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REVIEW ARTICLE

Potential roles of phytochemicals in combating severe acute respiratory syndrome Coronavirus infection

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Abstract

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the causative agent of the current ongoing global pandemic COVID-19 is yet far away from the clutches of contemporary western medicines. With the lack of conventional drugs for this deadly disease the scope for the development of herbal formulations and Ayurvedic medication is finding a sound basis in the current scenario. The past two years has witnessed detailed and focused investigations on the biologically active constituents derived from a range of medicinal plants and their potential antiviral properties against SARS-CoV-2. The promising results of these investigations have intrigued the medical and plant experts in pharmacognosy enough to consider herbal medicines and plant-based products as they are more effective in combating the COVID-19 crisis. However, a large-scale application of the same would require more focused and thorough research on this matter. This review is an attempt to describe the current and future prospects of using medicinal plants and herbal compounds as natural and sustainable alternative for treating COVID-19. The current article evaluates the various strong evidences from biochemical and molecular studies that have been investigated so far for the development of herbal formulations to combat COVID-19 with detailed focus on the most potential phytochemicals of medicinal plants studied in this regard namely, *Withania somnifera* (L.) Dunal, *Cinchona officinalis* L., *Curcuma longa* L., *Ocimum sanctum* L., *Azadirachta indica* A. Juss. and *Tinospora cordifolia* (Willd.) Miers.

Keywords

COVID-19, herbal drugs, phytochemicals, phytomedicine, SARS-CoV-2.

Introduction

The world today is dealing with one of the deadliest pandemics, COVID-19, which has not only resulted in more than 5.5 million causalities globally but is also the reason behind the great global economic recession and depression. The official name COVID-19 was given by the World Health Organisation on 12th of February 2020 and was declared as a pandemic in the next month (1). Severe acute respiratory syndrome Coronavirus-2, abbreviated as SARS-CoV-2, the causative agent of COVID-19, shows structural similarity with most of the previous coronaviruses belonging to the family of Coronaviridae (2).

The current situation of this pandemic has led to a revolution in the medical systems and sciences at an impeccable rate yet the situation is far from what can be considered normal. Certain countries, including India are dealing with a rather more infectious third wave of the pandemic. Clinical investigations for drug development are still in the process. Certain medicines like Ivermectin and Remdesivir have been recommended for the treatment of COVID-19, however, these conventional drugs have also been shown to have serious side effects and complications in infants, pregnancies and old age patients (3, 4).

Plant-based medicines or herbal formulations based on phytotherapy and research can play a crucial role in the development of more sustainable, natural and economic remedies for the treatment of COVID-19. Countries like China and India have a long history of natural, traditional and complementary medicines which can prove to be a turning point in the current phytotherapy based investigations (5). Some plants are already demonstrating to be effective against viral infections (6, 7). With the current burden on the medical systems, the researchers have resorted to a more detailed re-visitation to the herbal formulations for treating COVID-19. Several medicinal plants have been screened for isolation and characterisation of various phytochemicals that have shown promising results in combating COVID-19. Phytochemicals from medicinal plants such as *A. indica*, *C. officinalis*, *C. longa*, *O. sanctum*, *W. somniferum*, *Zingiber officinale* Roscoe, *Allium sativum* L. and *Aloe vera* (L.) Burm.f. and a few more have been recommended by the Ministry of AYUSH, India as common immunity boosters and preventive herbs for COVID-19 (7). However, some of these have been shown to have much greater potential at both molecular and biochemical levels as herbal drugs that can inhibit viral replication, suppress a large number of SARS-CoV-2 proteins, prevent the entry of SARS-CoV-2 in the host cell and suppress the symptoms caused by the virus, thereby reducing the viral load (8-10).

Herbal medications developed from plant-based phytochemicals can prove to be an effective option in the absence of any clinically meaningful treatment for COVID-19, and considering the side effects as well as the availability of conventional drugs However, the horizon of reaching and analysing plants with this intention is yet to be determined. The formulation of such Ayurvedic medicines can provide an easily accessible, natural, effective and cost-efficient mode of medication to the masses especially in the developing countries like India, which still have a great rural population.

This review aims to discuss the current state and future prospects of medicinal plant analysis in order to develop COVID-19 preventative and treatment remedies. Out of the several plants and phytochemicals that have been investigated so far for therapeutic use against SARS-CoV-2 by various researchers, this review mainly focuses on the six most significant plants and their phytochemicals which have the strongest biochemical and molecular evidences to support their potential against the virus. These include *W. somnifera, C. officinalis*, *C. longa*, O. *sanctum*, *A. indica* and *T. cordifolia* (Fig. 1).

Withania somnifera (L.) Dunal

Cinchona officinalis L.

Curcuma longa L

Ocimum sanctum L

Azadirachta indica A. Juss

Tinospora cordifolia (Willd.) Miers

Fig. 1. Medicinal plants showing promising results againstSARS-CoV-2 and have been recommended by the Ministry of AYUSH, India as common immunity boosters and preventive herbs for COVID-19 infection

Source of Information

The information and data related to various medicinal plants, their phytochemicals and the studies on their antiviral properties against SARS-CoV-2 was retrieved from the website of Ministry of Ayush, India and other research papers on the aforementioned topic as well as structure of SARS-CoV-2 were taken from various international journals indexed in Scopus, Web of Science and PubMed by searching keywords like antiviral properties, role of medicinal plants in COVID-19, ACE-2 receptor inhibition, Ayurvedic treatment, SARS-CoV-2 etc. The data collected was analysed for the biochemical and molecular evidence available for the phytochemicals in action against SARS-CoV-2 and was included in this review article.

