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Plant-Derived Secondary Metabolites as Potential Mediators against COVID-19: A Review

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ABSTRACT

The current pandemic of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has envisioned a global health concern. The scientists and physicians around the world have been racing to understand the pathophysiology and possible treatment régimes to discover an effective therapeutic resolution against the disease. Different secondary metabolites from plants exhibit substantial biological assets including antiviral activity. These compounds may be used against the infections of coronavirus. The research papers, reviews, and preprints were searched from the PubMed database using keywords like severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome (MERS), and traditional herbal medicine against COVID-19. The review focuses on those natural products which exhibited optimistic results against SARS-COV and SARS-CoV-2 in virtual as well as physical *in vitro* and *in vivo* tests. It summarizes the epidemiological characters, pathogenesis, structure, and targeting strategies of the virus. The compounds like lycorine, psoralidin, quercetin, glycyrrhizin, baicalin, caffeic acid, etc. could be the leads for the drug development against COVID-19.

KEYWORDS: Coronavirus, traditional herbal medicine, SARS-CoV, COVID-19, SARS-CoV-2

INTRODUCTION

The sudden outbreak of a contagious disease, COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created havoc on the global healthcare, social, and economic system. The disease was first observed in Wuhan city of China on 31 December 2019 and has started to spread around the globe since. Infected patients show the mild symptoms of dry cough, dyspnea, fever, and bilateral lung infiltrates on imaging. The disease is complicated by the antagonistic effects on lower respiratory tracts further developing pneumonia in humans (Sohrabi et al., 2020). The

older ones and those with pre-existing cardiovascular or respiratory disorders are at higher risk for serious complications like severe pneumonia, acute respiratory syndrome, multiple organ failure, and in some cases death (Zhu et al., 2020). World Health Organization (WHO) declared it as a pandemic on 11 March 2020 due to a rapid increase in the number of cases outside of China (Huang et al., 2020). According to John Hopkin's coronavirus resource center, SARS-CoV-2 had infected 17,053,700 people across the world and killed 667,693 people worldwide by July 30, 2020 (*Home - Johns Hopkins Coronavirus Resource Center*, n.d.). To this day, specific drugs and vaccines have not been discovered and the patients are provided with specific supportive care and preventive measures. The enforcement of quarantine, isolation, and physical distancing are adopted to break the transmission chain of the virus (Cowling et al., 2020).

It looks unrealistic to invent, manufacture, and deploy new drugs against a newly emerged pandemic from the point of safety and toxicity tests over a short period of time. There is an urgent need for intensive research on the newly emerged coronavirus to reveal the pathogenic mechanism and epidemiological characters to identify the potential drug targets that have a significant contribution to the development of actual preventive and curative strategies of the disease.

Medicinal plants and plant-based natural compounds are the rich source for the development of novel antiviral drugs. Some of the plant's secondary metabolites have shown potent antiviral activities against different viral strains including coronavirus, herpes simplex, influenza virus, human immunodeficiency virus, SARS and MERS (Xian et al., 2020). Various studies have been running to explore the antiviral mechanism of these natural compounds to inhibit viral entry, replication, assembly, as well as virus-host interactions. This review primarily attempts to present the structure, transmission, and infection mechanism of the newly emerged virus causing COVID-19. As there are many similarities between SARS-CoV and SARS-CoV-2, the compounds effective against SARS-CoV should also be effective against SARS-CoV-2. Besides, it provides an update on antiviral phytochemicals of different plants that could be considered for the development of a broad spectrum of antiviral drugs against any types of coronavirus including SARS-CoV-2.

METHODOLOGY

An extensive literature survey was conducted in the PubMed, Google and Google scholar to find the articles, reviews, and preprints published up to July 2020. The search was performed by using the keywords like "SARS," MERS," "SARS-CoV-2," "coronavirus," "COVID-19," "herbal drugs against COVID-19," "Traditional Chinese Medicine against COVID-19," etc. Only the articles written in the English language are used in the review. The majority of the papers describing the test of plant secondary metabolites on SARS-CoV-1 are used. Some of the important information were taken from the official websites: World Health Organization (<https://www.who.int/>), John Hopkins coronavirus resource center (<https://coronavirus.jhu.edu/>). A brief description of the origin, structure, mode of infection, and transmission of coronavirus is presented in the review. Moreover, the review summarizes some of the *in vitro*, *in vivo* and virtual screening tests of plant-based products on SARS-CoV-1, SARS-CoV-2, and other human coronaviruses.

RESULT AND DISCUSSION

Taxonomy and Structure

Coronaviruses comprises a large number of viruses that can infect a wide variety of mammals and avian hosts to cause a broad spectrum of diseases. The researchers of

the coronavirus have classified the novel SARS-CoV-2 in the family of coronaviridae, subfamily orthocoronavirinae, and β -coronavirus genera (Gorbalenya et al., 2020). It is an enveloped, positive-sense single-stranded ribonucleic acid (RNA) virus that can infect both animals and humans (McKee et al., 2020). The genomic sequence of SARS-CoV-2 is similar (about 79%) to that of the severe acute respiratory syndrome (SARS-CoV), a novel beta coronavirus that emerged in China in November 2002 and resulted in more than 8000 infections and 774 deaths in 37 countries (Lu et al., 2020). The virion particle consists of nucleic acid and nucleocapsid in a helical form. Spherical lipid envelop is studded by spike glycoprotein (S), Membrane glycoprotein (M) and envelop protein (E) (H. Li et al., 2020).

