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REVIEW ARTICLE

Potential Indian medicinal plants during COVID-19 pandemic

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ABSTRACT

Severe Acute Respiratory Syndrome (SARS) triggered by the novel coronavirus- SARS-CoV-2 has infected millions of the world population. India is among those countries severely affected due to SARS-CoV-2 with more than 4,20,000 deaths registered and approximately 31.5 million confirmed cases as of 30th July 2021. The 2nd infection wave, caused by the Delta variant of coronavirus was 4-times more transmissible than the original strain. Traditional plant materials are used globally and throughout India as complementary and alternative therapeutics for the control, prevention, and treatment of COVID-19, while no systematic review of studies specifically focussing on studies on Indian traditional medicinal plants against SARS-CoV-2 infection during COVID-19 outbreak has been conducted.

Aim of the study: *This review aims to estimate the comprehensive evaluation of Indian medicinal plants with anti-SARS-CoV-2 activities during the COVID-19 outbreak and to compile the crucial information required for further investigation of their potential role in the management of COVID-19. In-vitro, in-silico (computational docking), and in-vivo studies conducted on either crude extracts, phytochemical formulations, or isolated compounds with SARS-CoV-2 potential drug targets viz. Angiotensin-converting enzyme-2 receptors (ACE-2 receptors), SARS-CoV-2 Main Protease (Mpro), viral Spike protein (S Protein), and other humanized models for In-vitro studies have been reported. Hot water and hydroalcoholic extract of medicinal plants like Cissampelos pareira L, and Artemisia annua, have shown the In-vitro inhibition potential against SARS-CoV-2. Formulations based on Withania somnifera, Tinospora cordifolia, and Ocimum sanctum, Carica papaya are found to be potential viral inhibitors.*

INTRODUCTION

Origin of COVID-19, the Global pandemic and it's Etiology

During December 2019, several cases of Pneumonia disease caused by an unknown pathogen found in China, later the pathogenic agent of these cases was confirmed as a novel Coronavirus (SARS CoV-2), a new member of the family Coronaviridae of the order Nidovirales. The pneumonia-like respiratory illness i.e., Severe Acute Respiratory Syndrome caused by SARS CoV-2 was named as COVID-19 by WHO on 11 February 2020. On 30th January 2020, the WHO Emergency Committee advised the Director-General of WHO that the corona outbreak constituted a Public Health Emergency of International Concern (PHEIC), and very soon this new COVID Outbreak became a

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global emergency as per the WHO and later on 11 March 2020, WHO characterized COVID-19 as Pandemic. Till July 2021, more than 197 million (197,869,692) confirmed cases of COVID-19 have been recorded out of which this virus took the lives of 4,219,921 people. In India, this disease was even more fatal as it spread in its two waves: 1st wave in the start of summers of 2020 (March 2020) and 2nd wave in the middle of 2021 (Started from April 2021) causing the total deaths of 4,26,290 people among 31,812,114 confirmed cases till now.

Earlier to this outbreak, in 2002 the first coronavirus SARS-CoV outbreak was reported from China which took the lives of around 774 individuals with a mortality rate of 10% and infected about 8098 individuals (Li *et al.*, 2020). Later in 2012, another outbreak emerged from Middle East which was called Middle East Respiratory Syndrome, and the virus causing the outbreak was called as MERS CoV. The mortality rate of this MERS CoV was around 35%. All of these coronaviruses belong to the beta-coronavirus in the subgenus Sarbecovirus. These coronaviruses caused Respiratory Tract Infection and pneumonia like symptoms. With an officially unknown origin, this SARS CoV-2 is considered to be originated from an animal involving zoonotic transmission (Andersen *et al.*, 2020). Genome characterization studies have revealed that the SARS CoV-2 has been evolved from a coronavirus strain which is found in bats. The genome of SARS CoV-2 is 82% similar to the first coronavirus SARS CoV (Cascella *et al.*, 2021).

Coronaviruses have the positive sense, single stranded RNA as genetic material, which is made up of 29891 nucleotides encoding for 9860 amino acids and is enclosed in a capsid with spikes. The virus genome is extremely large (around 26-32 kilobases) in comparison to other RNA viruses and they have very complicated machinery to infect host cells (Abdullahi, 2020).

Pathogenesis of COVID-19 and Vaccines

Among all these coronaviruses, SARS CoV, MERS CoV, and SARS CoV-2 has a higher human to human transmission rate which can easily be seen as it has caused a global pandemic.(Zhu *et al.*, 2020) However, the mortality rate of this SARS CoV-2 (Global Mortality Rate 0.16%) is much lesser than both the previous viruses.

The rate of transmission of this SARS CoV-2 is extremely high which is causing a global pandemic and infecting more than 178 million individuals worldwide. The human-to-human transmission of this virus takes place through droplets carrying the infectious particle, breathing, sneezing, coughing, and through direct contact with the patients already infected with COVID-19. It has also been found that this virus can remain alive in the surfaces for a longer period like 9 days. Another study reported that the faecal-oral route can also be a potential source for the transmission of the disease as the researchers have found infectious virus particles in gastrointestinal-epithelial route, and collected faecal samples (Long *et al.*, 2021).

The pathogenesis or pathophysiology of COVID-19 can be illustrated in 3 steps:

- Viral replication
- Immunopathogenesis
- Cytokine storm

There are four main proteins present in the viral particle which contributes to the structure of this SARS CoV-2. These proteins are the surface spike (S) glycoprotein which is made up of 2 subunits S1 and S2, Nucleocapsid (N), Envelop (E) glycoprotein, and Membrane protein (M). Along with this there are 16 non-structural proteins. The surface spike protein (S1) recognizes the host's ACE-2receptorswhich are existing on respiratory epithelium such as type-II alveolar epithelial cells, and then binds to these receptors (Satarker & Nampoothiri, 2020). Lungs and gastrointestinal tract are the main organs which express these ACE-2 receptors and due to that, these organs are mainly damaged by COVID-19 infection. Along with that these receptors are also found on the other organs such as upper esophagus, myocardial and proximal tubular cells of the kidney, and urothelial cells of the bladder. After binding of S1 spike protein with ACE-2 receptors, spike protein subunit (S2) fuses with host transmembrane serine protease 2 (TMPRSS2), and then enters the host cell where it hijacks the machinery of host cell to start its replication and subsequent virion assembling.

As a reaction to SARS CoV-2, the normal immune response disrupts, and it leads to impaired immune response and unregulated inflammatory

responses in patients with severe and critical condition. The uncontrolled immune response results in the activated expansion of immune cells lymphocytes and macrophages. These immune cells produce immense amount of cytokines and result in cytokine storm. The Cytokine Storm (CS) is a life-threatening condition which is characterized by clinical presentation of overwhelming systemic inflammation, hyperferritinemia, hemodynamic instability, and multi-organ failure, and can leads to death if left untreated. The treatment of cytokine storm condition requires intensive care admission. Cytokine Storm has been reported in various viral infections including influenza H5N1 virus, influenza H1N1, and the two coronaviruses highly related to COVID-19; SARS-CoV and MERS-CoV. Both In the initial time of this global pandemic, it was very hard to determine the potential drugs for the treatment of COVID-19 because of very limited knowledge about its therapeutics. In that period of urgency scientists suggested using few popular antiviral drugs like Remdesivir and various other repurposed drugs like Dexamethasone and Hydroxy-chloroquine.