SARS Cov-2 and Covid-19: An Understanding of a Year

The virus belongs to the family Coronaviridae, order Nidovirales and is a positive sense RNA virus, which classifies as a retrovirus involving reverse transcription for the duplication of its genetic material (11). With a genetic similarity of more than 70% to the previously found SARS-CoV, this virus is likely the seventh virus to be added to the Coronaviridae family (2) As per the present reports on the anatomy of SARS-CoV-2, the genome of this virus codes for mainly the following four proteins: i) Nucleocapsid phosphoprotein, ii) Spike glycoprotein, iii) Membrane glycoprotein and iv) Envelope glycoprotein (12). With an understanding of these aspects, the world is currently trying to develop several vaccines and drugs that can potentially inhibit the synthesis of any of the above proteins, which are essential for the multiplication of this deadly virus.

As of January 26, 2022, the virus has infected more than 363 million people and has claimed around 5 million lives. In India alone, the lives lost to this novel SARS CoV-2 have crossed the 491k landmark (World Health Organisation, 2021). The disease manifests itself initially as an asymptomatic incubation in a majority of patients and then proceeds to mild infectious flu-like symptoms. However, in severe cases it leads to acute respiratory infection and pneumonia with a high viral load (13).

Current Measures: Prevention, Treatment and Vaccines

After over two years of coping with the global COVID-19 pandemic, various preventive measures have been implemented such as personal and social hygiene, use of face masks, physical distancing, implementation of national and state level lockdowns, avoiding closed gatherings and use of immunomodulatory products such as zinc and vitamin C tablets have been in place round the clock (14). However, most of these are in the line of preventing and tackling the issues of spread and limiting or breaking the infection chain. Even though these measures have proven to be effective up to some extent, they pose serious challenges, such as rolling back and relaxing these restrictions, which would result in a resurgence of infections and, to a large extent, a disruption of civilian life, as well as a sharp drop in economic activity.

India has seen a rise in the positivity rate and is dealing with a major pandemic wave. (World Health Organisation, 2021). Most of the treatments are inclined towards the use of plasma therapies and allopathic drugs such as Ivermectin and antibiotics like azithromycin and doxycycline. The use of the former finds its rationale in the *in vitro* studies which have reported that Ivermectin does cause an inhibition of certain nuclear transport proteins in the host especially the importin alpha/beta proteins that the virus manipulates and uses to inhibit the antiviral response in the host (15).

Vaccination and immunisation are yet another major step towards curtailing the spread of COVID-19 and there have been several vaccines that have come in force since the beginning of 2021. With respect to India, more than 1 billion people have been either partially or fully vaccinated against the SARS-CoV-2 as of January 26, 2022 (16). However, with a population of more than 133 crores there is still a long way to go for having a fully vaccinated population. Thus, there is an extensive need to investigate herbal medicines, which can prove to be a boon at a much lower cost as of now as opposed to the conventional drugs.

Perspective on Scope for Herbal Formulations and Plant Derived Products in Combating COVID-19

With most of the current allopathic drugs being effective but exhibiting some side effects while having regulated considerations in children and in pregnant women, plant derived medications can prove to be promising candidates for developing a more organic and natural treatment as well as prevention of COVID-19. Till the beginning of 2021 while the quest for development of vaccines was still on, the use of ethno-medicine and other plant derived products have been quite common in the Indian households in specific. Natural immunity boosters and other herbal treatments have also been advised by the Ministry of AYUSH for COVID-19 prevention (7).

Potential Medicinal Plants as Future Herbal Drugs in Prevention and Treatment of Covid-19

Since time immemorial, medicinal plants have been a vital source of folk medicine, as documented in ethnobotanical literature. The medical and pharmacology communities have put up huge and flawless efforts in producing vaccines and treatment recommendations for the ongoing epidemic. Ayurveda and herbal remedies are no exception to it. A large number of medicinal plants have been investigated for their pharmacological properties against the novel coronavirus. Plants such as *A. indica, W. somnifera, O. sanctum, A. sativum*, *Z. officinale*, *C. longa*, *C. officinalis*, *T. cordifolia* (8, 17, 18) have shown potential against the members belonging to the family of coronaviruses as well as some have shown pre-clinical trials against SARS-CoV-2 itself. A few of these plants and their potential phytochemicals investigated so far in relation to COVID-19 have been reviewed in this paper.

Withania somnifera (L.) Dunal

Commonly referred to as Ashawagandha in India, *W. somnifera* is a member of the family Solanaceae which has been long used in Ayurvedic, Unani and other natural systems of medical sciences whereas the accounts of its uses as a folk medicine are no less than 5000 years old (19) (Fig. 1A). It is a vital restorative in ayurvedic sciences and has the potential to be used as an effective herbal drug for combating COVID-19. Phytochemical constituents derived from this plant have been proven both preclinical as well as clinically useful against various viral agencies such as herpes simplex, parainfluenza, H1N1, SARS-CoV as well as SARS-CoV-2 (19-21).

