (Thermoprocesedastum), Shilajit Shuddh Asphaltum, Pan (Piper betle L.) Ras. Two tablets per day are recommended for the age group between 15 and 80 years and 1 tablet between 6 and 14 years old with warm water, half an hour after a meal (Tiwari and Talreja, 2020). Gaduchi ghan vati is an ayurvedic preparation of Gaduchi extract, known for its prophylaxis and treatment of COVID-19. In a clinical trial (DCT04480398), Gaduchi Ghan Vati was administered orally to SARS-COV-2 patients [2 tablets (500 mg each) B.I.D.] after meal for 28 days. The clinical efficacy was evaluated on 91 patients which revealed positive results in controlling the COVID infection (Radhakrishnan, 2020). In a randomized clinical trial, 1 g of Guduchi Ghan Vati (1 g) and positive results in controlling the COVID infection (Radhakrishnan, 2020). Another capsule developed with the name I-IMMUNE is a capsule brand that has the blend natural constituents of triphala (78 mg), haldri (32 mg), trikatu (45 mg), mulethi (55 mg), papaya leaves (62 mg) (Carica papaya L.), shigru (36 mg) (Moringa oleifera Lam.), manjistha (65 mg) (Rubia cordifolia L.), ashwagandha (50 mg), wheatgrass (17 mg) (Triticum aestivum L.), and guduchi (60 mg). The prescribed dose of this product is 1–2 capsules three times a day for 2–3 months continuously for boosting immunity, and the dose is not mentioned according to the age group.

6.3. Capsules

Recently, capsules of Neem were studied by Nesari et al. (2021) for the prophylactic treatment of SARS-COV-2 infection. Participants received 50 mg of Neem-leaf extract or placebo orally in capsules, B.I.D. for 28 days. Participants who administered neem capsules had a lower chance of COVID-19 infection, indicating that it might be used as a preventive therapy for SARS-COV-2 infection (Nesari et al., 2021). FLUCOMUNE™ (90) is the brand name of the capsule which contains Emblica Officinalis. It is a natural source of bioflavonoids and ascorbigen which is having strong antioxidant activity with immune modulator properties, as well as being an adaptogen. Vasaka (Lantus adhatoda L.), tulsi, guduchi, and liquorice are involved in this capsule for respiratory health support, immune-supportive properties, antispasmodic support, and healthy bronchial function, respectively. Trikatu acts are used as a digestive agent which increases the bioavailability of nutrients in the digestive tract. The dose is one capsule daily for all age groups (no specification regarding dose for the different age groups) with not many herbs recommended by the AYUSH ministry for COVID-19 like ginger, turmeric, ashwagandha, etc. The second product is “Inlife Ashwagandha Capsules 60’s” which contains Withanolides >7% as the active constituent. It has 500 mg of ashwagandha extract in each capsule. Further, the dose prescribed on the pack is two capsules in a day. “I-IMMUNE” is a capsule brand that has the blend natural constituents of triphala which has 500 mg of ashwagandha extract in each capsule. Another capsule developed with the name “Asth 15” capsule, a polyherbal combination can be used as prophylactic against Cov by boosting immunity, it shows bronchodilator properties and acts as a lung detoxifier (Rao et al., 2021). It can suppress infections and regulate allergic reactions. AYUSH 15 mainly acts on the nasal mucosa of the respiratory tract surrounding the walls of the lungs which acts in airways. It has an anti-inflammatory effect that reduces inflammation and congestion inside the lungs. The capsule of tulsi (200 mg; B.I.D.) was given to 41 patients and the data was compared with the standard drug salbutamol. Tulsi showed significant bronchodilator activity by diminishing the levels of IgG1 and IgG2a pointing toward a humoral immune response (Vinaya, 2017). Natural immunomodulatory Curcumaceae capsules have been developed by Lactonova NutriPharm (P) Ltd, Hyderabad. The active constituents present are flavonoid curcumin (diferuloylmethane) and volatile oils, including atlantone, tumerone, and zingiberone for COVID-19 treatment (Shukla, G. et al., 2021; Shukla, Rao et al., 2021).

6.4. Syrups

To overcome Cov infection researchers at the Central Institute of Medicinal and Aromatic Plants (CIMAP), Lucknow, produced two herbal products (CIM-Paushak and herbal Cough Syrup) which modulate immunity by decreasing dry cough. The formulation comprises twelve powerful Ayurvedic ingredients such as Puranva (Boerhavia diffusa L.), Ashwagandha, Mulethi, Harad (Terminalia chebula Retz.), Baheda
tested on A549 cell xenotransplant in the swim bladder of zebrafish
study performed by Balkrishna et al. (2020b), Divya-Swasari-Vati was
persons who are directly in contact with COVID-19 patients during their
system (Balkrishna et al., 2020b). Swasari ras is also active against
sinusitis, it escalates the immune response by improving the respiratory
bacteria and viruses. It is recommended as a prophylactic treatment for
boost immunity due to the presence of Shrigru (Terminalia bellirica (Gaertn.) Roxb., and Sataver (Asparagus racemosus Willd.) known for their nutritive values with Emblica Officinalis and sugar as the base. These are developed based on the latest guidelines of the AYUSH ministry, and it has been prepared based on the ‘Tridosha’ principle of Ayurveda.