Till now, there is no specific drug that has been developed to treat COVID-19 disease. Recently a few vaccines have been approved by WHO [Coronavirus Disease (COVID-19): Vaccines, 2020] which are:

- The Pfizer/BioNtech Comirnaty Vaccine
- The SII/Covishield and AstraZeneca/AZD1222 Vaccines- AstraZeneca/Oxford
- The Janssen/Ad26.COV 2.S-Johnson & Johnson,
- The Moderna COVID-19 vaccine (mRNA 1273)
- The Sinopharm vaccine-Beijing Bio-Institute of Biological Products Co Ltd
- The Sinovac-CoronaVac

After several studies it has been reported that virus based potential therapeutic drug targets can be the Spike (S) protein and its receptor binding domain RBD which serve as the structural component of the virus particle as the S protein is mainly responsible for recognition of ACE-2 receptors through the CD147 mediated potential entry route (Gil *et al.*, 2020). The non-structural protein (NSP) targets for COVID-19 therapeutics may be Proteases 3CLpro (3C-like protease) or the Mpro and PLpro (papain like protease) as these proteases are responsible for cleaving and transforming two large polyproteins pp1a and pp1ab into mature NSPs. Both of these proteases are encoded by ORF 1a/b of the main viral genome and play an important role in viral replication and host cell response. Other potential NSPs as drug targets include RNA dependent RNA polymerase (RdRp) essential for viral genome replication and it is conserved in all RNA viruses and helicase (nsp13) which is necessary for RNA viral synthesis (Gil *et al.*, 2020).

Host based potential targets for antiviral developments may be the ACE2 Receptor which activates with the viral S protein and the Transmembrane Serine Protease 2 (TMPRSS2) which activates the viral Spike protein by its protease action and ACE-2 receptor interaction with viral S protein (Gil *et al.*, 2020).

An extensive literature review was undertaken to reveal the studies of potential Indian medicinal plants effective against COVID-19 using search engines including, PubMed, SCOPUS, Science Direct, Google Scholar, ACS. The reported research studies are based on *In-vitro* and *in-vivo* studies and, *in-silico* computational analysis performed on various traditional medicinal plants. Most of the studies focused on the specific phytochemicals from various Indian traditional medicinal plants which have the potential to inhibit the viral particle and their subsequent studies against SARS-CoV-2.

POTENTIAL INDIAN MEDICINAL PLANTS AGAINST COVID-19

Since ages, Indian medicinal system explored the therapeutical properties of many of the medicinal plants and there have been mention of different therapeutical properties of various medicinal plants in Ayurveda. Also there have been vast use of these medicinal plants in culinary as spices and taste enhancer as well as immunomodulators. Though many medicinal plants have been used during the times of COVID-19 outbreak in the form of decoction (kadhas) and spices to increase immunity and metabolism, experimental studies of specific medicinal plants have shown therapeutic potential

against SARS CoV-2. These medicinal plants include *Tinospora cordifolia (Vern. Giloy)*, *Ocimum sanctum (Vern. Tulsi)*, *Withania somnifera (Vern. Ashwagandha)*, *Azadirachta indica (Vern. Neem)*, *Curcuma longa (Vern. Haldi)*, *Carica papaya (Vern. Papaya)*, *Allium sativum (Vern. Garlic)*, and *Cissampelos pareira L. (Vern. Laghu Patha)*.

Tinospora cordifolia

Tinospora cordifolia, is an herbaceous vine belonging to family Menispermaceae. This plant is indigenous to tropical regions of the Indian subcontinent and also found in Myanmar, Sri Lanka and China. Plant is also known as Giloy, Amrita or Guduchi in Hindi and has been used as a plant with immense therapeutical properties in Indian traditional medicinal systems like Ayurveda and Siddha. The plant has been reported to treat various medical conditions including urinary disorders, skin diseases, jaundice, diabetes, anaemia, inflammation, rheumatism, allergic responses and possess anti-periodic and radioprotective properties. The roots of this plant are used as potent emetic and used for bowel obstruction (Thakkar *et al.*, 2021). *Tinospora cordifolia* is also used for treating heart diseases, helminthiasis, rheumatoid arthritis, and leprosy. It boosts the immune system, the body's resistance to infections, function and levels of WBCs. Along with that it has also been helpful in digestive conditions (colitis, hyperacidity) and serious liver disorders including hepatitis (Sharma *et al.*, 2019).

The plant is used traditionally in the form of powder, as a component of decoction and certain parts of plants are used in the form of extracts like root extract is used for antidiabetic, hypolipidemic and anti-HIV activities. Since plants possess therapeutic properties because of some of the unique secondary metabolites like alkaloids, terpenoids, lignans and steroids which are produced by them as a result of various metabolic pathways occurring inside the plant body. As a result of these metabolic pathways, *Tinospora cordifolia* possesses various secondary metabolites like Tinosporide, Furanolactone diterpene, Tinosporine and Giloinsterol and many more (Sharma *et al.*, 2019). Since the plant has been reported to show anti-HIV properties, it has also been thought to use it against the recent global pandemic COVID-19 causing virus SARS-CoV 2.Recent study has shown that *Tinospora*

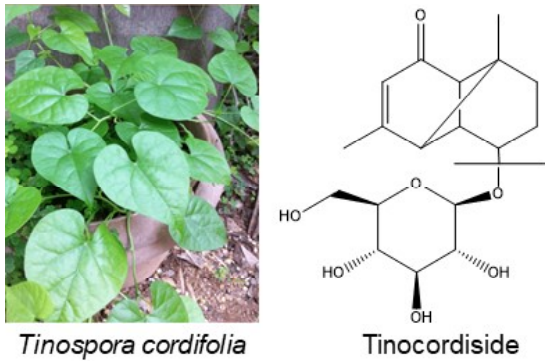


Figure 1: *Tinospora cordifolia* and Tinocordiside (its potential metabolite against COVID-19)

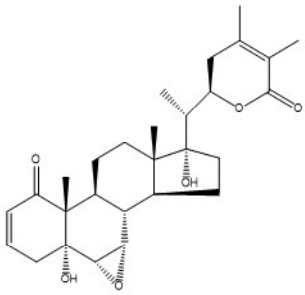
has anti-viral properties against the COVID-19 (Shree *et al.*, 2020). The study considered 112 compounds from *Tinospora cordifolia* (28), *Withania somnifera* (28) and *Ocimum sanctum* (56). The potential drug target was SARS CoV-2Mpro and they utilized AutoDock Vina based YASARA software and calculated binding energy (kcal/mol) and dissociation constant (pM) for comparison which revealed that out of 28 major phytochemicals from *Tinospora cordifolia*, a compound named Tinocordiside has the highest binding affinity (8.10kcal/mol) for SARS-CoV-2 Mpro which was significantly closer to binding energy of native ligand N3 (8.52kcal/mol) as per YASARA scoring and it was seen that the phytochemical Tinocordiside interacts and forms conventional and carbon-hydrogen bonds with the residues Gly 143, Leu 141 and Met 165 along with alkyl and p-alkyl interactions with Cys 145, His41 and Leu 27 (Shree *et al.*, 2020).