SARS-CoV-2 is known to facilitate its entry into the host cell via TMPRSS2 by binding to the Angiotensin-Converting Enzyme-2 (ACE2) receptors on the host cell surface. Withanone, a phytochemical derived from *W. somnifera* has shown to greatly reduce the expression of TMPRSS2 of the host and can thereby prevent the entry of the virus in the host cell (22). Further, other derivatives from the plant have shown inhibitory actions against RNA dependent RNA polymerase, viral proteases such as PL^{PRO} and also have demonstrated the antiviral property by inhibiting the viral S protein's interaction with the ACE2 receptors of the host cell (23). SARS-CoV-2 is known to cause what is called as "Cytokine Storm" in the cells wherein there is an over production of cytokine like IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1 and as such can result in complications like pulmonary edema, lung injury that can lead to stress in tissues of multiple organs such as heart, lungs, kidneys etc. whereas in more severe cases can lead to death due to multiple organ failure (24). Extracts from *W. somnifera* have been demonstrated to suppress a range of pro-inflammatory cytokines which has been medically related to improvement in the symptoms caused due to the cytokine storm (20). In another study on the targeting of non-structural proteins (NSPs) of SARS-CoV-2 (Table 1), it was found that

Table 1. List of different Non-Structural Proteins (NSPs) characterized in SARS-CoV and their functions in the life cycle of the virus (8)

Sl. No.	Protein	Role or Function	References
1	NSP1	Host Specificity and interaction	(26)
2	NSP2	Disruption of host signalling at intracellular level	(27)
3	NSP3	Translation of Mrna transcripts	(28)
4	NSP4	Replication and Assembly of replicative structures	(29)
5	NSP5	Protease like function	(30)
6	NSP6	Aids in creation of autophagosomes	(31)
7	NSP7	Primer independent RNA Polymerase Activity	(32)
8	NSP8	Primase Activity	(33)
9	NSP9	Replication and Virulence	(34)
10	NSP10	Cofactor for O6 methyltransferase	(35)
11	NSP11	Replication	(36)
12	NSP12	RNA Polymerase Activity	(37)
13	NSP13	RNA TPase and Helicase Activity	(38)
14	NSP14	Exoribonuclease Activity	(39)
15	NSP15	Endoribonuclease Activity	(38)

around 18 steroidal lactones from *W. somnifera* can be employed to target at least 6 NSPs out of the known 16 NSPs of SARS-CoV-2 which are essential for replication of virus and thus have the potential to be used in herbal formulations (8, 25). Some of the most important phytochemicals were included in this group, including withastramonolide, withanolide B, 12-deoxywithastramonolide, withanolide R and withaferin A (8) (Table 2, Fig. 2). Thus, the plant has shown some promising results in inhibiting various processes and proteins of SARS-CoV-2 thereby can be investigated further for the formulation of herbal and plant-based drugs. This plant is an asset to the Ayurvedic medical sciences, as it is one of the most widely available and widely utilised household plants, particularly in India and its phyto-constituents are prospective candidates for developing herbal formulations in preventing and treating COVID-19 infection.

Table 2. List of phytochemicals obtained from *W. somnifera* (L.) Dunal and their target NSP of SARS-CoV-2 (8).

Sl. No.	Name of the phytochemical obtained from *W somnifera* (L.) Dunal	Target NSPs of SARS-COV-2
1	27-Hydroxywithanolide, Anaferin	NSP 10
2	12-Deoxywithastramonolide	NSP12 D1
3	Withanolide B, Withanolide R, Withaferin A	NSP12 D2
4	2,3 Dehydrosomnifericin, Withanolide B, 27-Deoxy-14-hydroxywithaferin A	NSP 3
5	Somniferine, Vindolinine	NSP 15
6	27-Hydroxywithanolide B	NSP 9

Cinchona officinalis L

C. officinalis is a shrub or a tree belonging to the family Rubiaceae (Fig. 1B) and is remarkably known for its biologically active alkaloids, which have been used by humankind for