Key Targets of SARS-CoV-2 Infection

The virus uses the same receptor binding domain (RBD) and receptor binding motif (RBM) of the viral genome as SARS-CoV to infect human cells (Tai et al., 2020). The infection is initiated by the interaction between the spike (S) glycoprotein with angiotensin-converting enzyme-2 (ACE-2) of the host cell. Transmembrane protease/serine subfamily 2 (TMPRSS2) enzyme facilitates the ACE2-S protein complex to pass the viral RNA into the host cell. The viral RNA is synthesized via RNA-dependent RNA polymerase and the structural proteins are synthesized leading to the complete formation and release of new virus particles (Sanders et al., 2020).

The majority of the viruses which show emerging and re-merging trends are the membrane-enveloped pathogens that need to fuse with viral envelop-membrane to enter the host cell. So, the antiviral research paradigms are focused to discover a broad spectrum of agents that inhibit the target-membrane fusion (Vigant et al., 2015). The key therapeutic targets of SARS-CoV-2 include spike protein (S), RNA-dependent RNA polymerase (RdRp), 3-chymotrypsin-like protease (3CL^{pro}, also known as the main protease, M^{pro}), and papain-like protease (PL^{pro}). The drugs which interact with the targets like ACE 2, spike protein, or TMPRSS enzymes inhibit the entry of viruses on host cells. Similarly, the drugs which target RdRp, 3CL^{pro}, PL^{pro} inhibit the replication and building up of the viral genome and new progeny into the cell (Canrong Wu et al., 2020). When an infection occurs, our immune system is activated for the regulation of proinflammatory cytokine production, both at local and systemic levels. In many cases of COVID-19 patients, the SARS-CoV-2 infection has induced excess and prolonged cytokine/chemokine responses. The cytokine storm causes acute respiratory distress syndrome (ARDS) and multiple organ failure leading to death (Ye et al., 2020).

Treatments of COVID-19

Depending on the target-receptor mechanism, the therapies can be divided into two types. One directly attacking the coronavirus by inhibiting crucial enzyme activities or by blocking the entry and replication of the virus into a human cell. The other, by boosting the immune system or inhibiting the inflammatory process causing lung injuries (Tu et al., 2020). It is a bitter truth that no medicine or anti-virus has yet been officially approved for the treatment of COVID-19. Clinical management includes the prevention of infection, supportive care, delivery of adequate oxygen, ventilation, etc. Some of the compounds are still in the clinical trials and have not been approved yet. Remdesivir (GS-5734) has been recently known to be effective against different RNA viruses to fight Ebola, SARS-CoV, MERS-CoV, etc. It is an RdRp inhibitor that resists viral replication by premature termination of RNA transcription. It was found effective against COVID-19 by *in vitro* test on Vero E6 cells (Wang et al., 2020). Chloroquine (CQ) and hydroxychloroquine (HCQ) inhibit the viral entry of the host cells by inhibiting

acidification, glycosylation of viral proteins, nucleic acid replication, etc. The *in vitro* test of CQ and HCQ on SARS-CoV-2 infected Vero cells has shown good antiviral activity (Yao et al., 2020). Ritonavir/ lopinavir which inhibits the 3CL^{pro}, PL^{pro} activity and replication of the virus did not significantly accelerate the clinical improvement in the patients with COVID-19 (Cao et al., 2020). Favipiravir is an antiviral drug that inhibits viral RdRp, umifenovir (arbidol), can prevent S protein /ACE2 interaction and inhibits membrane fusion of viral envelope (Huang et al., 2020). Many other potential therapeutic compounds are in the pipeline of clinical investigation around the world.

Other adjunct therapies like stem cells, monoclonal antibodies, polypeptides, plasma therapy, etc. have given optimistic results in treating COVID-19 patients. Their safety, toxicity, and side-effects are still being evaluated for approval from the authorities.

Since COVID-19 caused by SARS-CoV-2 resembles SARS and middle east respiratory syndrome (MERS) phylogenetically and symptomatically, a variety of agents have been tested based on clinical experience from SARS and MERS epidemics (Zhong et al., 2020). Although the efficacy of many synthetic compounds and antiviral medicines are in clinical trials, no satisfactory results have been established yet. Based on the similarity, it is expected that the results of the studies about previous generations especially SARS could be implied for the research of SARS-CoV-2 to a high degree.

Traditional Chinese Medicine (TCM) against COVID-19

The application of many antiviral herbal drugs from TCM in the treatment of SARS-CoV-2 is largely inspired by the results of its use against the SARS-CoV epidemic in 2002. In China, more than 80% of COVID-19 patients received this treatment from the onset of its outbreak. In comparison to chemical drugs, plant-derived products are less understood mechanistically and several types of research are underway to evaluate their effects precisely (Y. Yang et al., 2020). Traditional herbs from different geographical sites and habitats are considered as potential sources of novel drugs for the treatment of diverse viral infections. A variety of plants and plant-derived compounds have been found to inhibit the proliferation of SARs-CoV and other viruses (Islam et al., 2020).