6.5. Nasal oil

Conventional Ayurvedic nasal oil hydrates, soothes the nasal cavity, 
relieves stress, heals supraclavicular problems, and improves health. 
Based on the clinical symptoms seen in COVID-19 patients, the treat-
ments must also aim to reduce inflammation of the upper respiratory 
tract (especially the nasal mucosa). 2-2 drops of Pratimarsha Nasya of 
Tila taila Anu taila, and Sarshap taila can be administered daily in each 
nostril. Pratimarsha Nasya (Anu taila/sesame oil) is crucial in reducing 
and treating Nasobronchial illnesses, as well as strengthening respira-
tory immunity (Shah et al., 2020). Anti-inflammatory phytocompounds 
exist in the herbal constituents of Anu taila (the nasal drop), which keep 
pro-inflammatory cytokines in control (Devpura et al., 2021). Nyasa is 
an Ayurvedic practice in which oil is instilled through the nostrils to 
boost immunity. It is a therapy for the nose, sinuses, throat, and head.
The oil is in the form of Desi ghee and Anu taila. One can also use natural 
Ayurvedic oils with herbs like Brahmi, and Basil (in small quantities). 
The common dosage of Chyawanprash is 12
– 250 ml) in the morning on an empty stomach to
improve immunity and prevent various ailments (Khan et al., 2016; Sharma et al.,
Yamada et al., 2011). It is used as a metabolic tonic used to foster im-

6.7. Chyawanprash

Chyawanprash is also known as Chyavanprasha, chyawanaprasam, etc. It is made from two lexes, “Chyawan” and Prasha”. The word Chyawan means sage, and symbolizes ‘degenerative change’ and Prasha indicates itaalla drug or foodstuff that presents consumption. Chyawan-
prash is a combination of more than 40 herbs and is made by different Ayurveda companies such as Dabur, Patanjali, etc. (Fig. 5). The primary ingredient of Chyawanprash is amla fruit pulp, which is useful in res-
piratory tract infections and tuberculosis. Amla possesses immunosti-
mulatory and inflammatory properties (Muthuraman et al., 2011), and 
other ingredients such as Ashwagandha and Guduchi have also been 
known due to their immunostimulatory properties (Aranha et al., 2012; 
Yamada et al., 2011). It is used as a metabolic tonic used to foster immu-

6.6. Swasari ras

Swasari ras is used for the treatment of severe cough, cold, Broncho-
pneumonia, and other respiratory infections. It helps to remove 
congestion in the chest and lungs and activates the oxygen supply to the 
lungs. Predominantly in allergic conditions of asthma, cough, cold, and 
sinusitis, it escalates the immune response by improving the respiratory 
system (Balkrishna et al., 2020b). Swasari ras is also active against 
bacteria and viruses. It is recommended as a prophylactic treatment for 
persons who are directly in contact with COVID-19 patients during their 
treatment or are in the containment zone (Balkrishna et al., 2021b). In 
a study performed by Balkrishna et al. (2020b), Divya-Swasari-Vati was 
tested on A549 cell xenotransplant in the swim bladder of zebrafish 
which was injected with recombinant spike protein of SARS-COV-2. In a 
dose-dependent manner, Swasari-Vati repressed the pro-inflammatory 
cytokines, IL-6 and TNF-α, and reduces the inflammatory damage trig-
gerred by the viral spike protein while increasing the survival of the 
experimental fish (Balkrishna et al., 2020a). The proposed prophylactic and symptomatic treatments recommended by the AYUSH health min-
istry are depicted in Table 3. Ayurvedic treatment in COVID-19 positive 
and negative people with the inclusion and exclusion criteria is shown in 
Fig. 4.

Fig. 4. Scope of application of Ayurvedic treatments in COVID-19 crisis.
that chloroform extract of Chyawanprash (Dabur India Ltd., Uttar Pradesh, India) and hydrolyzed Chyawanprash show antimicrobial activity as compared to the standard drug ampicillin (20 mg/ml) (Khan et al., 2016). Several research works have been carried out, but there is no evident information available on its toxicity. A randomized controlled study (open-label) was conducted by Gupta et al. (2021) on 193 health care professionals (ages 25–60) who had a high risk of contracting COVID-19. Group I received standard palliative care, whereas group II received standard preventive protocol with Chyawanprash (12 gm, B.I. D.) for 30 days. The major assessment tool was indeed the number of confirmed COVID-19 cases in both groups. At the end of one month, no one in either group was COVID-19 positive out of 193 people who finished the experiment. 4 and 2 COVID-19 positive individuals were recorded in Groups I and 2 of Group II, respectively post-intervention fol low-ups. During the trial, no major adverse events or adverse medication reactions have been recorded. Before and after the trial, there was no clinically drastic change observed in the safety measures. In Group II, there was a dramatic increase in serum IgG, but no other inflammatory or immunological indicators showed a statistically significant change. All of the individuals in the intervention group accepted it well, but a slightly longer-term clinical trial with bigger sample size is needed to show its apoptogenic impact and effectiveness as an add-on to standard treatments in avoiding the recurrence of COVID-19 (Gupta et al., 2021). In a randomized community-based study, Godatwar et al. (2021) evaluated the prophylactic activity of Chyawanprash in which 771 people were screened for the research. Participants in the DCP group aged 13–70 years old, and children aged 5–12 years, were instructed to take 12 gm and 6 gm of Chyawanprash, respectively. The control group was instructed to drink one cup of milk twice a day. In the DCP group, one subject, and in the Control group 8 subjects were found to be COVID positive. The DCP group’s quality of life (QoL) score was 66.79 ± 14.75 at the start of the trial and increased to 70.83 ± 13.57 on completion, whereas the control group’s QoL score was 66.52 ± 13.60 at the start of the trial and drastically dropped to 61.48 ± 12.33 by the end of the study. QoL score using Chyawanprash was 2.25 times higher than the control group suggesting the prophylactic potential of Chyawanprash for COVID-19 prevention. The favorable results might be owing to the synergetic effect of the powerful herbs, which are known to enhance immunity among healthy people (Godatwar et al., 2021).