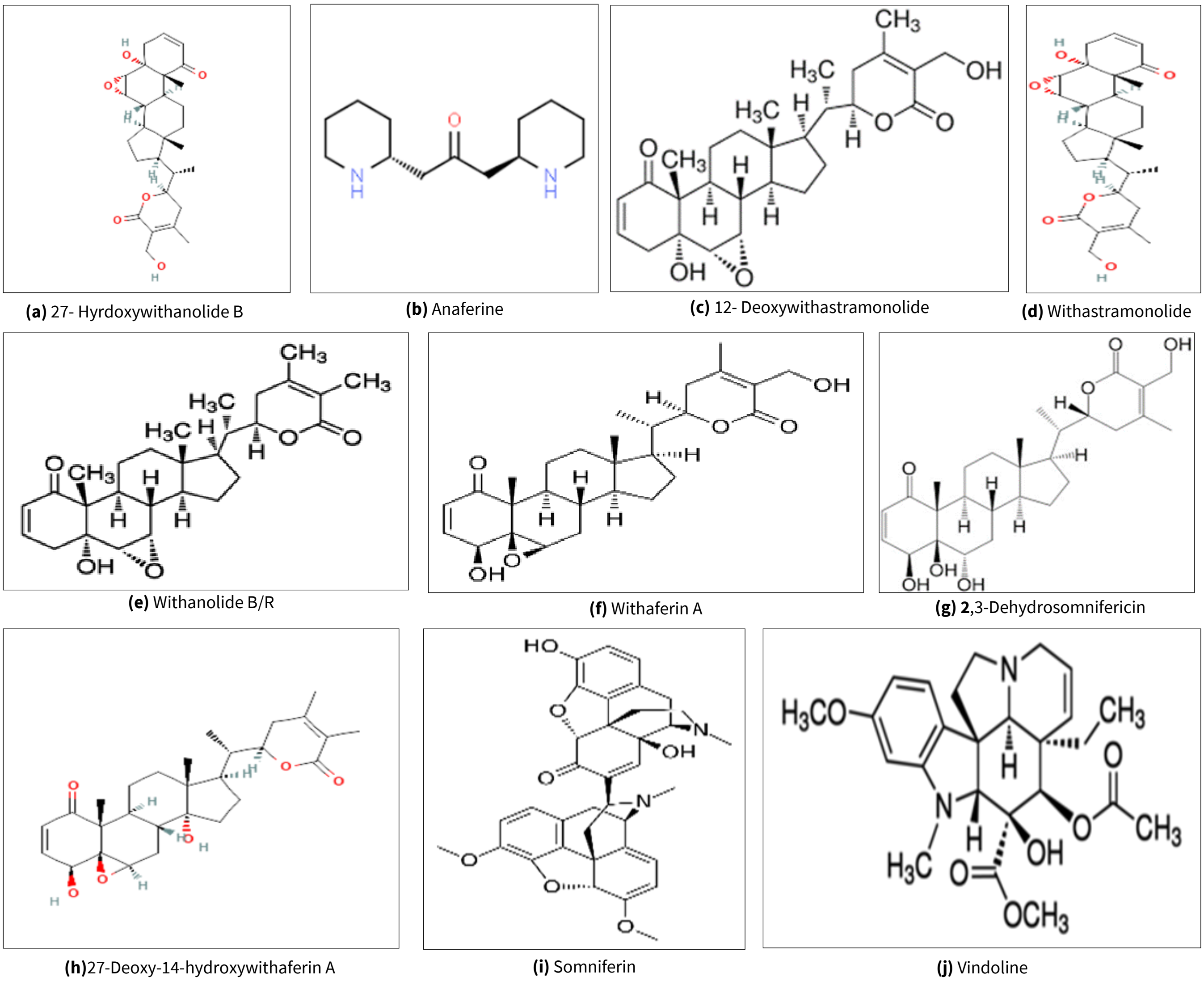


Fig. 2. Structure of different phytochemicals effective against NSPs of SARS-CoV-2 obtained from *W. somnifera* (L.) Dunal.

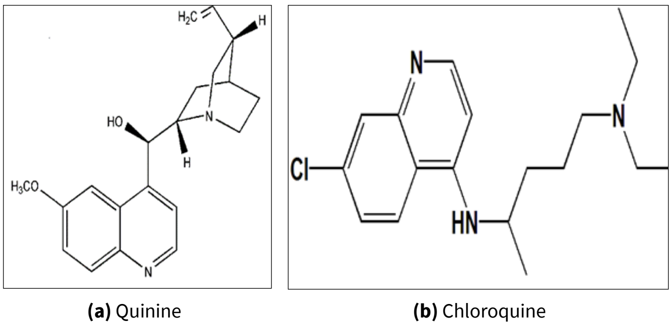


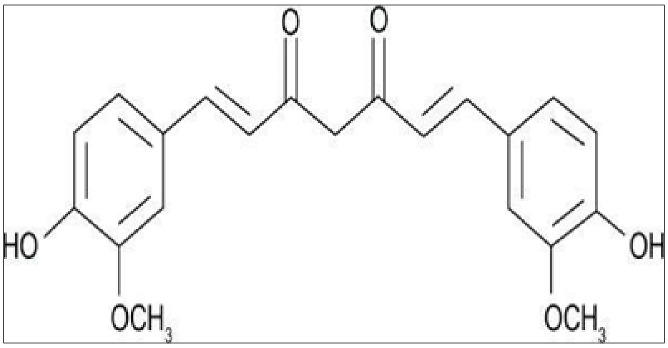
Fig. 3. Biochemical structure of quinine and chloroquine.

centuries against malarial parasites (40). Quinine is the major alkaloid extracted from the bark of the *Cinchona* plant (Fig. 3A). A synthetic derivative of quinine marketed as chloroquine (Fig. 3B), has been found to be clinically proven in combating SARS-CoV-2 (41). It was considered as a vital essential medicine in the mass campaigns of drug administration against malaria and is constantly being revisited and investigated for its active role against certain viruses such as SARS-CoV-1, which is very concurrent to SARS-CoV-2 at various levels (9).

