Phytotherapeutic Evidence Against Coronaviruses and Prospects for COVID-19

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ABSTRACT

The emergence of the novel β-coronavirus (SARS-CoV-2) and subsequent outbreak of COVID-19, is a global health challenge with no known treatment to date and has culminated in significant morbidity and mortality. This article highlights current understanding on SARS-CoV-2 based on the available scientific evidence on human coronavirus (HCoV) infections, which could offer novel insights and therapeutic targets for SARS-CoV-2, the causative agent of COVID-19. Specifically, the paper presents available phytotherapeutic evidence against pathogenic HCoVs with a view to identifying potent plant-derived antiviral agents that could be developed to aid the fight against coronaviruses and the current COVID-19. Evidently, elucidation of CoV integral proteins such as the spike protein, angiotensin-converting enzyme 2, 3C-like cysteine protease and papain-like protease, as good targets for drug developments has lent credence to the use of medicinal plants or their metabolites as prophylaxis or treatment interventions in CoV infections and holds promising ground for SARS-CoV-2. While some promising phytocompounds are currently under clinical trials for COVID-19, increased research into plants and in-depth characterization of their metabolites could reveal more interesting results that would benefit humanity in its fight against emerging and re-emerging viral infections including the current COVID-19. Overall, given the current body of evidence on the potential development of phytotherapeutics for COVID-19, fears need to be allayed while clinical trials continue. Conclusively, the lockdown and other preventive measures which have been implemented in most parts of the world should be humanely exercised and supported to ensure compliance and safety of lives.

Key words: Coronavirus; COVID-19; Antivirals; Drug target; Natural products; Plants; Plant metabolites; SARS-CoV-2.

INTRODUCTION

Globally, viruses are integral groups of etiological agents associated with significant morbidity and mortality.1, 2 Interventions such as the use of antiviral agents including drugs and vaccines are normally employed to reduce the rate and extent of comorbidities due to viral infections in animals and humans.3 Such interventions, however, remain under trial for use as palliatives to fight the current severe acute respiratory syndrome (SARS) infection called COVID-19. COVID-19 is caused by a novel coronavirus (CoV) named SARS-CoV-2.4 However, CoVs are not new in the emerging infections terrain and have been generally recognized as a large group of related viruses of medical and veterinary significance. The first Coronavirus-Infected Bronchitis Virus (IBV) - was isolated in 1931 by Schalk and Hawn, who thought it to be a respiratory disease of chicks.5 The studies that led to their characterization and acknowledgment as an agent of medical importance started in 1965, with the work of Tyrrell and Bynoe. Whilst working with IBV, mouse hepatitis virus and transmissible gastroenteritis virus of swine, the viruses were found to be morphologically similar under electron microscope. They were, thus, dubbed a new group of viruses in 1968, with the name "Coronaviruses". but only accepted as a new genus of viruses in 1975.6

While the initial classification of the genus was mainly based on microscopic examination,7 the advent of advanced molecular methods, such as nucleic acid amplification technologies, automated DNA sequencing and bioinformatics, have now elucidated CoVs as pleomorphic, enveloped viruses with a positive-sense single-stranded-RNA genome and a nucleocapsid of helical symmetry.8 Compared to other RNA Viruses, CoV has the largest viral genome of about 27 to 32 kb in length, with about 65-125 nm in diameter,9,10 and can diffuse among mammals and humans.11 This large genome confers them with high recombinant rates by constantly developing transcription error and RNA-Dependent-RNA-polymerase (RdRP) jumps.12 Structurally, CoVs are made up of nucleocapsid protein (N) which forms a complex with the RNA, the surface glycoprotein (S) which forms the petal-shaped surface projection (spike) that is responsible for virus entry into host cells, the membrane glycoprotein (M) which gives the virion its shape, and the envelop glycoprotein (E) that is involved in virion assembly13 (Figure 1). Just like the recent emergence of SARS-CoV-2 in December 2019 in Wuhan, a similar occurrence in the later part of the year 2002 also witnessed SARS infection that emerged in the Southern China
Coronaviridae, order Nidovirales and subfamily Orthocoronavirinae. Generally, CoVs constitute a genus within the family Coronaviridae, order Nidovirales and subfamily Orthocoronavirinae. To date, four CoV genera (alpha, beta, delta and gamma) have been elucidated, with human CoVs (HCoVs) identified in the alpha-CoV (HCoV-229E and HCoV-NL63) and beta-CoV (MERS-CoV, SARS-CoV, HCoV-OC43 and HCoV-HKU1) genera. The HCoV-229E, HCoVNL63, HCoV-OC43 and HCoV-HKU1 strains cause respiratory tract infections (RTIs) that are mostly non-virulent, mild and self-limiting like the common cold, while SARS-CoV or SARS-CoV-2 and MERS-CoV are associated with severe RTIs which may either cause significant morbidity or lead to death. The severe respiratory diseases caused by these viruses could also culminate into enteric infections or ‘cytokine storm’, an event which is indicative of an overreaction in immune responses.