6.8. Extract of herbs

6.8.1. Green tea/decocotion

Green tea (Camellia sinensis (L.) Kuntze) contains plenty of catechins and polyphenols. Polyphenols such as epicatechin-3-gallate, epicatechin, epigallocatechin-3-gallate (EGCG), and epigallocatechin (EGC) enhance the cell-mediated and humoral immunity. Oral Intake of EGCG and EGC influences the proliferation of lymphocyte T and cytokine production (Talley et al., 2021). EGCG can re-establish the natural immunological homeostasis in various autoimmune diseases (Menegazzi et al., 2020). The innate immune response is an important element in disease progression. Evidence suggests that tea polyphenols and micronutrients strengthen defensive mechanisms, such as infection resistance by altering immunological modulation; this might have a meaningful impact on COVID-19 cytokine storm management (Cena and Chieppa, 2020). Catechins show numerous pharmacological properties such as antimicrobial, antiviral, and antioxidants (Kumar and Sharma, 2020). Catechins are known to have a significant impact on COVID-19 cytokine storm management (Cena and Chieppa, 2020). The uptake of viruses on red blood cells was mostly hindered by these compounds of decoction (Li et al., 2005). Results indicate that green tea extract showed high immunomodulatory effects against Candida albicans infection (Rahayu et al., 2018). The efficacy of EGCG (Green tea polyphenol) was evaluated by Jang et al. (2021). The findings indicated that EGCG protects host cells. Treatment with EGCG increased the viability of infected cells while decreasing plaque formation. Furthermore, EGCG administration reduced the expression of viral protein. All these results confirm that green tea may be used as a preventive measure against COVID-19 (Jang et al., 2021). In another study, Zhang et al. (2021) reported that EGCG suppresses the ACE2 and TMPRSS2 via activating Nrf2. Through inhibition of SARS-COV-2 main protease, EGCG may inhibit viral reproduction. EGCG owing to its wide antioxidant action may protect against SARS-COV-2-induced mitochondrial ROS and neutrophil extracellular trap-induced ROS burst. EGCG can impede the SARS-COV-2 life cycle by reducing ER-resident GRP78 activity and expression. SARS-COV-2-induced cytokine storm, sepsis, thrombosis, and lung fibrosis may all be reduced by EGCG (Zhang et al., 2021). In a proof of principle study, Bettuzzi et al. (2021) reported the efficacy of green tea catechin. During their stay in the hospital, ten swab-positive individuals with SARS-COV-2 COVID-19 symptoms were treated effectively at home for 15 days with two sessions of inhalation and three capsules each day having total 840 mg total catechins: 595 mg total EGCG. At a median of 9 days, with a range of 7–15 days, all patients

![Diagram of herbs](https://example.com/diagram.png)

Fig. 5. The immunity-boosting potential of chief ingredients of Chyawanprash.
had healed and had no complications. At a median of 9 days, seven flipped to a negative SARS-COV-2 nasopharyngeal swab test, with a range of 6–13 days. One of the three patients who remained swab-positive showed a significant reduction in infection, dropping to a “very low” SARS-COV-2 nucleic acid load after five days. Because they were clear of symptoms at the end of treatment, all the patients were released from quarantine. The inflammatory markers –1 antitrypsin, C-reactive protein, and eosinophils had all reduced considerably. In seven out of ten patients, IL-6 and erythrocyte sedimentation rates were reduced. These findings confirm the potential role of green tea against COVID 19 (Bettuzzi et al., 2021). To make green tea, combine one or half a gram of dried green tea leaf with 200 ml boiling water and steep for 15 min. Herbal tea, according to Table 2, can assist to improve immunity.