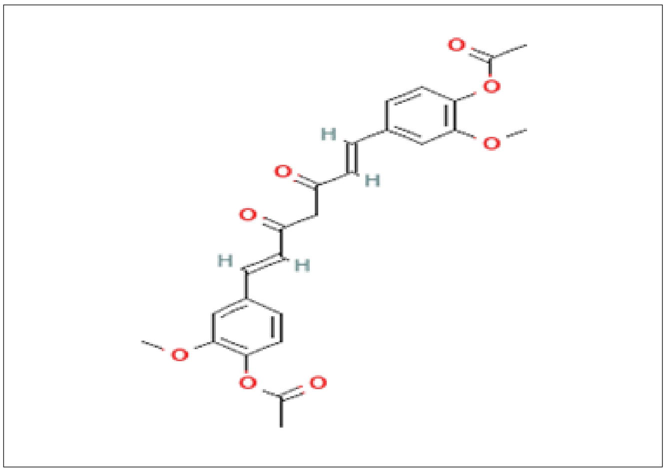
A research study revealed that chloroquine inhibits the replication of SARS, cells in a cell culture (9). Further, chloroquine has been suggested to be indeed effective against the replication of SARS-CoV-1 in combination with Remdesivir (42). Viruses usually tend to make the lysosome a bit more acidic in order to create autophagosomes, which is a crucial step of pathogenesis. Quinine and chloroquine have shown to raise the pH of the lysosome thereby interfering with the aforementioned step in viral replication (43). In particular, the research conducted on effectiveness of various pharmacological components against SARS-CoV (44), it was demonstrated that the chloroquine administered group showed remarkable decrease in the course of the disease as well as pneumonia exacerbation in contrast to the control (44). DENV-2, the dengue-causing virus is also an RNA Virus like SARS-CoV-2 and Cinchona bark extracts were proven to be 80% efficient in combating this virus, thus can be investigated for SARS-CoV-2 alike (45). The Department of Science and Technology and Health Commission of Guangdong province advised that 500 mg dosage of chloroquine can be prescribed to the mild to moderate patients of Covid-19 (46). *Cinchona* bark is the mother source for Chloroquine, the further research, testing, and investigation of cinchona bark efficacy against COVID-19 may be warranted, as it could be more economical and requiring less processing than that of its drug derivatives (47).

Curcuma longa L.

The plant is commonly referred to as Turmeric and is the backbone of the Indian Ayurvedic system. *C. longa* is a perennial herb belonging to the family Zingiberaceae (Fig. 1C). The plant has been extensively used for its medicinal properties over ages and continues to be the most accessible home remedy for viral and bacterial infections alike (10). There have been some recent studies indicating the antiviral properties of *C. longa* against SARS-CoV-2 (48). The phytochemical Diacetyl curcumin isolated from *C. longa* has shown high binding energies (-38.84 kcal/mol) to the receptors in SARS-CoV-2 proteins in docking experiments and thus, can potentially be used to disrupt the stability of the virus and decreasing the viral load (49) (Fig. 4).



(a) Curcumin



(b) Diacetyl Curcumin

Fig. 4. Biochemical structure of curcumin and diacetyl curcumin obtained from *Curcuma longa*

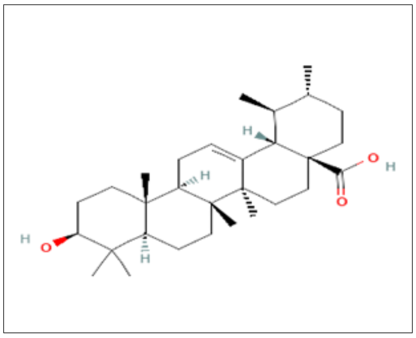
Curcumin, a polyphenolic secondary metabolite, is the chief phytochemical (77%) obtained from the rhizome of *C. longa*. Curcumin is one of the most investigated natural compound having anti-inflammatory (50), anti-cancer (51), anti-diabetic, antioxidant (50) and antidepressant (52), antibacterial and antiviral properties (53). Scientific reports describe that curcumin could be a promising drug to be used as an antiviral agent due to its broad-spectrum, low toxicity, and potential pharmacological mechanism against SARS-CoV2 (48, 53). Recently, it was suggested that curcumin can play a potential role in combating COVID-19 by inhibiting viral replication, administering immunological benefits as well it has shown the ability to reverse the pulmonary edema and other pathways linked with fibrosis in COVID-19 (54). As mentioned earlier while investigating the potential of drugs and natural compounds two routes are viewed viz inhibition of the protease named $3CL^{PRO}$ (also called as M^{PRO}), an enzyme essential for viral replication and the second important target site could be angiotensin-converting enzyme-2 (ACE-2) which is essential for the entry of SARS-CoV-2 into the host cell (55, 56). With a binding energy of -9.2 kcal/mol, curcumin has shown tremendous ability of inhibiting the SARS-CoV-2 $3CL^{PRO}$. This property is attributed to the capacity of curcumin to form a great number of Vander Wall as well as hydrogen bonds with the amino acids in the active site of the $3CL^{PRO}$ (10). In another study using the technique of Molecular Docking, it was shown that curcumin has inhibiting effect on SARS-CoV-2 protease $3CL^{PRO}$ which is comparable to conventional drugs like chloroquine and hydroxychloroquine (57). These findings are indicative of the potential herbal formulations that can be made using curcumin from *C. longa* in order to effectively combat SARS-CoV-2 (58).