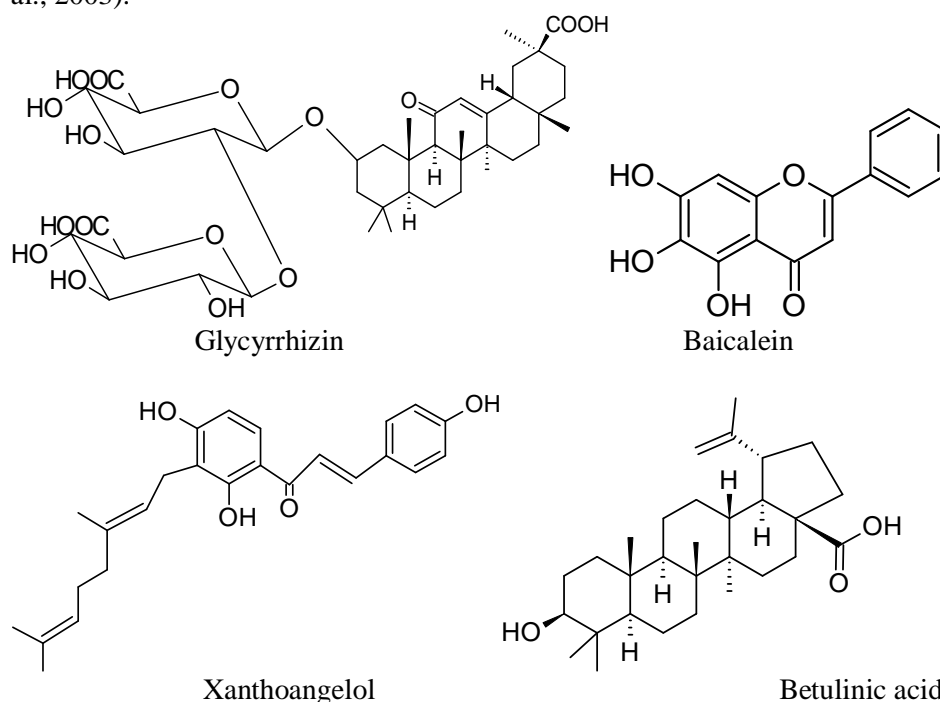
Scientists have performed physical as well as virtual screening methods for several natural compounds and extracts against COVID-19. Most of the screenings are performed against the key binding sites like 3CL^{pro}, PL^{pro}, RdRp, and spike protein. The speed and versatility of these screenings may be valuable for the rapid finding of the potent inhibitor of SARS-CoV-2 which is causing the current pandemic (Mani et al., 2020). The cytokine storm/inflammation responses in COVID-19 patients that contributed to many deaths in China were reported to have been controlled by using a TCM, *Qingfei paidu* decoction. The herbal formulae of this drug regulate immunity cytokine-related path and reduce inflammation to protect lungs and spleen. The TCM drugs *Sangju Yin* and *Yinqiao san* are used to clear lung-heat, expel phlegm, relieve cough, regulate and restore lung function and provide supportive treatment to the COVID-19 patients (R. Wu et al., 2020). Similarly, another TCM drug *Lianhuaqingwen* significantly inhibited the *in vitro* replication of SARS-CoV-2 in Vero E6 cells. This drug noticeably reduced the pro-inflammatory cytokine (TNF- α , IL-6, CCL-2/MCP-1, and CXCL-10/IP-10) production in mRNA. The study indicated that the use of *Lianhuaqingwen* effectively protects the virus attack (Runfeng et al., 2020). The most commonly used medicinal plants in TCM against COVID-19 in China include *Astragalus membranaceus*, *Glycyrrhiza uralensis*, *Saposhnikovia divaricate*, *Rhizoma Atractylodis Macrocephalae*, *Lonicerae Japonicae Flos*, *Fructus forsythia*, *Atractyl*

disrhizoma, *Radix platycodonis*, *Agastache rugosa* and *Cyrtomium fortune* J. SM. (Hui et al., 2020).

Natural Products against SARS-CoV and SARS-CoV-2

Plant's immunity is a highly sophisticated system that can efficiently notice and disable the invading pathogens by a variety of tackles using intracellular receptor proteins. Many plant secondary metabolites are known to inhibit the effects of specific enzyme proteins essential for the propagation of different viruses (Yonesi & Rezaadeh, 2020). The essential oils targeting lipid-envelop and the polyphenols targeting viral protein are active against free viruses whereas the intercalating alkaloids inhibit the replication of viruses inside the host cell. The DNA intercalator alkaloids (e.g. Chloroquine) that inhibit the replication, transcription, and translation of genetic material may be interesting candidates for the development of drugs against COVID-19 (Wink, 2020).