6.8.2. Ayurvedic Kadha

India’s health ministry, AYUSH, has announced several immunity-enhancing measures, Kadha is one of them. Kadha has been used for a long time and has the potential to assist the body in recovery from cold and flu infection with enhanced immunity. Distinct mixtures of herbs are being used to make different variations of regular Kadha (Maurya and Sharma, 2020) and some of these are recommended by the Ministry of AYUSH as ingredients in ‘AYUSH Kwath ‘AYUSH Joshanda’ or ‘AYUSH Kudinnee’ (Charan et al., 2021). The AYUSH Kwath concludes with dozens of health benefits such as antiviral, antioxidant, anti-platelet, reno-protective properties, anti-atherosclerotic anti-inflammatory, hepato-protective, and enhances immunity to regulate viral infections such as COVID-19. The ingredients are powdered and tea bags or sachets of 3 gm of powder in each or 500 mg tablet of the aqueous extract is recommended with 150 ml boiled water O.D. or B.I.D. It is generally taken with Drakash (Resins)/Gud (Jaggery) and/or with lemon juice. The AYUSH Kwath has demonstrated its importance in boosting immunity and preventing the spread of SARS-CoV-2 during the non-severe stage of COVID-19 (Gautam et al., 2022). The dose of each herb is mentioned in the Ayurvedic Pharmacopoeia of India) in the dose range of 2–3 g powder of Tulsi leaves, 1–3 g powder of cinnamon bark (Cinnamomum cassia (L.) J.Presl), and 1–2 g powder of ginger, 250 mg-1 g powder of form of black pepper (Ayurvedic Pharmacopoeia of India, 2016). Shukla et al. (2021) conducted an In Silico analysis to assess the targets of Ayurvedic decoction. The findings revealed that two of the 26 active compounds in Ayurvedic decoctions are significant binders for spike protein and the related Mpro, which plays a vital role in viral replication and transcription, making it a potential antiviral therapeutic target. One molecule was discovered to be the most active among the 26 components (Rao et al., 2021; Shukla et al., 2021).

7. Clinical trials

A large number of clinical trials have been registered worldwide to evaluate the efficacy of herbal medicines and yoga for SARS-COV-2 infection. In a clinical study (NCT04322228), anti-inflammatory, and antioxidants are used in the treatment of COVID-19. The study was based on the modulation of cytokinin production, which is a novel concept through immune-nutrition. Specific nutrients such as n3-fatty acids, antioxidants, and vitamins modulate the host immune response and ameliorate the cytokinin storm associated with this disease. They divide the 30 participants into two groups i.e., the first intervention group and the second is the placebo group. The composition of ONS includes protein 14.8 g, fat 22.2 g, 2 g carbohydrate 355 Kcal, eicosapentaenoic acid 1.1 g, docosahexaenoic acid 450 mg, gamma-linolenic acid 950 mg, 2840 IU vitamin A, β-carotene 1.2 mg, Vitamin C 205 mg, vitamin E 75 IU, Selenium 18 μg, and zinc 5.7 mg. This study revealed that the ONS group might help in the reduction of COVID-19 as compared to the other group based on biochemical parameters such as cytokine storm parameters (IL-6, TNF-α, and monocyte chemoattractant protein 1), total leukocyte count, and C-reactive protein, etc. Some recent clinical trials related to herbal/natural preparations are displayed in Table 4.

8. Computational approaches for identification of target

Computer-based tactics are being in use for the identification of the target and binding energies by molecular docking. Gandhi et al. (2020) performed in silico molecular docking study of Nagarad Kashaya which is the mixture of Sunthi, Pushkarmool (Inula racemosa Hook.f.), Guduchi, Kantakari (Solanum virginianum L.) for combating COVID-19 using Pyrx Software with Autodock. The binding energy and inhibition of 6-gingensulfonic acid from ginger were found to be greater than HCQ and quinine. Also, the target prediction of selected phytoconstituents was performed. These were found to be effective against SARS-COV-2 which improved humoral immunity and showed antiviral activity (Gandhi et al., 2020). Molecular docking analysis was performed to analyze the efficacy of phytochemicals. A total of 57 phytochemicals were examined virtually against four structural protein targets of SARS-COV-2 viz. 3CLpro, ACE-2, spike glycoprotein and RdRp. Advantageously, two bioactive from each of the three plants i.e., apigenin-o7-glucuronide and elagic acid from Eucalyptus globulus; vasicoline and anisotine from Malabar nut, eudesmol, and viridiflorene from Chinese chaste tree (Vitex negundo L.) were observed based on interaction energies, conventional hydrogen bonding numbers, and other non-covalent interactions. In this study, apigenin-o7-glucuronide was found to be a promising inhibitor of both protease and polymerase because it interacts with their active sites and showed notably high binding affinity. Phytochemicals from selected traditional herbs showed their potential for steam inhalation therapy for COVID-19 (Gowrishankar et al., 2021). Khaerunnisa et al. (2020) assessed the activity of