Ocimum sanctum L.

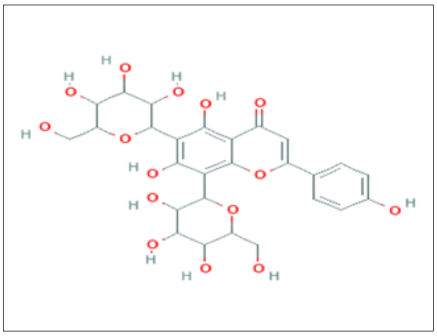
O. sanctum is a member of the family Lamiaceae. It is an aromatic perennial plant (Fig. 1D) and contains many bioactive compounds, therefore, is a major component of India's ayurvedic system. It has antibacterial, anticarcinogenic, antidiabetic and immunity booster properties, which is already proved by many *in vitro* and *in vivo* experiments on animals, including humans (59). *O. sanctum* has been found to protect organs and tissues against chemical, physical, metabolic and psychological stresses (18). Strong scientific evidence demonstrates the antiviral properties of *O. sanctum* against both DNA viruses like Herpes virus (HSV), Hepatitis virus, adenovirus (ADV) as well as for RNA viruses like enterovirus 71, coxsackievirus CVB1 (60). This plant has shown very fascinating properties by helping people curing their pain, fever, cough and even diarrhoea caused due to COVID 19 (61). Since COVID 19 is a viral infection and results in inflammation of lung tissues, antiviral and anti-inflammatory properties of *O. sanctum* may help to combat COVID 19 (18).

The COVID 19 virus becomes active in human body with ligand n3 binding to the main protease (M^{PRO}) of SARS-CoV-2. After binding, signal transduction initiates, stimulating the translation of viral RNAs into functional proteins like RNA polymerase, exoribonucleases and endoribonucleases. These 16 NSPs (non-structural proteins) (Table 1) formed after translation help the virus in replication and transcription resulting in more viral RNAs and Proteins (62). With the help of Molecular Dynamic Simulation and Molecular Docking studies, it was demonstrated that bioactive compounds of *O. sanctum* (Vicenin, Ursolic acid and Isoorientin 40-O-glucoside 200-P-hydroxybenzoate) effectively inhibit the main protease (M^{PRO} or Cl^{PRO}) of SARS-CoV-2 and does not allow its built-in ligand n3 to bind. These active phytochemicals (Tulsinol A, B, C, D, E, F, G and dihydroeugenol-B) after binding with main protease (M^{PRO}) affect the replication and transcription of virus and do not allow NSPs to be formed. These compounds have higher binding affinity than n3 along with stable MD runs, drug likeness properties and ADMET predictions (62) (Fig. 5).

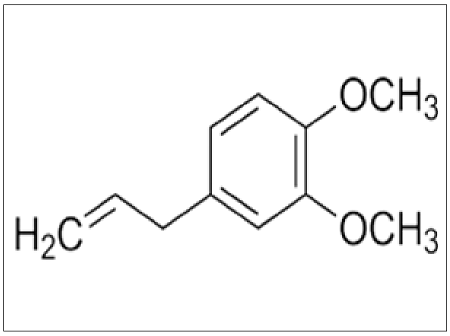
These phyto-constituents not only prevent viral pro-



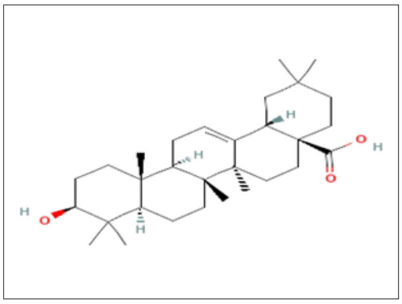
(a) Ursolic Acid



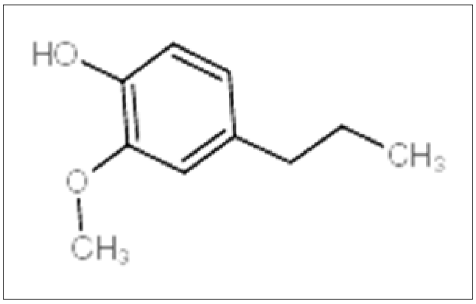
(b) Vicenin



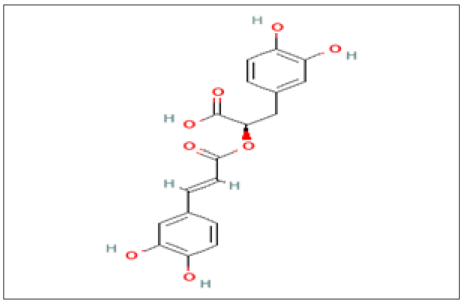
(c) Methyl eugenol



(d) Oleanolic Acid



(e) Dihydroeugenol



(f) Rosmarinic Acid

Fig. 5. Biochemical structures of some phytochemicals of *Ocimum sanctum* L. that are effective against SARS-CoV2.