Withania somnifera

Withania somnifera (Ver. Ashwagandha) is a plant with the medicinal properties against plethora of diseases. It contains a broad range of phytochemicals which enables it to show anti-microbial, anti-inflammatory, anti-cancer, anti-depression, neuroprotective, cardioprotective, and anti-diabetic properties. It also has been reported that it can reduce the reactive oxygen species in the body and can regulate mitochondrial physiology, regulate apoptosis, and reduce inflammation and enhance endothelial function (Rathi *et al.*, 2021). Because of all these medicinal properties, it is called as 'Indian ginseng'.

In-silico and *In-vitro* researches on humanized zebrafish model have revealed that the compound

Withania somnifera



Withanone

Figure 2: Withania somnifera plant and Withanone

Withanone from the plant *Withania somnifera* attenuates SARS-CoV-2 Receptor Binding Domain and Host cell ACE-2 receptor to rescue spike protein induced pathologies (Balkrishna *et al.*, 2021). The study utilized molecular docking, molecular dynamic simulations and electrostatic energy calculations. The binding energies of the compounds Withanone, Withanolide A, Withanolide B and Withaferin in ACE-RBD complex were found to be 9.4 kcal/mol, 9.6 kcal/mol, 9.4 kcal/mol, 9.1 kcal/mol respectively demonstrating that the Withanone binds with the ACE-2 RBD pocket very tightly through two Hydrogen bonds (D30 of ACE2 and R403 of RBD to withanone), alkyl, and van der Waals interactions at the ACE2-RBD interface.

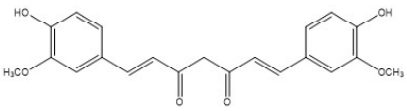
Further *In-vitro* validation of the inhibitory potential of Withanone was checked biochemically with ELISA based assays. The leaf extract of the *Withania somnifera* was taken which was enriched in Withanone and the weight by weight (w/w) amount of Withanone in the extract was 1.29%. Through HPLC, the w/w amount was confirmed to be around 8.93 ug/mg and it was found that with an IC_{50} value of 0.33ng/mL and IC_{100} value of 4.7 ng/mL, Withanone was found to inhibit the interaction of Angiotensin Converting Enzyme with Receptor binding domain (ACE-RBD) (Balkrishna *et al.*, 2021). Several researches, for the selection of a potential drug candidate for the treatment of COVID-19 has suggested the metabolite Withanolides from *Withania somnifera* to be used as an anti-viral, immunity booster and a potential drug candidate against COVID-19.*In-silico* studies have also reported that the plant can inhibit the SARS CoV-2 proteins and helps in destabilization of ligand-receptor complex. Also, it has been reported to modulate the immune pathways and inhibit the Granulocyte-macrophage colony-stimulating factor (GM-CSF). In this way it stabilizes the immune homeostasis and mitigates the cytokine storm.

The *in-silico* study that was done collectively with the *Ocimum sanctum, Tinospora cordifolia* and *Withania somnifera* revealed that the compound Withanoside V has the highest binding energy (10.32 kcal/mol) with the SARS CoV-2 Mpro and it was much more than the binding energy of native ligand N3 (8.52 kcal/mol) with the SARS CoV-2 Mpro making Withanoside V, the potential antagonist of Mpro as per YASARA scoring (Shree *et al.*, 2020).

Curcuma longa

Curcuma longa is a traditionally used Indian perennial herb which has been a part of Indian culinary since a long time. Known as 'Haldi' in Hindi or 'Turmeric' in English language, this perennial herbaceous plant is cultivated in many countries worldwide and its rhizome is used for diverse medicinal and culinary reasons traditionally in India. The yellow or turmeric color of its rhizome serves as a source of attraction towards food and this is why it is used as an integrated ingredient of Indian kitchen (Prasad & Aggarwal, 2011).

Curcuma longa



Curcumin (Bis-keto Form)

Figure 3: *Curcuma longa* (Haldi) plant and Curcumin which is the principal phytochemical in the plant

The plant belongs to family *Zingiberaceae*, and contains major phytochemicals like curcumin, demethoxycurcumin, bisdemethoxycurcumin and their derivatives. Curcumin is the principal phytochemical found in the plant *Curcuma longa* and has immense therapeutical properties like anti-oxidant in nature, anti-inflammatory, anti-cancer and anti-viral properties (Wilken *et al.*, 2011). Because of its precious traditional properties, it has been a topic of excessive researches. Due to its antiviral properties against influenza-A virus, molecular docking study has been done for studying its potential against the novel coronavirus SARS CoV-2 and the study manifested that curcumin and its derivatives have promising binding affinities

to the virus spike protein (Rattis *et al.*, 2021). A derivative of curcumin, bisdemethoxycurcumin has shown optimal binding affinity to the SARS CoV and SARS CoV-2 spike protein (Patel *et al.*, 2021). The results of such *in-silico* investigations lays the foundation of its future therapeutics as an antiviral drug against COVID-19.Another study involving *Curcuma longa* and *Andrographis paniculata* revealed that the phytochemical from *Curcuma longa* exhibits inhibitory properties for the SARS CoV-2 Mpro enzyme (Rajagopal *et al.*, 2020). These phyto-chemicals are turmerone, curlone, curcuphenol, curcumin (CUR), demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC) and cyclocurcumin. The molecular docking study explains the protease inhibitory property of these phytochemicals with Glide G score values of "6.13 kcal/mol of Curcumin, "6.77 kcal/mol of Cyclocurcumin compared with the recommended drugs for COVID-19 which were hydroxychloroquine (G score " 5.47) and nelfinavir (" 5.93). Comparing with the popular antiviral drug remdesivir (Glide G Score -6.38), cyclocurcumin was found to be more active.

Ocimum sanctum

Ocimum sanctum known as Tulsi, Holy Basil or Queen of herbs has been used extremely as a medicinal plant and also considered as a sacred plant in Indian ancient literature (Pattanayak *et al.*, 2010). In a randomized placebo-controlled study trial, it has been found that the phytomedicine tablets made up of *Withania somnifera* (Ashwagandha), *Ocimum sanctum* (Tulsi), *Tinospora cordifolia* (Giloy), Swasari (traditional herbal-mineral formulation) and nasal drop named Anu Taila (traditional nasal drop) promotes faster recovery from the COVID-19 (Devpura *et al.*, 2021). The parameters studied included serum level of high sensitivity C-Reactive protein, TNF-á and Interleukin-6 (IL-6) resulting in control of inflammatory cascade of the immune response (Devpura *et al.*, 2021).

Another study involved the metabolite profiling of *Ocimum menthiifolium,* the group of secondary metabolites like flavonoidal glycosides, iridoids and phenolic acids which are found in the plant, flavonoidal glycosides along with some other flavonoids form the same plant has been docked against the drug target of COVID-19 using molecular docking approaches. The study revealed that among all the flavonoids found in the *Ocimum* plant, apigenin 7-O rutinoside, prunin and acaciin have the maximum binding affinities against the nsp16/10 complex which is a heterodimer and is important for capping viral mRNA transcripts for methodical transcription and save itself from immune response (Albohy *et al.*, 2020.; Rosas-Lemus *et al.*, 2020).