Glycyrrhizin, an important secondary metabolite in *Glycyrrhiza glabra* (licorice) root, was found to inhibit the replication of clinical isolates of the SARS-associated virus. It also hinders the absorption and penetration of the virus in early-stage (Cinatl et al., 2003).



Out of many components isolated from the ethanol extracts of the roots of *Scutellaria baicallensis* Georgi; baicalein strongly inhibited the SARS-CoV-2 3CL^{pro} activity with an IC₅₀ of 0.39 μM. The molecular docking also supported the anti-SARS-CoV-2 activity of the compound (Liu et al., 2020). The antiviral activity of tetra-O-galloyl-β-d-glucose (TGG) was evaluated for a wild-type SARS-CoV by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay. TGG, one of the major components of *Galla chinensis*, used in TCM exhibited a prominent activity with a 50% effective concentration (IC₅₀) of 4.5 μM and a selective index of 240.0. The compound resisted the viral entry by inhibiting the spike protein and ACE-2 receptor (Yi et al., 2004). The ethyl acetate leaf extracts of *Angelica keiskei* showed significant inhibition against target SARS-CoV proteases 3CL^{pro} and PL^{pro} (75% inhibition at 30 μg/ml) and (88% inhibition

at 30 µg/ml) respectively. Thirteen isolated compounds were subjected to cell-based assay on 3CL^{pro} and PL^{pro} proteases. The alkylated chalcone substituted with per hydroxy group, xanthoangelol exhibited the maximum inhibitory activity with an IC₅₀ value of 11.4 µM and 1.2 µM for 3CL^{pro} and PL^{pro} respectively (J. Y. Park et al., 2016).

Wen et al. (2007) evaluated 221 phytochemicals against SARS-CoV using a cell-based assay by measuring SARS-CoV-induced cytopathogenic effect (CPE) on Vero E6 cells. Twenty compounds, including abietane-type and labdane-type diterpenes, lupine-type triterpenes, limonoids, and curcumins were further evaluated to SARS-CoV 3CL^{pro} inhibition activity. They showed a potent inhibition in the concentration range of 3.3-10 µM. Betulinic acid, a triterpenoid that can be isolated from *Betula pubescens*, possessed the highest inhibitory effect on enzymatic activity of 3CL^{pro} with IC₅₀ of 10 µM. J.-Y. Park et al. (2012) evaluated the SARS-CoV PL^{pro} and 3CL^{pro} inhibition activities of the nine isolated diarylheptanoids from ethanol extracts of *Alnus japonica* barks. The PL^{pro} inhibition activity was determined using a continuous fluorometric assay. The compounds exhibited a dose-dependent inhibitory effect. Among the tested compounds, hirsutenone which contains an α-β-unsaturated carbonyl group and a catechol moiety in the backbone was found to be most effective with an IC₅₀ value of 4.1±0.3 µM. The compound also exhibited a moderate inhibition against SARS-CoV 3CL^{pro} with IC₅₀ of 36.2±0.2 µM. The compounds isolated from water extracts of roots of *Isatis indigotica* were characterized for the anti-SARS-CoV 3CL^{pro} activity by cell-free cleavage and cell-based cleavage assays. The cell-based assay revealed that hesperetin (IC₅₀=8.3µM) and sinigrin (IC₅₀=217 µM) are the potent inhibitors of SARS-CoV 3CL^{pro} (Lin et al., 2005).

Homoharringtonine is an alkaloid derived from *Cephalotoxus fortunei*. It is a Food and Drug Administration (FDA)-approved drug against myeloid leukemia that has a significant antiviral activity towards herpesvirus, coronavirus, rhabdovirus and others. The compound was found to inhibit the replication of SARS-CoV-2 in Vero E6 cells with 50% effective concentration (EC₅₀) at 2.55 µM (Choy et al., 2020). J. Park et al. (2017) evaluated the 3CL^{pro} and PL^{pro} inhibition activity of the polyphenol compounds isolated from *Broussonetia papyrifera* against SARS-CoV and MERS-CoV. One of the compounds papyriflavonol A, was found to be the most active against SARS-CoV PL^{pro} causing 50% inhibition (IC₅₀) with a concentration of 3.7±1.6 µM while that of quercetin was 8.6±3.2 µM. Antiviral activities of more than 200 medicinal plants against SARS-CoV were evaluated by using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2H-tetrazolium inner salt (MTS) assay for virus-induced cytopathic effect (CPE). The ethanol stem extract of *Lycoris radiata* showed the highest 50% effective concentration (EC₅₀=2.4±0.2 µg/ml) against SARS-CoV. An alkaloid, lycorine isolated from the plant exhibited potent activity with EC₅₀ value of 15.7±1.2 nM. The result of the study provides a strong support for the use of the plant to develop herbal medicines against SARS-CoV. The extracts of *Artemisia annua*, *Pyrrosia lingua* and *Lindera aggregata* also exhibited significant inhibition effects against SARS-CoV strain (S. Li et al., 2005). Five new geranylated flavonoids, tomentin A, tomentin B, tomentin C, tomentin D, and tomentin E were isolated from methanol fruit extracts of *Paulownia tomentosa* from Korea. Their SARS-CoV PL^{pro} inhibition activity was studied by using a fluorogenic assay. The compounds were found to be more potent than their parent molecules. Among the isolated compounds, tomentin B displayed the maximum dose-dependent inhibition with IC₅₀ of 6.1±0.02 µM (Cho et al., 2013).