For antiviral drug development, viral penetration and its subsequent replication are usually the targets and these processes have been well established on integral proteins of CoVs. The most studied of the CoV integral proteins which make good targets for drug developments are the spike (S) protein, 3C-like protease (3CLpro) and papain-like protease (PLpro). Notably, studies have shown the capability of natural compounds to inhibit these proteins associated with SARS or MERS CoV infections. Following the release of the SARS-CoV-2 gene sequence which showed high similarities with SARS or MERS proteins, it was theorized that existing effective anti-MERS or anti-SARS interventions could be invaluable in the race to find a drug that is anti-SARS-CoV-2 to fight the COVID-19 infection. SARS-CoV-2 and SARS-CoV also bind to the same host cell receptor, but SARS-CoV-2 binds more easily and tenaciously, and this could give an insight into why COVID-19 seems to be more effectively spread through human-to-human interaction. However, more research data is still required to support this insight.

Generally, although, CoV infections are controllable, there remains the possibility of sporadic new cases if humans continue to encounter their animal hosts. Therefore, to ensure some level of preparedness, active antiviral moieties which abound in medicinal plants could form a formidable force to fight such outbreaks, especially when control measures fail. Hence, science may have to resort to nature, plants, their metabolites and/or extracts for some level of succour. The online resources and database range for this article included PubMed, Google Scholar, MeSH, ScienceDirect, National Institute of Health (NIH) and Nation Centre for Biotechnology Information (NCBI) web resources. Word combinations and phrases pertinent to the subject under review were used. Some of these include coronaviruses, emerging topics on COVID-19, plant-based antivirals against coronaviruses, plant antiviral agents, plant metabolites for CoV prophylaxis, potent plant metabolites for CoV treatment, potential plants and their antiviral activity against CoVs, among others. Records and reports included relevant information from inception till May 2020 to help fine-tune results for thorough discussion on the appraised topic. Following the gathering of data, a mechanistic model (Figure 2) was generated to show inclusion and exclusion basis used for screening research records.

RESULTS AND DISCUSSION

Mode of transmission and life cycle of SARS-CoVs and MERS-CoV

Different strains of CoVs infect different hosts, and they normally deploy species-specific approaches for attachment and entry into the host cell. Studies have identified how CoVs enter the host cells and the definite manner through which each species of CoVs interact with the unique cellular receptors of the host. Such efforts have found that CoVs demonstrate a complex pattern for receptor recognition. Even when different species of CoVs infect similar hosts, they usually vary in the degree of diseases they cause, including acute, persistent, severe and highly lethal infections. While bats have been recognized as the reservoir for SARS-CoVs and MERS-CoV, their intermediate hosts differ considerably ranging from palm civets, dromedary camels to Malayan pangolin for SARS-CoV, MERS-CoV and SARS-CoV-2, respectively.

For CoVs, the S glycoprotein has two subunits (S1 and S2) and has been reported responsible for binding to host-receptor on the cell surface, and consequently entry into the cell. While the S1 subunit contains N- and C-terminal domains (S1-NTD and S1-CTD, respectively), the S2 subunit has the N- and C-terminal domains (S2-NTD and S2-CTD, respectively). The S2 subunit contains the receptor-binding domain (RBD), which binds to the host cell receptor.