Molecular docking studies based on YASARA scoring revealed that out of 46 various phytochemicals present in *Ocimum sanctum,* vicenin (8.97 Kcal/mol), Isoorientin (8.55 Kcal/mol) and ursolic acid (8.52 Kcal/mol) have remarkable binding affinities with the Mpro of SARS CoV-2compared to the native ligand N3 for SARS CoV-2 Mpro and thus they can be probable inhibitors for the SARS CoV-2. Further drug likeness and ADMET profile analysis has been done which explained that these compounds follow more than 2 parameters of Lipinski rule of five and can be explained as drug like compounds on purpose (Rathi *et al.*, 2021).

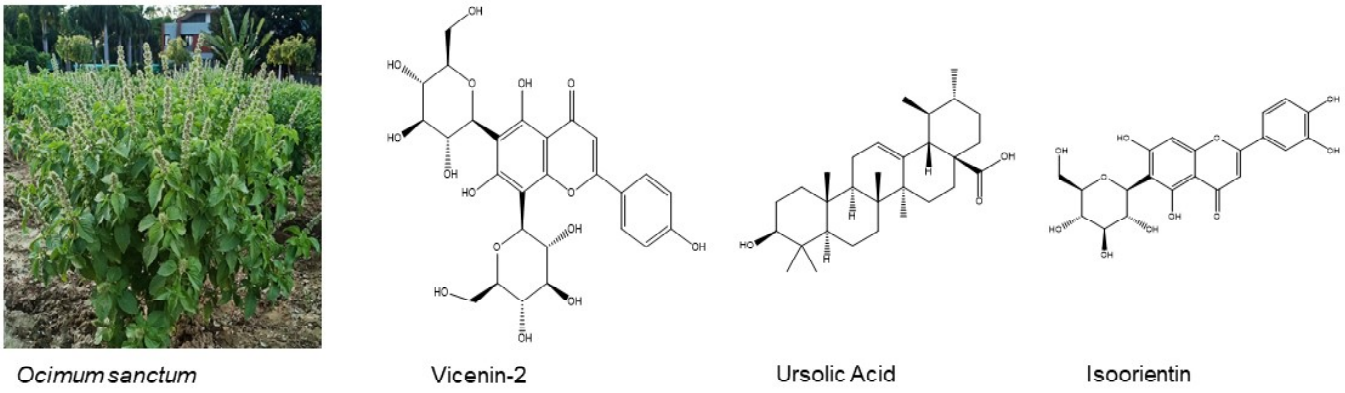


Figure 4: Ocimum sanctum *and its metabolites having inhibitory potential against SARS-CoV 2 Mpro*

Allium sativum

The plant *Allium sativum* is an integrated part of Indian kitchen and has been used a spice since a long time. The plant possesses antimicrobial properties due to the presence of diallyl sulphides (diallyl tetrasulphide, diallyl trisulphide, diallyl disulphide and diallyl monosulphides) (TSAO & YIN, 2001).

Image Source (Salgado *et al.*, 2011): Breno Salgado *et al.*, Jan 2011

An *in-silico* study which considered around 75 phytochemicals from various traditional Indian spices plants, revealed that a flavonoid from *Allium sativum*, myricetin and a flavone from *Pimpinella anisum* L, Isovitexin were the most potential ligand against SARS CoV-2 spike (S) protein and main protease (Kumar *et al.*, 2020). The study also showed that the other spices plants do possess some phytochemicals which have the inhibitory potential against SARS CoV-2 and this anti-viral property of various spices justifies their use in Indian culinary.

In another study, the major phytochemical S-Allylcysteine found in *Allium sativum* was docked against the viral RNA dependent RNA Polymerase (RdRp) and 3CLpro (Mehmood *et al.*, 2021). It was found that S-Allylcysteine was interacting with RdRp through hydrogen bonding with Arg553,