The water extract of *Huttyunia cordata* was evaluated for immunomodulatory and anti-viral activity against SARS-CoV. The 3CL^{pro} inhibition activity was evaluated by a protein-based fluorogenic assay. A dose of 1000 µg/ml was found to reduce the

activity of control by 50%. Similarly, a significant RdRp activity with 26% inhibition at the concentration of 800 µg/ml was observed. The flow cytometry experiment revealed that the *H. Cordata* extract stimulated the proliferation of CD4⁺ helper T cells that support to produce virus specific antibodies and CD8⁺ cytotoxic T cells which kill the infected host cells respectively. The study concluded that the plant has a capacity to inhibit the SARS-CoV invasion, replication as well as to develop a cell-mediated immunity of the host (Lau et al., 2008). The aqueous extract of the leaves of an herb used in TCM, *Toona sinensis* Roem inhibited the replication of SARS-CoV with EC₅₀ value ranging from 30 - 40 µg/ml (C. J. Chen et al., 2008).

Out of 312 Chinese medicinal herbs screened, three were found to block the interaction of SARS-CoV spike protein (S) and ACE2 in a dose-dependent manner. The IC₅₀ values of root tubers of *Rheum officinale* Bail., root tubers of *Polygonum multiflorum* Thunb., and vines of *P. multiflorum* ranged from 1 to 10 µg/ml. The authors suggested that an anthraquinone type compound emodin might be considered as a potential lead therapeutic agent in the treatment of SARS-CoV infection (Ho et al., 2007). Flavones and biflavones isolated from the ethanol leaf-extract of *Torreya nucifera* exhibited significant SARS-CoV 3CL^{pro} inhibitory activity. An abiflavone, amentoflavone showed the most potent activity with IC₅₀ value of 8.3 µM on fluorescence resonance energy transfer (FRET) analysis which is quite higher than that of flavones apigenin, luteolin and quercetin (Ryu et al., 2010). Six flavonoid compounds isolated from the ethanol extracts of the seeds of *Psoralea corylifolia* inhibited the SARS-CoV PL^{pro} in a dose-dependent manner with IC₅₀ ranging from 4.2 -38.4 µM. On the basis of inhibition kinetics and IC₅₀ value, isobavachalcone and psoralidin were found as the principal contributors to the PL^{pro} inhibition (Kim et al., 2014).

The cell-protective effects of the coumarin derivatives isolated from *Boenninghausenia sessilicarpa* were evaluated on SARS-CoV infected Vero E6 cells. Leptodactylone showed potent activity with the ratio of 60% at 100 µg/ml and another compound rutamarin exhibited a weak activity (Q.-Y. Yang et al., 2007). The inhibition activity of SARS-CoV 3CL^{pro} and PL^{pro} of the tanshinones isolated from ethanol extracts of roots of *Salvia miltiorrhiza* was evaluated. Most of the compounds exhibited a dose-dependent 3CL^{pro} inhibition with the maximum for dihydrotanshinone with IC₅₀ value of 14.4±0.7 µM. The compounds exhibited a time-dependent inhibitory effect on PL^{pro} activity with the maximum for cryptotanshinone with IC₅₀ value of 0.8±0.2 µM (J. Park et al., 2012). A natural product library of 720 compounds were screened for inhibitory effects against SARS-CoV 3CL^{pro}. The polyphenolic compounds in black tea tannic acid, 3- isothaflavin-3-gallate and theaflavin-3,3'-digallate were found to show potent activity with IC₅₀ values 3, 7 and 9.5 µM respectively (C. Chen et al., 2005).

More than 200 herbal extracts of Chinese medicine were screened for *in vitro* anti-SARS-CoV activities by using a cell-based assay on Vero E6 cells. The extracts of rhizome of *Gentiana scabra*, tuber of *Discoreae batatas*, seeds of *Cassia tora* and *Taxillus chinensis*, and rhizome of *Cibotium barometz* were found to be potent inhibitors of 3CL^{pro} activity at concentrations between 25 and 200 µg/ml. The methanol fractions of *C. barometz* and *D. batatas* showed the most significant inhibition with IC₅₀ values 39±3 µg/ml and 44±2 µg/ml respectively (C. Wen et al., 2011). The inhibitory activity of the active compounds isolated from butanol fraction of *Cinamomi cortex* against wild-type SARS-CoV infection was evaluated by plaque reduction assay. Procyanidin A2, procyanidin B1 and cinnamtannin B1 showed moderate activity with IC₅₀ values of 29.9±3.3, 41.3±3.4 and 32.9±3.9 µg/ml respectively (Zhuang et al., 2009).