The S glycoprotein of SARS-CoV-2 is the main target for the development of antiviral therapies. It is a class I transmembrane protein containing two functional domains, S1 and S2, which are responsible for attachment and penetration, respectively. The S1 domain, in turn, is further divided into two subdomains, S1-NTD and S1-CTD, which are responsible for receptor binding and conformational changes, respectively. The S2 domain is responsible for fusogenic activity and membrane fusion.

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both of which are receptor-binding domains (RBD), the S2 subunit, an elongated structure which forms the stalk, is mainly involved in ensuring attachment of viral envelop to the target cell membrane. To facilitate entry, the S1-CTD of MERS-CoV and SARS-CoVs interact with dipeptidyl peptidase 4 (DPP4) and angiotensin-converting enzyme 2 (ACE2), respectively. The ACE2 is an ectoenzyme anchored to the plasma membrane of the cells of several tissues, especially the lower respiratory tract, heart, kidney and gastrointestinal tract. Following S1-CTD’s interaction with the receptor, the viral nucleocapsid gets deposited into the cytoplasm, where consecutive replication, assembly and release of a new viral particle occurs. RNA replication in MERS-CoV and SARS-CoVs takes advantage of their open reading frames (ORFs) with the involvement of replicase genes (rep1a and rep1ab), a slippery sequence (5′-UUUAAC-3′) and polyproteins (pp1a and pp1ab). The polyproteins encode important non-structural proteins (NSP1–11 and NSP1–16) of the beta-CoVs. Specifically, the RNA replication which occurs on double-membrane vesicles (DMVs), involves the positive stranded RNA genome as a template which facilitates the production of the negative strand RNA. Using the replicase gene encoded enzymes, the negative stranded RNA genome was used to produce overlapping mRNA molecules which, subsequently, gets translated into the four structural proteins (N, M, E and S). While the NSPs serve to assemble the RNA into a helical twisted structure, the membrane-bound structural proteins get packed into the endoplasmic reticulum (ER) before translocation into endoplasmic reticulum-Golgi intermediate compartment (ERGIC). The nucleocapsids formed from the encapsidation of progeny genomes by N protein are then merged with the membrane-bound components, forming virions by budding into the ERGIC. Subsequently, the new virions get exported by Golgi bodies and are exocytosed into the extracellular space of the host cell, that allows attack by virions and possible transmission to other individuals (Figure 3).

Person-to-person transmission of SARS-CoV is through respiratory droplets, close contact with infected persons, faecal-oral route and aerosols. MERS-CoV is transmitted through respiratory droplets, close contact with diseased patients/camels and ingestion of camel milk. For SARS-CoV-2, current data shows major transmission routes are droplets transmission, contact transmission, with possibility of faecal-oral and aerosol transmission. Table 1 presents an overview of the characteristic clinical features of MERS-CoV and SARS-CoVs.

Some potent drugs, metabolites and interventions against SARS-CoV-2

The recent outbreaks of viral diseases such as Ebola, Zika and SARS-CoV-2, among others called for the development of new host-targeted
therapeutics, as well as a revisit of the drug reprofiling/repositioning methodology (DRM). DRM implies producing an added value from pre-existing medications and is usually achieved by channelling known drugs to another disease/infection besides that for which it was originally targeted.\textsuperscript{39,40} The major advantages of DRM over new drug formulations are that the pre-existing drug production process is already established, safe, reliable, and there is also reduced cost and timeline to clinical availability, plus the significantly improved success rate to market profitability. In addition, early drug developmental phases and drug-interaction properties from animal models used in pre-clinical trials are readily available.\textsuperscript{51,62}