### Table 2

| Type       | Effect                          | Procedure                                                                 |
|------------|---------------------------------|--------------------------------------------------------------------------|
| Haldi tea  | It boosts immunity due to its   | In 50 ml of boiling water, add some Haldi powder, ginger slices, and     |
|            | antiviral, antibacterial, and   | pepper. Then boil for 15 min. Filter the water and add some lemon juice   |
|            | antioxidant properties.         | and honey.                                                               |
| Ginger tea | Ginger tea can help in the     | In boiling water add some slices of ginger. Strain the tea and discard   |
|            | treatment of respiratory issues | the pieces of ginger. Then add some honey, cinnamon, haldi, or lemon      |
|            | and nasal congestion.          | juice.                                                                   |
| Tulsi tea  | It can prevent respiratory     | Add 2-inch ginger, 12 holy basil leaves, and 100 mg cardamom powder in   |
|            | illnesses and reduce phlegm    | 2 cups boiling water. After boiling for 10 min, strain the water. Add     |
|            | when you have a cough.         | some honey and ½ lemon. You can also get goodness using tulsi leaves.     |
| Lemon tea  | Lemon is a rich source of vitamin C that boosts immunity. It relieves    | In boiling water, add turmeric and add lime juice, and a dash of honey.   |
|            | chest infections and phlegm    | Take this tea in the morning.                                            |
|            | when suffering from a cold and |                                                                        |
| Peppermint tea | Peppermint is free from caffeine and boosts antibacterial and        | Take 2 cups of boiling water and add some mint leaves and stay for boiling |
|            | antiviral properties.          | 10 min till the water turns pale yellow. Filter the tea and add some     |
|            |                                 | honey and lime. It may be taken in the morning as well as at night.      |
|            |                                 | Firstly, Separate the flower from the calyx. Then wash the petals and    |
|            |                                 | steep the petals in hot water and some honey and lime juice.             |
some phytochemical compounds, one of which was curcumin. The activity was analyzed by the molecular docking method. Curcumin exposed comparatively low binding energies and inhibition constants. They proposed that curcumin could inhibit COVID-19 Mpro and act as a therapeutic agent (Khanal et al., 2020). By the computational approach, Azim et al. (2020) performed screening and drug ability analysis of herbal compounds to evaluate their efficacy in COVID-19. Twenty-seven plant metabolites were screened against main protease proteins (MPP), spike receptor binding, domain, Nsp9 RNA binding protein, HR2 domain, and spike ectodomain. Among them, asiatic acid, avicularin, guajaverin, and withaferin exposed optimum binding affinity. The key binding sites and drug surface hotspots were unraveled for each viral protein. To examine the drug profile, these four metabolites were subsequently evaluated for ADME analysis, and none of the compounds rendered unsolicited fallouts that could reduce drug resemblance properties (Fig. 6 A-D.). The targets of these drugs were also evaluated in well explained in Fig. 6 (E-H) (Azim et al., 2020).

Most drug targets were found to be on enzymes, oxidoreductases, phosphatases, kinase proteins, and lyases. In another study efficacy of catechin and curcumin (both are polyphenols) was evaluated by Jena et al. (2021) using computational. Both the catechin and curcumin potentially bind with ACE2 and viral S-protein with the binding energy of $-10.5 \text{ kcal/mol}$ and $-8.9 \text{ kcal/mol}$, respectively. Compared to the curcumin, catechin showed a greater resemblance with the binding energy of $-7.9 \text{ kcal/mol}$ and $-7.8 \text{ kcal/mol}$ respectively for catechin and curcumin. This in silico method suggested their potential for the prevention of COVID-19 (Jena et al., 2021).

Khanal et al. (2020) used a different database for the prediction of a protein-based target of withanolides. Their protein-based targets were determined employing DigePred and the protein-protein interaction was analyzed using STRING. Withanoloid Q was predicted to control the protein-based target of withanolides. Their protein-based targets were determined employing DigepPred and the protein-protein interaction is indented withanolide Q to target the mutual network interaction is indented withanolide Q to target the
Table 4
Clinical trials of herbal medicines registered in (A) clinical trials registry in India (CTRI) and clinicaltrials.gov.