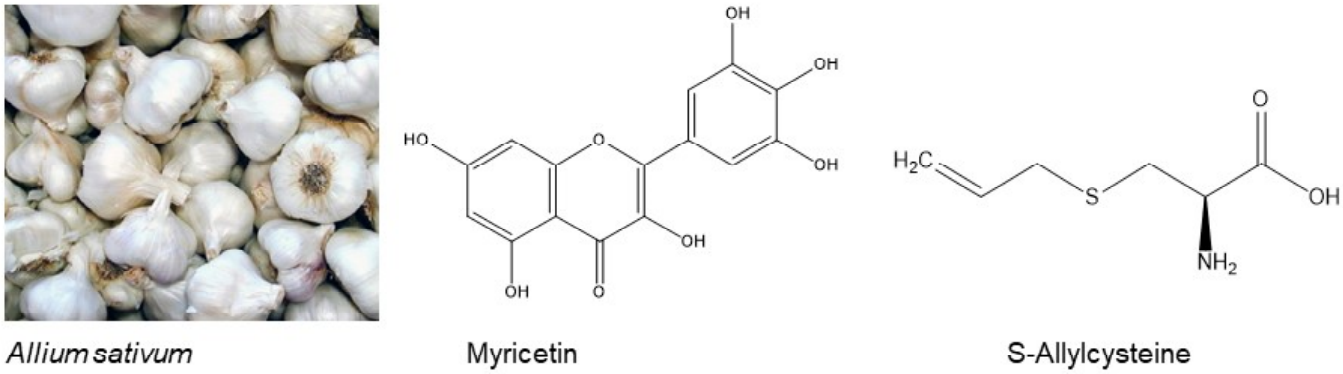


Figure 5: Allium sativum *and its derived metabolites against COVID-19*

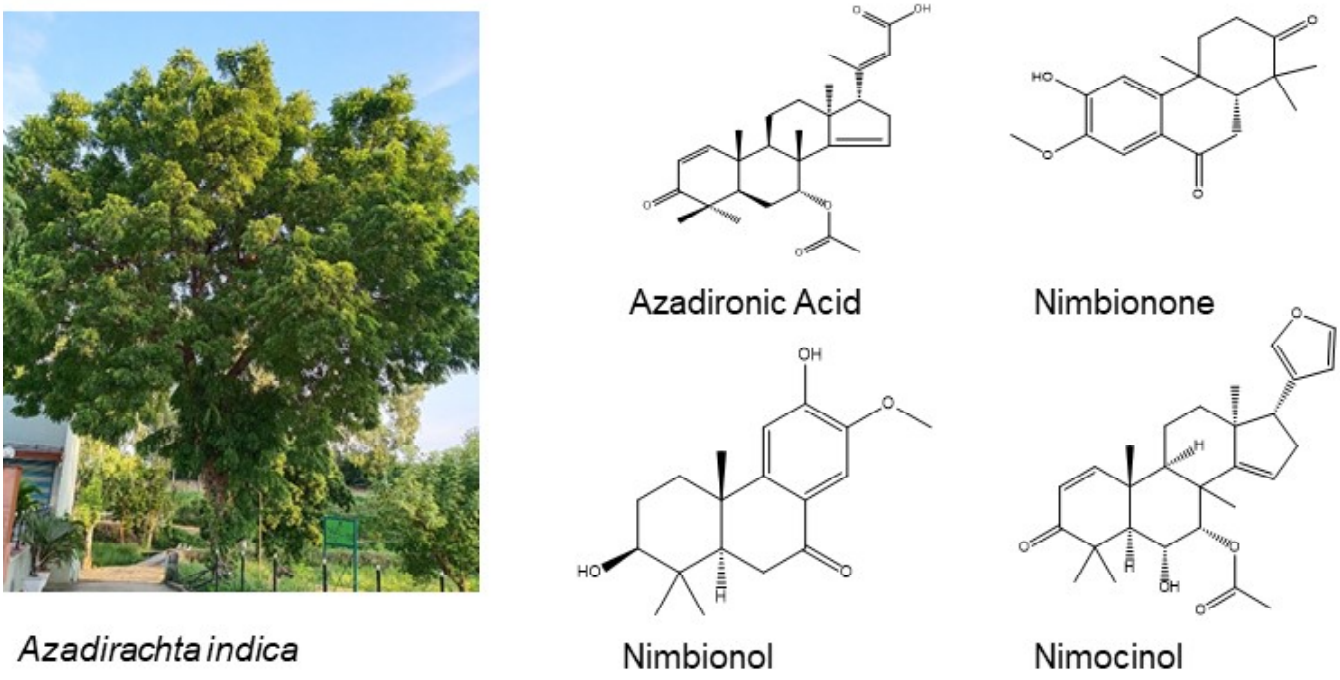


Figure 6: Azadirachta indica treeand its potential metabolites

Ser682 and alkylbonding with Ala558. The binding energy of this interaction was -5.0 kcal/mol. The study also involved docking RdRp with some other phytochemicals and it was found to best interact with kaempferol, monoterpene and S-Allylcysteine. Viral Mpro was also docked against various phytochemicals and interaction between S-Allylcysteine and 3CLpro was seen having binding energy -5.5 kcal/mol and this interaction was showing hydrogen bonding with Asn112, Gln8, Asn150 with the bond distance of 3.29 A^0, 2.68 A^0, 2.75 A^0 respectively.

Azadirachta indica

Azadirachta indica has been considered as a plant with diverse therapeutic properties as it contains a range of phytochemicals for treating various diseases. It has been traditionally used not only as a medicinal plant but also used for its insecticidal properties (Islas *et al.*, 2020). A molecular docking and ADMET based study which involved the docking of 47 phytochemicals obtained from 3 different plant; *Azadirachta indica, Allium cepa* and *Xylopia aethiopica* revealed that 23 out of 47 reported phytochemicals demonstrating negative Gibb's free energy have shown significant binding affinity with both the viral and host protein. Later, the ADMET profiling of these metabolites was done and we found that only the Azadironic acid, Nimbionone, Nimbionol and Nimocinol from *Azadirachta indica* can serve as a potential drug candidate against SARS CoV-2. The study involved Dexamethasone as a reference drug which was used as a steroidal drug against COVID-19 and has been found to decrease the mortality rate among COVID-19 hospitalized patients (Adegbola *et al.*, 2021; Group, 2021).

In another *in-silico* study, which considered 22 active phytochemicals from the plants *Azadirachta indica, Moringa oleifera* and *Mangifera indica* and the popular repurposed drug hydroxychloroquine as reference, for studying their binding affinities before the novel SARS CoV-2 Mpro, it has been found that these phytochemicals such as mangiferin, kaempferol, lupeol, nimbolide, and quercetin possesses the antiviral properties against the COVID-19 Mpro (Umar *et al.*, 2021).

Artemisia annua

This plant is native to China and it has been used to produce the drug Artemisinin for the treatment of malaria disease caused by the pathogen *Plasmodium falciparum (Artemisia Annua* - Wikipedia, 2021).

The plant has been narrated to possess antiviral properties against various viral diseases like hepatitis-B virus, bovine viral diarrhoea virus, Herpes simplex virus Type-1, Epstein-Barr virus. It also contains high phenols which provide this plant antioxidant properties (Merarchi *et al.*, 2021). *In-vitro* studies of the ethanolic extract of the whole plant of *Artemisia annua*, revealed its antiviral properties against SARS CoV (the first coronavirus) during the 2002 outbreak, leading to support its use against respiratory infections (Haq *et al.*, 2020). Since, the pathogenesis of novel coronavirus SARS CoV-2 is very much similar to that of the first coronavirus SARS CoV, this potential herb can be used against the newly emerged SARS CoV-2.

Molecular docking studies showed that artemisinin and its derivatives obtained from Artemisia, such as artemisinin, artesunate and artenimol produced significant Vina docking score (artelinic acid -7.1 kcal-mol^{-1} than the conventional repurposed drug Hydroxychloroquine (-5.5 kcal-mol^{-1}) being used against the COVID-19 (Sehailia & Chemat, 2020). The hydroxychloroquine interacts with the S glycoprotein receptor binding domain and prevent it. The HCQ binds with Lys353 hotspot binding pocket. In case of artemisinin and its derivative compounds, it has been found that the interaction between the phytochemical and the hotspot binding pocket is similar to HCQ but they show additional interaction with Lys31 binding pocket; confirming the interaction of formed

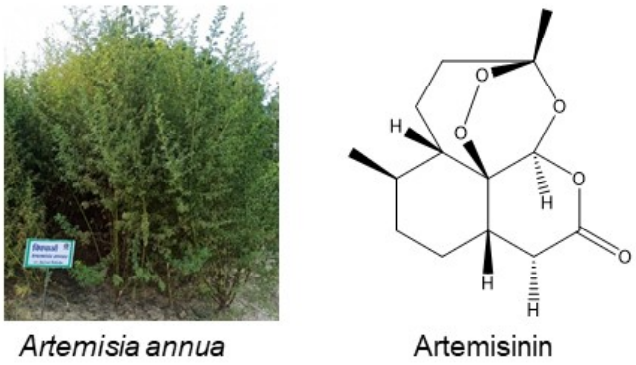


Figure 7: *Artemisia annua* and the drug Artemisinin

complexes and their stability in the active site of their respective targets. This study strongly promotes the repurposing of anti-malarial drug Artemisinin for treating the patients of COVID-19 (Sehailia & Chemat, 2020). An *In-vitro* study on the Vero E6 cell lines which are obtained from the kidney of *Cercopithecus aethiops*, an African green monkey have revealed that the hot water leaf extract of the different varieties of *Artemisia annua* having artemisinin contents in the range of 20.1 ± 0.8 to149.4 ± 4.4 µg.mL^{-1}and composite flavonoid content of the leaf in the range of 7.3 ± 0.2 to 37.2 ± 0.7 µg/mL have the potential to inhibit the *in-vitro* duplication of the SARS CoV-2 and its two variants which were named as UK and South African Variants B1.1.7 and B1.351. The IC_{50} values based on the leaf weight ranged from 13.5 to 57.4 µg dry weight (DW). Scientists also calculated the IC_{50} values based on artemisinin content per mL and IC_{50} values ranged from 0.03 to 2.5 µg/mL However, when they correlated the IC_{50} and IC_{90} values with the artemisinin content and flavonoid content present in the extract, it was found that the artemisinin or total flavonoid content is inversely related to their Anti SARS CoV-2 activity demonstrating that artemisinin is not the responsible phytochemical behind the Anti-SARS CoV-2 activity of *Artemisia annua* hot water extract (Ammerman *et al.*, 2008; Nair *et al.*, 2021).