As part of DRM, compounds which target viruses belonging to two or more viral families known as broad-spectrum antiviral agents (BSAAs) which are safe for use in humans have been proposed to provide herd protection against re-emerging and emerging viral infections while also broadening possible antiviral options.\textsuperscript{22} Some notable examples of BSAAs include etemine (an antiprotozoal capable of inhibiting HCoV-OC43, Zika and Ebola viruses and HIV-1 infections), enoxacin (anti-Zika and anti-HIV-1),\textsuperscript{43} amodiaquine (antimalarial and anti-Zika),\textsuperscript{44} and niclosamide (anthelmintic and anti-Zika).\textsuperscript{45-48} Several other BSAAs including chloroquine, azithromycin, cyclosporine, rapamycin, mycophenolic acid, etximtube and nitazoxanide are currently undergoing phase IV surveillance studies under this concept.\textsuperscript{49} A wide assortment of safe BSAAs which could be subjected to further studies as potential SARS-CoV-2 drug candidates are available from the database at https://drugvirus.info/. Study data must however be fused and harmonized for greater efficiency.\textsuperscript{19}

Another therapeutic is the cyclooxygenase (COX) mediator/inhibitor, indomethacin. Indomethacin/indocin has been shown to be an effective inhibitor of SARS-CoV-2 \textit{in vitro}.\textsuperscript{49} It is a non-steroidal anti-inflammatory drug (NSAID) with good antiviral potential against canine CoV \textit{in vivo}.\textsuperscript{46} It also showed similar potential against human SARS-CoV-2.\textsuperscript{46} In a study involving canine models, the feacal shedding of the control dog group increased steadily and peaked on the seventh day post-infection, while the viral titre in the indomethacin-treated group reduced drastically after resumption of treatment post-infection. Viral shedding in the treated dog group reached minimal levels at day seven post-infection.\textsuperscript{16}

Again, human monoclonal antibodies (MAb) targeting the viral spike protein may be useful prophylactically against SARS. Fusion inhibitors like enfuvirtide which is used in HIV may be redesigned for SARS-CoV. Nonpeptide inhibitors and peptide mimics which target viral 3C-like cysteine protease (3CPro) in CoVs with high selectivity index may show promise for SARS-CoV inhibition. Short interfering RNAs (ribavirin), α- interferon and β-interferon could also show promise for SARS control. Also, compounds with known \textit{in vitro} inhibition of SARS such as calpain inhibitors, valinomycin,\textsuperscript{50} glycopeptidase antibiotics, nelfinavir,\textsuperscript{51} plant lectins, aurantripyrroxylic acid and hesperetin\textsuperscript{52} could be subjected to further studies targeting SARS-CoV-2. Other identified anti-SARS-CoV agents include HIV protease inhibitors,\textsuperscript{53} anthraquinone-based compound,\textsuperscript{54} carbohydrate-binding agents,\textsuperscript{55} an antipsychotic\textsuperscript{54} and a nucleoside analogue.\textsuperscript{56} Hsieh et al.\textsuperscript{57} further expanded the list from their report on the successful test of a combination therapy that involved nelfinavir and agglutinin from \textit{Galanthus nivalis} which showed synergistic antiviral efficacy, although used in the treatment of feline SARS-CoV. Nelfinavir is a known safe anti-HIV-1 protease inhibitor with remarkable activity \textit{in vivo}\textsuperscript{57} and its efficacy in SARS-CoV-2 infection has been demonstrated since 2004.\textsuperscript{55}

Agglutinin from \textit{G. nivalis} belongs to a class of antivirals called carbohydrate-binding agent and has the ability to bind to both the membrane and spike proteins of CoVs.\textsuperscript{58} As the foremost study that showed anti-HIV-1 protease inhibitors as effective blockers of feline CoV replication, it serves as a classical and successful example of DRM.\textsuperscript{54} A CoV-membrane active compound denoted as K22 was reported to actively interfere with the DMVs formation, a process which is integral to the establishment of CoV replication. This effect was followed by a significant inhibition of viral RNA synthesis in MERS and HCoV-229E. This research finding points further studies toward a new drug development target for the treatment of pathogenic HCoVs including SARS-CoVs.\textsuperscript{60}