| Clinical trial Id | Agent | Phase | Estimated starting date | Period | Patients | Age group | Dose |
|-------------------|-------|-------|-------------------------|--------|----------|-----------|------|
| CTRI/2020/05/025156 | AYUSH-64 | 3/4 | May 18, 2020 | 1 year | 60 | 18-60 years | 2 Tablets (500 mg each) T.I.D. after meal for 1 month |
| CTRI/2020/05/025338 | AYUSH-64 | 2/3 | June 02, 2020 | 3 month | 40 | 18-60 years | 2 capsules (500 mg each) T.I.D. Orally for 14 days |
| CTRI/2020/05/025341 | Kiratikatdi Kwath and Ashwagandha Churna with Yoga | N/A | June 02, 2020 | 3 months | 30 | <20 or >60 years | Guggulshoodhaspan B.I.D. in COVID-19 wards. AYUSH Kadha O.D. in the early morning. Kiratikatdi kwath: 30 ml B.I.D. Ashwagandha churna 5 gm O.D. with lukewarm water. Yoga sessions twice a day. Samshamanati Vati 250 mg B.I.D. after food with water. Application of Anutaila 2 drops in each nostril O.D. after bath. Gargle with warm water mixed with rock salt and turmeric. Yoga and Pranayama: for 8 weeks. 12 gm Avalahe B.I.D. orally Onan empty stomach at least 1 h before breakfast and 2 h after dinner at night. Anupana: Warm water. Duration of therapy: 30 days. Ashwagandha capsule with standard prophylactic care. Ashwagandha 500 mg B.I.D. orally for 30 days. | |
| CTRI/2020/05/025171 | Samshaman Vati, Anutaila, rock salt, and turmeric | 2 | May 16, 2020 | 3 months | 5000 | 19-60 years | |
| CTRI/2020/05/025425 | Chyawanprash | 3/4 | June 02, 2020 | 2 month | 50 | 20-60 years | |
| CTRI/2020/05/025429 | Ashwagandha | 2/3 | June 10, 2020 | 3 months | 5000 | 18-68 years | 500 mg B.I.D. orally for 30 days. |
| CTRI/2020/05/025370 | Guduchi Ghan Vati | N/A | June 04, 2020 | 1 month | 40 | 18-60 years | |
| CTRI/2020/05/025093 | Yashtimadhu tablet | 2/3 | May 18, 2020 | 1 month | 1200 | 18-68 years | 250 mg 2 tablets B.I.D. for 1 month. |
| CTRI/2020/05/025166 | Ashwagandha tablet | 2/3 | May 19, 2020 | 6 months | 1200 | 18-68 years | |
| CTRI/2020/05/025088 | Guduchi tablet | ½ | May 20, 2020 | 6 months | 1200 | 18-68 years | |
| CTRI/2020/05/025205 | Arsenicum album 30C | 2/3 | May 24, 2020 | 2 months | 33000 | 1-90 years | Arsenicum album 30C will be given to the high danger COVID-19 patients and those located in the containment zone, 4 pills of medicine will be given orally B.I.D. for 7 days. 90-100 ml of Kashaya of Guduchi stem added with 2 gm of powdered dried long pepper B.I.D. 250 mg, 2 tablets B.I.D. for 12 weeks. |
| CTRI/2020/04/024882 | Kashaya (Decoction) | 3 | April 28, 2020 | 1 year | 60 | >18 years | |
| CTRI/2020/05/025332 | Ashwagandha tablet | 2 | May 28, 2020 | 3 months | 400 | 20-69 years | |

Clinical trials registered in clinicaltrials.gov

| Trial Id | Status | Period | Study type | Participant | Age group | Description |
|----------|--------|--------|------------|-------------|-----------|-------------|
| NCT04716647 | Completed | Jun 2020–July 2020 | Intervventional | 28 | 20-70 years | In this trial, the therapeutic efficacy of ashwagandha and Guduchi was evaluated |
| NCT04480398 | Completed | May 2020–June 2020 | Intervventional | 91 | 18-75 Year | Guduchi Ghan Vati was tested in asymptomatic COVID 19 patients. |
| NCT04920773 | Completed | May 2020–June 2020 | Intervventional | 216 | 18-60 years | Guduchi Ghan Vati was tested as prophylaxis for COVID-19. |
| NCT04395976 | Not yet recruiting | Jun 2020–Oct 2020 | Intervventional | 120 | 18 years and older (Adult, Older Adult) | The study is aimed to prevent people from COVID-19 and those who must met confirmed, COVID-19 patients. The treatment is based on the combination therapy by herbs, nutritional advice, food items, lifestyle, yoga along with standard approvals and it relies on symptoms and personality. The study is based on the Ayurvedic-based assessment; self-managed approaches were recommended. |
| NCT04351542 | Completed | Mar 2020–Apr 2020 | Intervventional | 32 | 18-60 years | In this, participants are advised to self-isolate for seven days and maintain self-care according to directions. The participants were advised to Constitution-based Ayurveda treatment using herbs, lifestyle, and yoga. Participants were suggested to use Ginger/lemon/turmeric/honey recommended as per individual. |
| NCT04345549 | Completed | Feb 2020–Mar 2020 | Intervventional | 18 | 18-60 years | |
| NCT04387643 | Completed | Mar 2020–Apr 2020 | Observational | 52 | 18-60 years | Ayurvedic Kadha was suggested in this study. |
Ashwagandha. The four constituents, namely Withanoside II, Withanoside V, and Sitoindoside IX showed maximum docking energy −11.30 kcal/mol, −11.02 kcal/mol, −8.96 kcal/mol, and −8.37 kcal/mol respectively. Additionally, Withanoside V showed better binding potential and hydrogen-bonding interactions with the protein active site and so indicating stability in the active site (Tripathi et al., 2020). Adem et al. (2020) performed in silico study of natural polyphenols to inhibit COVID-19 Mpro. In this, COVID-19 Mpro was docked with 80 flavonoid compounds. hesperidin, rutin, diosmin, apiin, diacetylcurcumin, (E)-1-(2-Hydroxy-4-methoxyphenyl)-3-[(E)-3-(2-hydroxy-4-methoxyphenyl)-3-oxoprop-1-enyl] phenyl prop-2-en-1-one, and beta-(4-Methoxy-1,3-phenylene) bis (2’-hydroxy-4’,6’-dime thoxyacrylophenone have been found as more effective on COVID-19 than nelfinavir. The effective flavonoids found in this study can be ordered as follows affinity hesperidin > rutin > diosmin > apiin > diacetylcurcumin (Adem et al., 2020). Lung et al. (2020) in the computational study evaluated the potential of theaflavin. The theaflavin showed a high docking score with good binding with the RBD in SARS-CoV-2. The driving forces of these interactions were hydrophobic interactions with hydrogen bonds at sites such as ARG454, ASN460, ASN501, GLN493, PHE456, CYS480, and VAL503 of SARS-CoV-2 RBD, interactions with hydrogen bonds at sites such as ARG454, ASN460, ASN501, GLN493, PHE456, CYS480, and VAL503 of SARS-CoV-2 RBD, near the ACE2-S protein. For the utmost promising interaction of theaflavin with the RBD in SARS-CoV-2, the binding energy was found to be −8.53 kcal/mol (Lung et al., 2020). In a molecular docking study, Shree et al. (2020) worked to identify the SARS-COV-2 Mpro (Main protease) inhibitors. A molecular docking study showed six probable inhibitors against SARS-COV-2 Mpro (Main protease). In their study, one from Guduchi, two from ashwagandha (Withanoside V and Somniferin), and three from Tulsi (Viccin, Isorientin 4’-O-glucoside 2’-O-p-hydroxybenzoate, and Ursolic acid) were found to inhibit SARS-COV-2 Mpro. The best-docked phytochemicals from this study were found to be safe and had drug-like effects, according to ADME/Tox profile assessment (Shree et al., 2020).