Carica papaya

The plant *Carica papaya*, belonging to family Caricaceae is known for its delicious Papaya fruits which are cultivated in tropical and sub-tropical regions worldwide that are reported to contain an enzyme Papain, which is essentially helpful in digestion and boosts digestive system. All the parts of this plant seeds, leaves, barks and root have been used for their diverse therapeutic properties since ages. Use of papaya seeds as oral contraceptive because of their effect on sperm motility has been mentioned in the ancient literature and has been also studied recently (Ghaffarilaleh *et al.*, 2019). In Indian subcontinent, the leaves of this plant are used by patients infected with dengue fever and they are useful in increasing the platelet count of the body when consumed in the form of hot water extract. The plant has been reported to possess ample of phytochemicals which are anti-cancerous in nature and can be potential drug against cancer (Nguyen *et al.*, 2013). Nowadays, papaya extract is being sold in the form of tablets called 'Caripill' which helps in increasing the platelet count in the body. The caripill is an herbal formulation and can be used to treat several medical conditions like Thrombocytopenia, Oxidative stress and wound healing along with Dengue fever (*Can Caripill Tablets Really Cure Dengue? | Catch News*, 2018).

In a recent *in-silico* study which exploited Lipinski's rule, carcinogenicity test, pharmacokinetics profiling and molecular docking approaches screened 40 phytochemicals obtained from the leaves of *Carica papaya* for selection of potential drug candidate using computational docking approaches against the potential drug targets viz. 3CLpro, PLpro, RdRp, EndoU (SARS CoV-2 endoribonuclease), S1 and S2 (Hariyono *et al.*, 2021). The docking studies revealed that out of these 40 phytochemicals, 20 interacts with the 3CLpro, PLpro, RdRp, EndoU, S1 and S2 protein in the range of binding energy of -4.2 kcal.mol^{-1} to -8.2 kcal.mol^{-1}. Among all of these viral based drug targets, only the 3CLpro, EndoU and S1 interacts more with these 20 ligands with the binding energies from -4.5 to -7.8 kcal.mol^{-1}, -4.6 to -7.7 kcal.mol^{-1} and -4.9 to -8.2 kcal.mol^{-1} systematically showing promising results. Few of the significant compounds are catechin which binds with binding energy of -7.7kcal.mol^{-1} to EndoU, Kaempferol which binds to

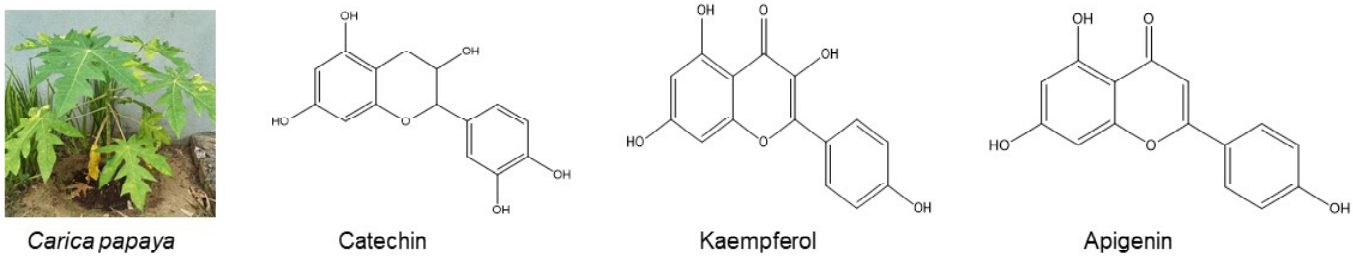


Figure 8: Plant of *Carica papaya* and chemical structure of molecule of Catechin, Kaempferol and Apigenin

Table 1: Medicinal plants and their potential activities exhibited by docking studies:

Plant	Utilized Resource	Potential Activity	References
Tinospora cordifolia	Molecular Docking based on YASARA scoring	Tinocordiside has the potential to inhibit SARS CoV-2 Mpro	Thakkar *et al.*, 2021
Withania somnifera	Humanised zebrafish model, ELISA Essay	Several phytochemicals have the ability to bind with ACE-RBD complex and inhibit the viral drug targets including Mpro.	Balkrishna *et al.*, 2021
Curcuma longa	Molecular docking	Inhibition of SARS-CoV-2 Mpro by Cyclocurcumin.	Rajagopal *et al.*, 2020
Ocimum sanctum	Molecular docking based on YASARA scoring, ADMET profiling	Phytochemicals Vicenin, isorientin and ursolic acidhave significant binding energy with the viral main protease and can inhibit it.	Albohy *et al.*, n.d.; Rosas-Lemus *et al.*, 2020
Allium sativum	Molecular Docking	Major phytochemical S-Allylcysteine has been found as a potential inhibitor of the RdRp and 3CLpro of SARS CoV-2	Adegbola *et al.*, 2021
Azadirachta indica	Molecular Docking, ADMET Profiling	Azadironic acid, Nimbionone, Nimbionol and Nimocinol have the potential to bind and inhibit both the viral and host-based drug targets.	Adegbola *et al.*, 2021; Group, 2021; Umar *et al.*, 2021
Artemisia annua	Vero E6 cell line	*In-vitro* inhibition of SARS CoV-2	Ammerman *et al.*, 2008; Haq *et al.*, 2020; Nair *et al.*, 2021; Sehailia & Chemat, 2020
Carica papaya	Molecular Docking	Out of 40 compounds, 20 have inhibition potential against viral 3CLpro, EndoU and S1 proteins.	Hariyono *et al.*, 2021
Cissampelos pareira L.	Vero Cell lines	*In-vitro* up to 98% inhibition of viral RNA by its whole plant hot water and hydroalcoholic extract	Haider *et al.*, 2021

S1 protein with -8.2 kcal.mol^{-1} of binding energy and epigenin which binds to S2 protein with-6.3 kcal.mol^{-1} of binding energy. This binding has been supported by the H-bond interaction and hydrophobic interactions between the various amino acid residues and the ligands. This study concluded that 20 out of 40 compounds show interaction with the various drug targets of SARS CoV-2 and are worth to be studied further *in-vitro* and *in-vivo* (Hariyono *et al.*, 2021).

Cissampelos pareira L.

The plant *Cissampelos pareira L.* a velvet leaf plant *(vern. Laghu patha)*, is widely used as a hormone modulator and it used as an inhibitor of protein synthesis and estrogen receptor. The plant has been traditionally used for the treatment of various reproductive disorders and fever (Haider *et al.*, 2021).

Cissampelos pareira L.