teins from interacting with host cells, preventing them from transmitting and propagating inside the human body, but they are also safe to use against COVID-19 without inducing side effects (63) (Table 3). These phytochemicals bind to spike proteins (6VSB) and inhibit RNA dependent RNA polymerase (6Y84). They do not allow COVID 19 virus to modulate ACE II. The pharyngeal epithelial cells exhibit a significant preference for SARS-CoV-2 (64). Because oral formulations can easily carry the extract to the pharyngeal regions, hence they are significantly useful in the medical care of SARS-CoV-2 infections. Some phytochemicals like oleanolic acid, methyl eugenol, ursolic acid and rosmarinic acid (Fig. 5) also prevent the attachment and replication of virus in the host cell by binding to the glycoproteins present in Spike proteins of SARS-CoV-2 virus, due to their high binding efficacy (65). In this way, phytochemicals can interfere with viral machinery in two ways, either direct inhibition of viral intracellular growth or non-specifically inhibiting the interaction between host cell and virus by inhibiting the HA glycoprotein (66). The binding efficacy of natural compounds from *O. sanctum* was greater than that of the Lopinavir/Ritonavir and Remdesivir (67).

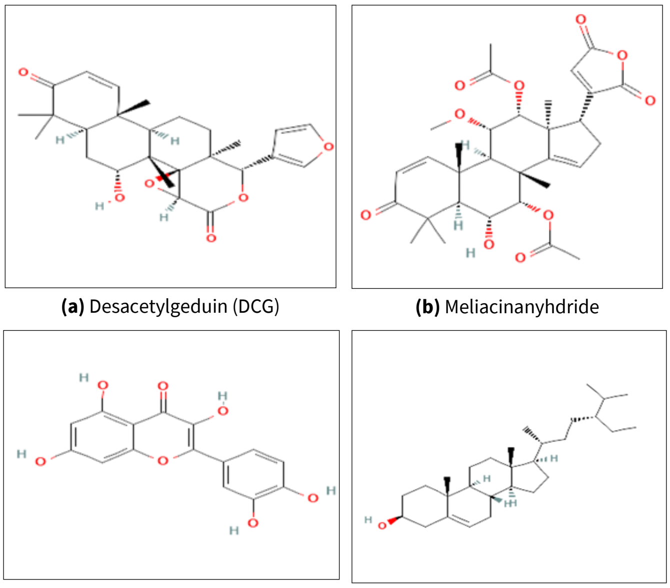
Azadirachta indica A. Juss.

A. indica (Neem) belongs to the family Meliaceae (Fig. 1E) and is known for its health-promoting properties. It contains several types of natural compounds with varying medicinal properties. In Ayurvedic and Unani medicine, particularly in the Indian Subcontinent, the natural compounds of neem have been used to cure and prevent a variety of diseases. Fever, cough and asthma are all frequent clinical signs of COVID-19, and neem is frequently used as an Ayurvedic medicine to treat them. It has also been used to treat viral infections in humans and animals' due to its antimicrobial and immunostimulant properties (67). During viral infection, neem has been shown to boost both humoral and cell-mediated immune responses (68). For COVID-19 infected patients, diarrhoea is another typical clinical sign, and neem leaves have been traditionally used to treat diarrhoea (69). Furthermore, neem leaves, stem bark and blossom extracts of neem were found to have high antioxidant activity (70).

Different parts of *A. indica* hold different compounds that can potentially inhibit Papain like protease (PL^{PRO}) of SARS-CoV-2. One such compound is desacetylgeduin (DCG) with highest binding affinity for PL^{PRO} and not allowing its ligand to bind. In fact, Desacetylgeduin showed greater affinity in comparison to other active compounds and drugs like Chloroquine, Hydroxychloroquin and Remdesivir. According to molecular dynamic studies, DCG has a significant impact on PL^{PRO} structure. The interactions responsible for bonding between the two may include hydrogen bonding, Vander Waals Interaction and Electrostatic interactions (71).

Ingesting some neem compounds like meliacinanhydride, crude neem leaves or leaves extract powder may inhibit the replication of SARS-CoV-2 virus. These extracts of neem leaves have been shown to lower blood sugar levels while simultaneously acting as ACE inhibitors (72). The antiviral and anti-inflammatory activity of neem may reduce the rate of infection but the exact mechanism is not yet known. Neem extract has been demonstrated in preclinical trials to significantly reduce circulating inflammatory cytokines like cyclooxygenase-2 (COX2), nuclear factor-kappa B (NFkB), IL-6, IL-1, IFNγ and TNFα (73). Nesari et al. (74) evaluated the prophylactic effects of neem capsules in 190 healthcare workers at a hospital or their relatives suffering from COVID-19 infection. The study found that the participants taking neem capsules orally in any form were at low risk of SARS CoV-2 infection; however, warrant further investigation (74). Recently, Borkotoky and Banerjee

(75) identified promising inhibitors of the E and M proteins of SARS-CoV-2 using molecular docking, MD simulation and binding free energy calculations. They found that bioactive compounds, Nimbolin A, Nimocin and Cycloartanols (24-Methylenecycloartanol and 24-Methylenecycloartan-3-one) showed strong binding free energy with both E and M proteins (75) (Fig. 6). It was also revealed a likely effect of neem



(a) Desacetylgeduin (DCG) **(b)** Meliacinanyhdride

(c) Quercetin **(d)** Nimbosterol

Fig. 6. Biochemical structures of some phytochemicals obtained from *A. indica* A. Juss.

bark extract on propagation and pathophysiology of mouse hepatitis virus (76). neem bark extract could directly bind to the virus-host attachment Spike glycoprotein and suppresses mouse hepatitis virus-induced neuroinflammation and neuropathogenesis by inhibiting cell-to-cell fusion and viral replication. These results substantiate the potential of neem compounds as possible therapeutic options; however, warrant the experimental validation and optimization of these natural compounds to add value to the development of specific therapeutics against SARS-CoV-2.