9. Pitfalls and pharmaceutical perspectives

Medicine is prepared by natural constituents does not assure that it is effective and safe. The Government of India’s Ministry of AYUSH has recommended prophylactic and symptomatic treatment for the management of health in the COVID-19 epidemic. The advisory created is very helpful in fighting SARS-CoV-2, but it has some shortcomings which need further improvement for the safe and effective use of ancient Indian medicinal science. FDA has not approved herbal medicine. It means that the herbal medicines have not passed the stringent criteria of safety and efficacy and are not even recommendations for emergency use. In the recommended advisory, the dose criteria for any age group have not been suggested. As any medicine could have potentially toxic effects and maybe lead to severe toxicity to the liver or kidney. Still, no severe side effects have been reported. Most of the home remedies such as turmeric, methi (Trigonella foenum-graecum L.), and vitamin D3 are used for vitamin C, Zinc, Ginger, ‘Kadhas’, many herbas, homeopathic e.g., Arsenicum alba and Ayurvedic e.g., ashwagandha, to boost up the immunity have been taken which may cause side effects. Licorice supplementation may lead to an elevation in blood pressure due to its effect on the renin-angiotensin-aldosterone system. The overdose of ashwagandha may stimulate the thyroid and causes thyrotoxicosis in some humans and mice (Das et al., 2014). Some common side effects such as constipation, cough, headache, and abdominal pain may be seen in patients taking herbal immune boosters.

The toxic effects of these sources used in traditional cultures have ordinarily not been notified, and this is in the later stage mentioned in terms of safety. Amongst the dozens of approaches, Arsenicum album-30 (homeopathic treatment) is recommended for prophylactic therapy for three days for the prevention form SARS-COV-2 infection. Generally, it is the drug prescribed for the prevention of influenza or similar infections. No evidence confirms its efficacy in the prevention of SARS-COV-2. Similarly, the use of Khas Khas (12 gm) is recommended, but the way to intake and dose according to age group or vulnerable population comprising patients having some existing disease or disorder or dysfunction is still not warranted. It is well appreciated that it helps promote immunity and also relieves cough and sore throat. However, the recommendation does not verify that the use of Khas Khas may fight SARS-COV-2. In the case of the kadha or other herbs there must be specific regarding the number of ingredients, and whether it needs boiling or not, if yes, then it’s boiling time and quantity to be taken...
otherwise, it may lead to serious health concerns. Such concerns should be diagnosed in the advisory, and they must include the possible side effects and drug interactions. There are many such recommendations with insufficient guidelines without any scientific methodologies. The advisory must include proper dosing criteria with a suitable dosage form and regimen. Sometimes self-medication may pose a risk to the patients. These may cause drug-related interaction issues with the other ongoing treatment and potentiate the effect of each other or can cause toxicities. There must not be a communication gap between doctors and patients on the topic of alternative medicine, well this gap is due to the patients being embarrassed or the misunderstanding the potency of these compounds both the patient and physicians need to understand that these drugs have the potential to cause problems while you are taking these for prophylactic or symptomatic treatment. Work should be done in the direction to prepare; besides, these are economical and biocompatible.

There is an urgent need to look into the pharmacokinetics of these complex mixtures of bioactive. India is a leading player in ayurvedic medicines at the world level, and premature decisions may lead to untoward aftermeths on the long-term use of these natural plants in raw form. Their active constituents are properly either admixed or transformed into a suitable formulation so that dosing and dosage regimen may be decided. With the advent of nanotechnology, nanocarriers have earmarked tremendous progress in improving the safety and efficacy of potent drugs. These advances can be utilized by formulators working at laboratory, research, and development sections at industries and scientists in collaboration with clinical practitioners to bring upon a fruitful sight of nano-ayurvedic medicines.