Figure 9: ***Cissampelos pareira* L.** ***plant***

[Image Source: (Sudhakaran, 2012) Sudhakaran Vasu, University of Calicut]

Recently researchers from CSIR-IGIB and IHBT have discovered the anti-SARS CoV-2 potential of whole plant extract (*Cipa* whole plant extract) (Haider *et al.*, 2021). The *in-vitro* study utilized the Vero cell line and it was found that the whole plant aqueous extract can inhibit the SARS CoV-2 *in-vitro*. The inhibition potential of hot water extract lies around 60% and that of hydroalcoholic extract of whole plant was found to be most effective, around 98%. The small constituents of this hydroalcoholic extract put together a synergistic effect towards viral inhibition. These constituents are salutaridine, cissamine, pareirarine and magnoflorine. On analysis of inhibitory potential of single molecule

constituents of Cipa, it was found that the phytochemical pareirarine has the highest inhibitory potential against the SARS CoV-2 *in-vitro*. Other constituents like cissamine and magnoflorine have the inhibitory potential more than 40% (Haider *et al.*, 2021).

The newly emerged novel coronavirus SARS CoV-2 has caused a global pandemic COVID-19 and affected millions of individuals worldwide. It is not only taking the lives of the people but also the affecting the global economy and impacting the mental health of left ones. The negative impact of this COVID-19 pandemic is not restricted only to the healthcare system but also it has damaged every sector globally. Successfully countering this newly emerged pandemic is very challenging and it can't be done without the discovery of immediate drugs against.

Till date, there is no promising medicine is available for treating COVID-19 except few broad-spectrum antiviral and repurposed drugs. However, these drugs are not that much reliable because they aren't discovered for the SARS CoV-2.

Using herbal formulations and their medicinal properties for the treatment can help us to cope with the situation because herbal formulation and medicinal plants have been used since ages for their medicinal properties and most of thedrug molecules for many severe diseases are derived from plant extracts. In the race of the anti-COVID-19 drugs, we have found many potential drug candidates which are obtained from traditionally used medicinal plants and their derivatives specifically molecules from *Withania, Tinospora, Artemisia, Curcuma and Ocimum*. These medicinal plants need immediate attention and further *in-vivo*, human clinical research needs to be done on these plant derived molecules. Going through the extensive, we have found that the traditionally used medicinal plants possess therapeutic properties to combat COVID-19. A summary of these plants and their potential anti SARS CoV-2 activity is given in the following table 1.

CONCLUSION

Plants have been an age-old source for various herbal medicines against the diverse diseases traditionally throughout the world including India. Upon studying the various studies based on medicinal and aromatic plants of Indian sub-continent, we have found that most of the traditional Indian plants possess the potential anti SARS CoV-2 properties. Most of these studies are based on *In-vitro*, *in-silico* and *in-vivo* testing of various phytochemicals against both the host and pathogen-based drug targets. Though based on above studies, we need to further perform more clinical studies and trials on phytochemicals derived drugs. We can conclude that there is a need for high-quality clinical studies with enough sample size and more comprehensive evolution of outcomes are needed on these medicinal plants extracts to pave the way for the development of improved standardized herbal drugs for curing COVID-19. On the basis of this review, we can hope for these plants derived phytomedicines against the COVID-19 and push the field further.

FUTURE PROSPECTS

As described in this review, many of the studies suggested extensive therapeutic properties of traditional Indian medicinal plants against COVID-19. Upon validation of *in-silico* and *In-vitro* studies of the therapeutic properties of these medicinal plants against COVID-19, effective compounds can be extracted from these medicinal plants and also the formulations having the extract of many potential medicinal plants can be prepared. Production of such formulation from individual and combined medicinal plants without validation from *in-vivo* studies is not sufficient. These *in-silico* and *In-vitro* studies are just a step in the development of medicinal plant-based formulations against COVID-19.

This study gives us hope that we can research further in the development of herbal drugs which are effective against COVID-19.

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REFERENCES

Abdullahi AM. 2020. Virology and Epidemiology of the 2019 Corona Virus Disease (Covid-19). *J Comm Med Pub Health Rep*, 1–8. 1(1): https://doi.org/10.38207/jcmphr20213

Adegbola PI, Semire B, Fadahunsi OS, Adegoke AE. 2021. Molecular docking and ADMET studies of *Allium cepa, Azadirachta indica and Xylopia aethiopica* isolates as potential anti-viral drugs for Covid-19. *Vir Dis* **32**: 85–97.

Albohy A, Maher Zahran E, Ramadan Abdelmohsen U, Alaraby Salem M, Al-Warhi T, Al-Sanea MM, Abelyan N, Ezzat Khalil H, Yehia Desoukey S, Ahmed Fouad M, Salah Kamel M. 2020. Multitarget *in-silico* studies of *Ocimum menthiifolium*, family Lamiaceae against SARS-CoV-2 supported by molecular dynamics simulation Multitarget *in-silico* studies of *Ocimum menthiifolium*, family Lamiaceae against SARS-CoV-2 supported by molecular dynamics simulation. *J Biomol Str Dyn* **15**: 1-11 doi: 10.1080/07391102.2020.1852964.

Ammerman NC, Beier-Sexton M, Azad AF. 2008. Growth and Maintenance of Vero Cell Lines. *Current Protocols in Microbiology*, *Appendix* (Suppl. 11), Appendix.

Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. 2020. The proximal origin of SARS-CoV-2. *Nat Med* **26**: 450–452.

Artemisia annua-Wikipedia(2021). Wikipedia; https://en.wikipedia.org/wiki/*Artemisia_annua*

Balkrishna A, Pokhrel S, Singh H, Joshi M, Mulay VP, Haldar S, Varshney A. 2021. Withanone from Withania somnifera Attenuates SARS-CoV-2 RBD and Host ACE2 Interactions to Rescue Spike Protein Induced Pathologies in Humanized Zebrafish Model. *Drug Design, Development and Therapy*, *Volume 15*, 1111–1133.

Can Caripill tablets really cure Dengue? | Catch News. 2018. http://www.catchnews.com/health-news/can-caripill-tablets-really-cure-dengue-138340.html

Cascella M, Rajnik M, Aleem A, Dulebohn SC, di Napoli R. 2021. Features, Evaluation, and Treatment of Coronavirus (COVID-19). In: *StatPearls*. StatPearls Publishing.

Devpura G, Tomar BS, Nathiya D, Sharma A, Bhandari D, Haldar S, Balkrishna A, Varshney A. 2021. Randomized placebo-controlled pilot clinical trial on the efficacy of ayurvedic treatment regime on COVID-19 positive patients. *Phytomed* **84**: 153494.

Gil C, Ginex T, Nozal V, Barrado-Gil L, Ngel Cuesta-Geijo MA ì, Urquiza JJ, Ramírez D, Alonso C, Campillo NE, Martinez A. 2020. COVID-19: Drug Targets and Potential Treatments. *J Med Chem* **63**: 12359–12386.

Group TRC. 2021. Dexamethasone in hospitalized patients with Covid-19. *New England J Med* **384**: 693–704.

Haider M, Anand V, Dholakia D, Enayathullah MG, Parekh Y, Ram S, Kumari S, Anmol, Bokara KK, Sharma U, Prasher B, Mukerji M. 2021. Anti-SARS-CoV-2 potential of *Cissampelos pareira* L. identified by Connectivity map-based analysis and *In-vitro* studies. *BioRxiv* 2021.06.11.448155.

Haq FU, Roman M, Ahmad K, Rahman SU, Shah SMA, Suleman N, Ullah S, Ahmad I, Ullah W. 2020. *Artemisia annua*: Trials are needed for COVID 19. *Phytother Res* **34**: 2423–2424.