The *Urtica dioica* agglutinin (UDA) extracted from stinging nettle was found to inhibit the SARS-CoV infection. The *in vivo* assessment on the BALB/c mice model has

revealed that the treatment of 5 mg/kg dose for four days significantly protected the death of infected mice. Further, *in vitro* test on SARS-CoV Urbani strain by neutral red (NR) dye uptake assay on Vero 76 cells has shown that UDA inhibits the replication of the virus with IC_{50} of $2.6 \pm 3.7 \mu\text{g/ml}$. The study has proposed that UDA prevents the viral entry by binding spike (S) glycoprotein (Kumaki et al., 2020). Seven flavonoid compounds isolated from *Pichia pastoris* were evaluated for the *in vitro* inhibition activity against SARS-CoV 3CL^{pro}. Quercetin, epigallocatechin gallate and gallic acid exhibited good inhibition at 200 μM towards 3CL^{pro} with IC_{50} values of $73 \pm 4 \mu\text{M}$, $73 \pm 2 \mu\text{M}$ and $47 \pm 0.9 \mu\text{M}$ respectively. The best inhibitor, gallic acid showed a competitive inhibition pattern with K_i value of $25 \pm 1.7 \mu\text{M}$. The molecular docking and structure-activity relation analysis was performed. Gallic acid had the highest binding affinity (docking score = -14 Kcal/mol). The molecule has numerous hydrophobic and H-bond interactions with amino acid residues in the active site pocket of 3CL^{pro} of SARS-CoV (Nguyen et al., 2012). Aescin isolated from *Aesculus hippocastanum* (horse chestnut tree) and reserpine, a common alkaloid present in different *Rauwolfia* species showed significant anti-SARS-CoV activity with the concentration for 50% maximal effect (EC_{50}) values of 3.4 and 6 μM respectively (Chung-yi Wu et al., 2004).

A table of a partial list of medicinal plants showing a significant activity against SARS associated virus may provide valuable information to develop a possible remedy of novel coronavirus. This focuses on the target action of phytochemicals against SARS-CoV-1 which is analogous to the SARS-CoV-2 causing the existing pandemic.

Table 1

Partial list of antiviral plants inhibiting coronavirus

S. No	Medicinal plants	Active compounds	Antiviral activity	Virus	Reference
1	<i>Alnus japonica</i>	Hirsutenone	Inhibit 3CL ^{pro} and PL ^{pro} activity	SARS-CoV	(J.-Y. Park et al., 2012)
2	<i>Angelica keiskei</i>	Xanthoangelol	Inhibit 3CL ^{pro} and PL ^{pro} activity	SARS-CoV	(J.Y. Park et al., 2016)
3	<i>Betula pubescens</i>	Betulinic acid	Inhibition of enzymatic activity of 3CL ^{pro}	SARS-CoV	(C.C. Wen et al., 2007)
4	<i>Boennighausenia sessilicarpa</i>	Leptodactylone	Protects the infected cells	SARS-CoV	(Q. Y. Yang et al., 2007)
5	<i>Broussonetia papyrifera</i>	Papyriflavonol A	Inhibit PL ^{pro} activity	SARS-CoV	(J. Park et al., 2017)
6	<i>Cephalotoxus fortunei</i>	Homoharringtonine	Inhibit replication	SARS-CoV-2	(Choy et al., 2020)
7	<i>Cinamomi cortex</i>	Procyanidin A2, Procyanidin B1, and Cinnamtannin B1	Inhibition of endocytosis	Wild-type SARS-CoV	(Zhuang et al., 2009)
8	<i>Galla chinensis</i>	tetra-O-galloyl- β -D-glucose (TGG)	Inhibit spike protein and ACE-2	SARS-CoV	(Yi et al., 2004)

9	<i>Glycyrrhiza glabra</i>	Glycyrrhizin	Inhibit replication, adsorption	SARS-associated virus	(Cinatl et al., 2003)
10	<i>Huttuynia cordata</i>	Water extract	Inhibit 3CL ^{pro} , RdRp activity, and develop immunity by T cells	SARS-CoV	(Lau et al., 2008)
11	<i>Isatis indigotica</i>	Hesperetin Sinigrin	Inhibit 3CL ^{pro} activity	SARs-CoV	(Lin et al., 2005)
12	<i>Lycoris radiata</i>	Lycorine	Inhibit infection	SARS-CoV	(S. Li et al., 2005)
13	<i>Paulownia tomentosa</i>	Tomentin B	Inhibit PL ^{pro} activity	SARS-CoV	(Cho et al., 2013)
14	<i>Pichia pastoris</i>	Gallocatechin gallate	Inhibit 3CL ^{pro} activity	SARS-CoV	(Nguyen et al., 2012)
15	<i>Psoralea corylifolia</i>	Isobavachalcone, Psoralidin	Inhibit PL ^{pro} activity	SARS-CoV	(Kim et al., 2014)
16	<i>Rheum officinale</i> Bail, <i>Polygonum multiflorum</i>	Emodin	Inhibit spike protein and ACE2 interaction	SARS-CoV	(Ho et al., 2007)
17	<i>Salvia miltiorrhiza</i>	Cryptotanshinone	Inhibit enzymatic activity of 3CL ^{pro} and PL ^{pro}	SARS-CoV	(J. Park et al., 2012)
18	<i>Scutellaria baicallensis</i> Georgi,	Baicalin	Inhibit 3CL ^{pro} activity	SARS-CoV-2	(Liu et al., 2020)
19	<i>Toona sinensis</i> Roem	Water extract	Inhibit replication	SARS-CoV	(C. J. Chen et al., 2008)
20	<i>Torreya nucifera</i>	Amentoflavone	Inhibit 3CL ^{pro} activity	SARS-CoV	(Ryu et al., 2010)
21	<i>Urtica dioica</i>	<i>Urtica dioica</i> agglutinin (UDA)	Prevents viral attachment to cell by binding glycoprotein	SARS-CoV	(Kumaki et al., 2020)