With clinical trials underway, a reprofiled Ebola medication, remdesivir, seems to show great promise for use in COVID-19 therapy compared to other SARS-CoV-2 test drugs. Remdesivir is a nucleotide analogue thought to act by halting the ability of the virus to replicate, thus reducing the infection of healthy body cells. Nonetheless, a study in China showed remdesivir as being more effective against SARS-CoV-2 when combined with chloroquine. Additional data on the drug efficacy and safety are however expected soonest.\textsuperscript{61,62} Another oral pill intervention being tested is favipiravir known as Avigan and is favoured over remdesivir which is intravenously injected.\textsuperscript{63} Other promising antiviral drugs undergoing test and clinical trials include SPL7013 from Starpharm, an antiviral dendrimer,\textsuperscript{64} Kaletra (a combination of lopinavir and ritonavir), EIDD-2801 (similar action as remdesivir and may be available as a pill), ivermectin, Actemra, Kevzara and Calquence. The use of stem cells, blood plasma from recovered COVID-19 patients and pluristems are also being investigated for potential use in COVID-19 prophylaxis or treatment.\textsuperscript{65}

Antibody-based treatments capable of preventing viral entry and infection like SAB-301 have also shown great promise. Again, MAbs such as REGN3048 and REGN3051 were shown in initial trials to be well tolerated and are at advanced stages of clinical trial.\textsuperscript{66} With regards to vaccines for SARS-CoV-2, the National Institute of Allergy

| Table 1: Comparative representation of biological features of SARS-CoVs and MERS-CoV. |
|-----------------|------------------|------------------|
| Virus           | SARS-CoV          | MERS-CoV         | SARS-CoV-2       |
| Disease caused  | SARS              | MERS             | COVID-19         |
| Emergence       | 2002              | 2012             | 2019             |
| Reservoir host  | Bat               | Bat              | Bat              |
| Intermediate host | Palm Crevet | Dromedary Camel | Malayan Pangolin? |
| Incubation period | 2-7 days | 5-6 days | 2-14 days |
| Host receptor   | ACE2              | DDP4             | ACE2             |
| Case fatality rate | 9.50% | 34.40% | 7.10% |
| Symptoms        | Fever, dry cough, headache, difficulty in breathing, muscle aches, loss of appetite, diarrhoea | Fever, chills, diarrhoea, nausea, vomiting, congestion, sneezing, sore throat | Fever, cough, shortness of breath, fatigue |
| Complications   | Heart, liver and respiratory failure in adverse condition. | Acute pneumonia and kidney failure in adverse condition. | Acute pneumonia, septic shock and respiratory failure in adverse condition. |

Jamiu, et al.: Phytotherapeutic Evidence Against Coronaviruses and Prospects for COVID-19
Pharmacognosy Journal, Vol 12, Issue 6, Nov-Dec, 2020

1255
and Infectious Diseases (NIAID) in conjunction with other research institutes would be conducting clinical trials for a vaccine named mRNA-1273. The vaccine would however not be publicly available till 2021.67 Another vaccine in form of a microneedle patch called PittCoVacc, developed by the University of Pittsburgh School of Medicine has been shown to evoke the production of anti-SARS-CoV-2 antibodies within two weeks of the patch prick.68 Several other vaccines are also being designed with possible clinical trials underway.

Plants and plant secondary metabolites as antiviral agents and prospects for COVID-19

Antiviral agents and prospects for COVID-19

Natural products from plants including plant extracts and plant-derived compounds have wide applications as nutraceuticals and with potential use in the prevention and treatment of several communicable and non-communicable diseases.44 Unsurprisingly, synthesis of conventional drugs is greatly dependent on medicinal plants and a staggering one-quarter of the commonly used conventional drugs were originally synthesised from plant-derived compounds.70 A typical example is chloroquine phosphate, a structural analogue of quinine derived from the bark of the Cinchona tree. This drug is traditionally used for the treatment of malaria however, it has been reported to exert considerable antiviral and immunomodulating properties.97,98 Another antimalarial drug, artemisinin is obtained from Artemisia annua.71 Again, while emetine, an amoebicidal drug is obtained from Cephaelis ipecacuanha, others such as quinidine, topotecan, taxol, morphine, aspirin, digitalis Cinatl and co-workers 77 evaluated the antiviral potential of liquorice plant derived compounds such as apigenin, berbamine, lycorine and Lycoris radiata.72,73,74 Demand for novel, highly potent, less toxic and cost-effective antivirals especially amidst the current COVID-19 pandemic.77-80 Natural compounds may confer antiviral activity via the modulation of immune system against the virus or through direct inhibition or blockage of viral entry, replication, infection, reverse transcription, protein expression, assembly, release or host-specific interactions.3,78