For a global fight against this pandemic, approval from national and international authorities is required. Without following proper guidelines for the development of universally accepted means to pacify the needs of patients and approving authorities in terms of bioavailability and bioequivalence studies, these ayurvedic magic bullets will remain unseen and of no use for the betterment of mankind. The remedies from herbal derivatives need an influential and profound evaluation of their pharmacological profile and safety; it is possible by the use of techniques such as pharmacogenomics, metabolic and microarray tactics. The beneficial roles of phytochemicals recommended in advisory can be explored by in silico methods, and molecular docking, to identify the chief compound against viral or host proteins. Rational drug design against COVID-19 may shorten the time and reduce the cost based on the genomic information and pathological features of the virus (Wu et al., 2020). In the preclinical phase, it is well-known that pharmacology offers a prevailing perspective for drug discovery, but still, there is a need for research and development endeavors to outrun a drug to the market from the clinical stage, and it is only possible with the proper experiments and their documentation.

Natural products target multiple sites, and about 35% of natural drugs are known for being active against more than one target (Xie, L. et al., 2009). Such type of activity may affect the overall treatment of SARS-COV-2 infection and may cause toxicities. For example, curcumin, a natural polyphenol product isolated from, at least, has ten molecular targets associated with antiviral, anti-cancer, antiinflammatory, antioxidants, anti-inflammatory, and immunomodulatory properties (Pan et al., 2013). Similarly, Guduchi, tulsi, and garlic show multiple efficacies. In a case study of a 43-year-old patient, who is a banker in New York Ayurvedic Vaidya in Chennai, India. The symptoms associated were cough, loss of smell and taste, body and abdominal pain. Fever (Jwara) is well known to be cure. Guduchi, Mulethi, Anuthaila, Tulsi, herbal tea, Golden milk, etc. are in use to cure this Global disease due to their couple of profits including immunomodulatory and antiviral effects. There are ample opportunities to focus on research for the treatment of COVID-19 using herbal medicine. During viral infections, immunobalances in minerals and micronutrients are linked to poor clinical outcomes. The nutrients such as zinc, vitamin C, Vitamin D, Vitamin A, B vitamins, omega-3 polyunsaturated fatty acids, and iron, should be considered in the evaluation of micronutrients in COVID-19 patients. Thus, providing daily vitamin and trace element intakes is imperative for malnourished individuals. (Agagündüz et al., 2021; El Zakhem et al., 2021). There is also a wide prospect of research, and it is the right time to execute translational and operational research on Ayurvedic medicines on COVID-19 as preventive and curative measures on a large scale. The use of nanotechnology can cure many problems associated with the treatment of this disease due to their targeting potential, and consequently, it will reduce the dose and dosing frequency which directly reduces the toxicity concerns. Researchers should be encouraged to evaluate their potential in terms of efficacy and toxicity. Medical researchers need to investigate precisely how specific herbal preparations affect the body, unlike prescription medications, alternative medicines are not subject to strict guidelines the FDA has for prescription drugs. The manufacturer of herbal preparation is neither required to prove efficacy nor to track complications caused by the use of such preparations. Recently various clinical studies of herbal medicines and the medicines recommended in the AYUSH advisory are being conducted to ascertain their potency in SARS-COV-2 infection.

10. Conclusion and future perspectives

CoV infection is rising day by day at a very rapid pace. But there is no medicine or vaccine available up till now for their treatment. Various Allopathic, as well as natural therapy such as Ayurveda, Siddha, Unani, Homeopathic as well as Yogasan, are being used in the treatment of CoV infection. Some antiviral medicines or immunomodulators are proposed in high doses which may cause severe health illnesses. Herbal medicinal products supremely have different effects and are supportive in a diversity of ailments, for valuable health effects. Globally, the use of herbal medicine as immunostimulants is traditionally not limited to India, but it has been in use in almost all civilizations of Asia, America, Africa, etc. The department of AYUSH has issued a guideline because of the problem of the SARS-COV-2 pandemic. The advisory suggested the use of various Ayurvedic, Homeopathic, and Unani medicines for the prophylactic and symptomatic treatment of SARS-COV-2 infection. Various herbal medicinal plant and their product such as Ashwagandha, Mulethi, Anuthaila, Tulsi, herbal tea, Golden milk, etc. are in use to cure this Global disease due to their couple of profits including immunomodulatory and antiviral effects. Researchers need to investigate precisely how specific herbal preparations affect the body, similar to prescription medications, alternative medicines are not subject to strict guidelines the FDA has for prescription drugs. The manufacturer of herbal preparation is neither required to prove efficacy nor to track complications caused by the use of such preparations. Various clinical studies of herbal medicines and the medicines recommended in the AYUSH advisory are being conducted to ascertain their potency in SARS-COV-2 infection.

CRediT authorship contribution statement

Shiv Kumar Prajapati: Writing – original draft, Formal analysis.
Akanksha Malaiya: Data Collection, Writing, Gaurav Mishra: Formal analysis.
Payal Kesharwani: Review & Editing, Nishi Mody: Review & Editing, Amirhossein Ahmadi: Formal analysis, Rishi Paliwal: Formal analysis, Ankit Jain: Conceptualization, Supervision, Formal analysis.
Declaration of Competing interest
All authors declare no financial/commercial conflicts of interest.

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