Virtual Screening of Natural Compounds against SARS-CoV-2

As the pandemic is soaring up, it is an urgent demand to discover effective drugs for the treatment of the disease. The development of any effective drugs or vaccines is a lengthy process that takes many months or years, which will deteriorate the health, economic, and social setting of the world. Only a few research reports on SARS-CoV-2 have been made available since its emergence. Many scientists have used computer modeling techniques to search for potential and specific inhibitors of coronavirus. Typically, these models determine the free binding energy of a particular ligand and receptor. Lower the free binding energy, stronger the ligand-receptor bond, and vice versa (Forli et al., 2016). This modeling allows for the comparison of the relative binding affinity of the library of molecules towards a particular receptor. It also reduces the time and cost associated with the physical screening of a large number of molecules or

extracts for bioactivity. It helps predict binding affinities to a particular target for ADME (absorption, distribution, metabolism, and excretion). The compounds emphasized by this method can be forwarded on cell-based assays, *in vitro* toxicity, and clinical trials for the herbal remedy (Y. Chen et al., 2017).

A compound library of more than 606 million molecules was virtually screened for binding affinity with the recently solved crystal structure of the main protease (M^{pro}) of SARS-CoV-2. The molecular docking and pharmacokinetic studies have reported two natural compounds (-) taxifolin and rhamnetin together with a list of nine compounds for drug repurposing. The study has expected the experimental validation and optimization of the proposed lead compounds to develop a valuable treatment against the COVID-19 pandemic (Fischer et al., 2020). Theaflavin, a polyphenolic compound present in black tea (*Camellia sinensis*) was docked to target RdRp of SARS-CoV, SARS-CoV-2, and MERS-CoV. The compound showed a lower dock scores in all of the targets and lowest binding energy (-8.8 kcal/mol) when docked in the catalytic pocket of SARS-CoV-2 indicating to be a potential RdRp inhibitor (Lung et al., 2020).

An important essential oil from gum trees (*Eucalyptus* spp.) eucalyptol (1,8 cineole), was found effective against SARS-CoV-2 M^{pro} receptor by molecular docking study. The presence of hydroxyl, ketonic and ether groups in the oil molecules play the main inhibitory role against the virus (Sharma & Kaur, 2020). A library of 318 phytochemicals from 11 plants was subjected to molecular docking against main protease (M^{pro}) and ACE2 targets. The study revealed that seven plants namely *Piper longum*, *Phaseolus vulgaris*, *Curcuma longa*, *Ocimum gratissimum*, *Syzygium aromaticum*, *Artemisia abstinidium*, *Inula helenium* have better and significantly lower binding energies towards the receptors. Top ten compounds having expressively low binding energy could be used against coronavirus infection (Joshi et al., 2020). A known anticoagulant apixaban was found to be a potent 3CL pro inhibitor of SARS-CoV 2 by virtual screening. Due to suitable pharmacotherapeutic profile, toxicity and side effects the compound would be suitable for the future treatment of COVID-19 (Hage-Melim et al., 2020).

A total of 27 plant metabolites were docked against SARS-CoV-2 key binding proteins. Based on binding affinity, the active compounds asiatic acid from *Centella asiatica*, avicularin, guajaverin from guava leaves, and withaferin from *Withania somnifera* were further analyzed for ADME properties, toxicity, and drug-likeness. The study has made a way for *in vitro* analysis of the compounds for validation (Azim et al., 2020). A small library of 38 antiviral phytochemicals was screened for drug-likeness and toxicity properties by computational approach. Their inhibition against SARS-CoV-2 M^{pro} was studied using molecular docking. Three of them having higher binding affinity were identified as the lead molecules. Bonducellpin D and caesalmin B from *Caesalpinia minax* seeds and 5,7-dimethoxyflavone-4'-O- β -d-glucopyranoside from *Viscum album* which also exhibit a broad spectrum of antiviral activities against SARS-CoV M^{pro} and MERS-CoV M^{pro} are concluded to further *in vitro* and *in vivo* studies for developing suitable drug candidate molecule (Gurung et al., 2020).