Tinospora cordifolia (Willd.) Miers

T. cordifolia (commonly referred to as Giloy or Guduchi in India) belongs to the family Menispermaceae (Fig. 1F). It is well-known in traditional Ayurvedic literature for its extensive use in the treatment of numerous diseases. Due to their well-known attribute of having minimal side effects as compared to drugs, the phytochemicals of this plant are progressively gaining importance in clinical research (Table 3). Lactones, glycosides, sesquiterpenoid, alkaloids, diterpenoid, phenolics, polysaccharides, flavonoids and aliphatic compounds are among the numerous biologically important phytoconstituents found in it, all of which have immunomodulatory properties in the human body (77). These compounds are effective in preventing SARS-CoV-2 replication and attachment of viruses to the host cell. Sagar and Kumar (78) evaluated antiviral activity of natural compounds from *T. cordifolia* against SARS-CoV-2 using *in silco* tools against 4 targets of SARS-CoV-2, which includes RNA dependent RNA polymerase, main protease, surface glycoproteins and receptor binding domain. Receptor binding domain and surface glycoproteins are involved in the virus attachment to the host cell. Main protease and RNA dependent RNA polymerase helps the virus in replication in the host cell. Thus, four natural compounds viz. Berberine, Isocolumbin, Magnoflorine and Tinocordiside from *T. cordifolia* showed high binding efficacy against SARS-CoV-2; hence, validating the importance of using *T. cordifolia* in the clinical management of SARS-CoV-2 infection (78, 79). Furthermore, *T. cordifolia* extract can be consumed orally to improve our immune system's ability to combat many infectious ailments (43). The famous herbal formula that has gained a lot of attention because of its effective curing properties in COVID 19 condition is -: *T. cordifolia*, *O. sanctum*, *Z. officinale*, *Piper nigrum* together with honey to make herbal tea which is effective against COVID 19 symptoms like cough, fever and also enhance immunity (43) (Table 3).

Conclusion

On the basis of the above review and discussion, it can be concluded that Ayurveda and its associated herbal remedies based on plant extracts and phytochemicals showcase tremendous potential in fighting against SARS-CoV-2 and can prove to be a boon in the current scenario of COVID-19. Plant based herbal formulations as compared to the conventional drugs cannot just help in curing severe acute respiratory issues associated with COVID-19 but also aid in developing an immunity for a longer term against the virus. The availability of such Ayurvedic medicines can be a natural, healthy and sustainable mode of medication as plant derived products pose lesser risk of side effects and complications. Moreover, such herbal drugs can be made available at much lesser prices as compared to the conventional western drugs. The aforementioned discussion clearly reveals the biomolecular evidences for various phytochemicals derived from a range of plants that have proved to be effective against SARS-CoV-2 at the level of the entry of the virus into the host cell as well as in relieving the symptoms associated with COVID-19 (23). However, there is yet a zenith that needs to be realized in making these herbal drugs at research and industrial level. Further investigations in this matter are the need of the hour keeping in mind the impeccable effectiveness of phytochemicals from different medicinal plants in fighting against SARS-CoV-2 (23).

Plants secondary metabolites can serve as potential anti-SARS-CoV-2 molecules; therefore, elegant experiments need to be conducted to establish their role in preventing viral replication by limiting duplication, transcription and other critical processes (80). Essential oils (EOs) are known to display anti-inflammatory, antioxidant, immunomodulatory and antiviral properties; therefore, have been anticipated to have activity against SARC-CoV-2 (81). Reports are on a molecular docking analysis of 171 essential oil components with the SARS-CoV-2 showing the best docking ligands for the SARS-CoV-2 proteins were (*E*,*E*)-α-farnesene, (*E*)-β-farnesene, and (*E*,*E*)-farnesol (82). However, majority of the existing information regarding role of EOs against SARS-CoV-2 are based on the data accomplished from computer-aided docking; therefore, the well-planned *in vitro* and *in vivo* studies deserve to validate the efficacy of essential oils against SARC-CoV-2. Flavonoids like amentoflavone, quercetin, and puerarin have also shown to suppress the activity of SARS-CoV chymotrypsin-like protease, and so can be tested against SARS-CoV-2 (59). On the basis of data presented, it is pertinent to state that tremendous potential is present in the plant-derived phytochemicals and herbal formulations, which can be exploited to the benefit of humankind in the current situation of COVID-19 pandemic.

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Authors contributions

The authors confirm contribution to the paper as follows: Study conception and design was by HP and BG, Data Collection by HP and VK, Overall writing of the manuscripts by HP and VK, Overall review and draft preparation by VP, VK, BG and AS, Final Editing and Review: All authors. All authors reviewed the results and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflicts of interest to report regarding the present study.

Ethical issues: None.

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