Hariyono P, Patramurti C, Candrasari DS, Hariono M. 2021. An integrated virtual screening of compounds from *Carica papaya* leaves against multiple protein targets of SARS-Coronavirus-2. *Res in Chem* **3**:100113.

Islas JF, Acosta E, G-Buentello Z, Delgado-Gallegos JL, Moreno-Treviño MG, Escalante B, Moreno-Cuevas JE. 2020. An overview of Neem (*Azadirachta indica*) and its potential impact on health. *J Funct Foods* **74**: 104171.

Kumar B, Zaidi S, Haque S, Dasgupta N, Hussain A, Unni S, Singh V, Mishra BN. 2020. *In-silico* studies reveal antiviral effects of traditional Indian spices on COVID-19. *Curr Pharm Design* 26.

Li Y.-D, Chi W.-Y, Su J.-H, Ferrall L, Hung C.-F, Wu T.-C. 2020. Coronavirus vaccine development: from SARS and MERS to COVID-19. *J Biom Sci* **27**: 104.

Long JY, Yang W, Zhen Q, Hao M, Yi Z, Ning ZA, Yan L, Yuan XZ, Long JY, Yang W, Zhen Q, Hao M, Yi Z, Ning ZA, Yan L,Yuan XZ. 2021. The Pathogenesis and Treatment of COVID-19: A System Review. *Biomed Env Sci* **34**: 50–60.

Mehmood A, Khan S, Khan S, Ahmed S, Ali A, Xue M, Ali L, Hamza M, Munir A, Ur Rehman S, Mehmood Khan A, Hussain Shah A, Bai Q. 2021. *In-silico* analysis of quranic and prophetic medicinals plants for the treatment of infectious viral diseases including corona virus. *Saudi J Biol Sci* **28**: 3137–3151.

Merarchi M, Dudha N, Das BC, Garg M. 2021. Natural products and phytochemicals as potential anti SARS CoV 2 drugs. *Phytoth Res*, ptr.7151.

Nair MS, Huang Y, Fidock DA, Polyak SJ, Wagoner J, Towler MJ, Weathers PJ. 2021. *Artemisia annua* L. extracts inhibit the *In-vitro* replication of SARS-CoV-2 and two of its variants. *J Ethnopharm* **274**: 114016.

Nguyen TTT, Shaw PN, Parat MO, Hewavitharana AK. 2013. Anticancer activity of *Carica papaya*: A review. *Mol Nutr Food Res* **57**: 153–164.

Patel A, Rajendran M, Shah A, Patel H, Pakala SB, Karyala P. 2021. Virtual screening of curcumin and its analogs against the spike surface glycoprotein of SARS-CoV-2 and SARS-CoV. *J Biom Str Dynamics* 1–9.

Pattanayak P, Behera P, Das D, Panda SK. 2010. *Ocimum sanctum* Linn. A reservoir plant for therapeutic applications: An overview. *Pharmac Rev* **4**: 95–105.

Prasad S, Aggarwal BB. 2011. Turmeric, the Golden Spice: From Traditional Medicine to Modern Medicine. In: *Herbal Medicine: Biomolecular and Clinical Aspects*. CRC Press/Taylor & Francis.

Rajagopal K, Varakumar P, Baliwada A, Byran G. 2020. Activity of phytochemical constituents of *Curcuma longa* (turmeric) and *Andrographis paniculata* against coronavirus (COVID-19): an *in-silico* approach. *Fut J Pharma Sci* **6**: 104.

Rathi V, Dhingra AK, Chopra B. 2021. *Withania somnifera*. In: *Naturally Occurring Chemicals Against Alzheimer's Disease* (pp. 401–407). Elsevier.

Rattis BAC, Ramos SG, Celes MRN. (2021). Curcumin as a potential treatment for COVID-19. *Front Pharmacol* **12**: 1068.

Rosas-Lemus M, Minasov G, Shuvalova L, Inniss NL, Kiryukhina O, Wiersum G, Kim Y, Jedrzejczak R, Maltseva NI, Endres M, Jaroszewski L, Godzik A, Joachimiak A, Satchell KJF. 2020. The crystal structure of nsp10-nsp16 heterodimer from SARS-CoV-2 in complex with S-adenosylmethionine. *BioRxiv*, 2020.04.17.047498.

Salgado B, Monteiro L, Rocha N. 2011. *Allium* species poisoning in dogs and cats. *J Venomous Anim Toxins Including Trop Dis* **17**: 4–11.

Satarker S, Nampoothiri M. 2020. Structural Proteins in Severe Acute Respiratory Syndrome Coronavirus-2. *Arch Med Res* **51**: 482.

Sehailia M, Chemat S. 2020. Antimalarial-agent artemisinin and derivatives portray more potent binding to Lys353 and Lys31-binding hotspots of SARS-CoV-2 spike protein than hydroxy-chloroquine: potential repurposing of artenimol for COVID-19. *J Biomol Str Dyn*, 1–11.

Sharma P, Dwivedee BP, Bisht D, Dash AK, Kumar D. 2019. The chemical onstituents and diverse pharmacological importance of *Tinospora cordifolia*. *Heliyon* **5**: e02437.

Shree P, Mishra P, Selvaraj C, Singh SK, Chaube R, Garg N, Tripathi YB. 2020. Targeting COVID-19 (SARS-CoV-2) main protease through active phytochemicals of ayurvedic medicinal plants – *Withania somnifera* (Ashwagandha), *Tinospora cordifolia* (Giloy) and *Ocimum sanctum* (Tulsi) – A molecular docking study. *J Biomol Str Dyn*, 1–14.

Sudhakaran MV. 2012. Histo-morphological, fluorescent and powder microscopic characterization of *Cissampelos pareira* Linn. *Pharma J* **4**: 57–68.

Thakkar SS, Shelat F, Thakor P. (2021). Magical bullets from an indigenous Indian medicinal plant *Tinospora cordifolia*: An *in-silico* approach for the antidote of SARS-CoV-2. *Egyptian J Pet* **30**: 53–66.

TSAO S.-M, YIN MC. 2001. *In-vitro* antimicrobial activity of four diallyl sulphides occurring naturally in garlic and Chinese leek oils. *J Med Microbiol* **50**: 646–649.

Umar HI, Josiah SS, Saliu TP, Jimoh TO, Ajayi A, Danjuma JB. 2021. *In-silico* analysis of the inhibition of the SARS-CoV-2 main protease by some active compounds from selected African plants. *J Taibah Univ Med Sci* **16**: 162–176.

V Ghaffarilaleh, D Fisher, R Henkel. 2019. *Carica papaya* seed extract slows human sperm. *J Ethnopharm 241*.

Wilken R, Veena MS, Wang MB, Srivatsan ES. 2011. Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. *Mol Cancer* **10**: 12.

World Health Organization 2020. Vaccines. https://www.who.int/news-room/q-a-detail/coronavirus disease (Covid-19) vaccines.

Zhu Z, Lian X, Su X, Wu W, Marraro GA, Zeng Y. 2020. From SARS and MERS to COVID-19: a brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses. *Resp Res* **21**: 224.