The molecular docking study was carried out for 37 phytoconstituents from Siddha official formulation *Kabasura kudineer* and JACOM against spike protein of SARS-CoV-2 (PDB ID: 6VS). The result showed that chrysoeriol from *Plectranthus ambonicus*, luteolin from *Costus speciosus* and quercetin from JACOM formulation have very good binding affinity. Further *in silico* evaluation of pharmacokinetics (ADME) properties and safety profile had suggested the compounds to be used for clinical trials against COVID-19 (Kiran et al., 2020). Chlorogenic acid is an important polyphenol found in tea, coffee and other plants has good antioxidant, antibacterial, antiviral,

hepatoprotective, cardioprotective etc. properties (Naveed et al., 2018). Phillyrin is an active compound in *Forsythia suspense* is used to clear away heat and toxin, antioxidant and antiviral, etc. properties. These two compounds which are used in Mongolian medicines were subjected to computational investigation using pharmacological analysis, protein, and molecular docking. The compounds are found to inhibit the combination of SARS-CoV-2 S-protein and ACE2 at the molecular level. The result has provided a theoretical basis for using them against COVID-19 (Yu et al., 2020).

A flavone glycoside, hesperidin (hesperetin-7-rutinoside) abundant in many citrus plants (orange, lemon, etc.) showed a remarkable binding affinity to SARS-CoV-2 receptors. The molecular docking study was performed for the protease domain, receptor-binding domain of spike glycoprotein and the receptor binding domain of the ACE2. Similarly, curcumin from *Curcuma longa*, brazilin from *Caesalpinia sappan* and galangin from *Alpinia galangal* also showed a good inhibiting activity against viral infection and replication causing COVID-19 (Utomo et al., 2020). Thuy et al., (2020) reported the anti-SARS-CoV-2 property of *Allium sativum* (Garlic) essential oil by molecular docking simulation method. The essential oil containing allyl disulphide and allyl trisulphide as main constituents (51.3%) was found to have strong interactions with the host receptor ACE-2 protein and PDB6LU7 protease of the SARS-CoV-2 virus. The result suggests that natural *A. sativum* essential oil contributes to preventing the invasion of coronavirus to the human body.

A group of 115 antiviral phytochemicals used in TCM were virtually screened against SARS-CoV-2 receptors by molecular docking, network pharmacological and ADME analysis. The study highlighted the 13 compounds including quercetin, kaempferol etc. to further *in vitro* and *in vivo* studies against COVID-19 infection (Zhang et al., 2020). A molecular database of 32,297 phytochemicals were subjected to virtual screening against SARS-CoV-2 3CL^{pro} by molecular docking and qualitative assessment of absorption, deposition, metabolism, excretion and toxicity (ADMET). On the basis of docking score and binding affinity, nine of them are suggested to further *in vitro* and *in vivo* analysis. 5,7,3',4'-tetrahydroxy-2'-(3,3'-dimethylallyl) isoflavone from *Psoralea argyrea* showed the highest binding affinity (-29.57 kcal/mol) and docking score (S= -16.35). The molecules may be valuable in the exploration and development of novel natural anti-COVID-19 drug (Tahir ul Qamar et al., 2020).

Structural modification of naturally derived molecules may increase the potency of their biological activity. The change in the functional group, ligand, molecular framework, etc. leads to an increase in the efficacy of the molecule as an inhibitor. For example, the addition of 2-acetamido- β -D-glucopyranosyl amine to the glycoside chain of glycyrrhizin has increased its antiviral activity by ten times in a CPE assay ($EC_{50} = 365 \pm 12 \mu\text{M}$ to $40 \pm 13 \mu\text{M}$) due to the increased attraction with S- proteins. Similarly, amides and conjugates with amino acid residues and free -COOH group increased the activity by 70-fold with EC_{50} $139 \pm 20 \mu\text{M}$ to $5 \pm 3 \mu\text{M}$) in the CPE assay (Hoever et al., 2005). The antiviral activity against animal coronavirus strain of quercetin-7-rhamnoside is over 100 times higher than that of the parent compound, quercetin with the concentration required to reduce cell growth by 50% (CC_{50}) values of 1.7 ± 0.8 and $0.014 \pm 0.005 \mu\text{g/ml}$ respectively (Choi et al., 2009).

The natural products having good antioxidant and antibacterial properties have been frequently utilized in traditional and alternative therapies for treating various infections because of their nominal side effects. Due to the abrupt outbreak of devastating COVID-19 and unavailability of approved medicines, plant-derived compounds could be extremely promising substitutes and complementary treatment for the management of the disease.

CONCLUSIONS AND FUTURE PROSPECTS

The later studies have shown that the pandemic is spreading via non-symptomatic infections also in the world. It is essential to follow the WHO guidelines to prevent the spread of COVID-19 until an adequate drug or vaccine will be certified. The development of any antiviral drug or vaccine is a challenging task within a short time frame. Different phytochemicals present in plants provide a valued repository of chemicals having substantial antiviral properties. Chemical modification of the structures and computer-based simulations can increase their potency against a particular target. The computer molecular docking studies have shown some natural compounds like glycyrrhizin, lycorine, quercetin, baicalin, caffeic acid, psoralidin, etc. have good binding abilities to the virus and host targets. These compounds may be subjected to further *in vitro* and *in vivo* tests to determine safe and therapeutic levels before conducting clinical trials on humans. Solidarity and good cooperation among the scientists in the world are essential to developing an effective drug to conquer the current pandemic and future potential infection of SARS-CoV-2.

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