Medicinal plants have rich bioactive components which could be explored for therapeutic leads. In fact, in recent times medicinal plants and their products have gained greater attention and a variety of herbs have been investigated for their antiviral potential. Extracts of plants such as Lycoris radiata, Artemisia annua, Pyrosis lingua, and plant derived compounds such as apigenin, berbamine, lycorine and glycyrrhizin are not only potent antiviral agents, but they also possess remarkable anti-human coronaviral (HCoV) properties. These make them excellent lead compounds for novel antiviral drug development, especially amidst the current COVID-19 pandemic.78,79 Natural compounds may confer antiviral activity via the modulation of immune system against the virus or through direct inhibition or blockage of viral entry, replication, infectivity, reverse transcription, protein expression, assembly, release or host-specific interactions.3,78

Interestingly, traditional or herbal medicine has been previously employed to treat HCoVs, and studies have confirmed its efficacy either as a holistic intervention or as combined therapy with conventional medicine.78,81,82 For instance, during the SARS-CoV outbreak in 2002, Cinatl and co-workers77 evaluated the antiviral potential of licorice roots-derived compounds such as ribavirin, 6-azauridine, pyrazofurin, and glycyrrhizin against two clinical isolates of SARS-CoV (FFM-1 and FFM-2) isolated from German patients in Vero cell cultures. Of the five compounds, glycyrrhizin had the most potent activity with 50% effective concentration (EC50) of 300 mg/L and selectivity index of 67. The mode of action of glycyrrhizin against SARS-CoV was obscure; however, it could be due to its induction of nitrous oxide synthase since nitrous oxide is a known inhibitor of replication in several viruses (e.g. Japanese encephalitis virus).83 The Camellia sinensis plant has been reported to contain theafalin,84 water soluble tannic acid and theaflavin-3-gallate85 which contribute to its antiviral function against rotavirus and SARS-CoV. Eleutherococcus senticosus containing theafalin and catechin has also been shown to be effective against rotavirus and HCoVs.86,87 Glycyrrhizin is also a good inhibitor of hepatitis B virus; it is capable of stimulating endogenous production of interferons and with remarkable antioxidant activity.88 Similarly, a further study by Hoever and co-workers89 reported the increased anti-SARS-CoV activity of chemically modified glycyrrhizin derivatives, however the modified derivatives had increased cytotoxicity and reduced selective index compared to the original compound.89 Ginsenoside-Rb1, a steroid from Panax Ginseng, a traditional Chinese medicine, shows considerable activity against SARS-CoV at a concentration of 100 µM. The same study also demonstrated the anti-SARS-CoV potential of acesic and reserpine, with EC50 values of 6.0 µM and 3.4 µM, respectively.90 Similarly, baicalin, a flavonoid from another traditional Chinese medicine, Scutellaria baicalensis has also been reported to possess anti-SARS-CoV activity.91 Furthermore, the anti-HCoV-229E activity of glucosidic compounds, saikosaponins (A, B, C and D) has been shown. The strongest potency was displayed by saikosaponin B and its mechanism of action was attributed to the interference of early stages of viral replication such as viral attachment, adsorption and penetration.92 In another study by Yi and co-workers93 that involved the screening of small molecules from 121 Chinese herbs extracts resulted in the identification of two molecules, tetra-O-gallloyl-β-d-glucose (TGG) and luteolin from Gallia chinensis and Rhodiola kirilowii, respectively with substantial effects on SARS-CoV.94 The proposed mechanism of action of these two compounds was via the blockage of viral entry. The high selective index (SI) value of TGG (SI: 240) compared to luteolin (SI: 24) might make it a better lead compound, since this means that it can be used at high concentration with no significant cytotoxic effects.95 A high throughput screening of 200 Chinese medicinal herb extracts has demonstrated the significant anti-SARS-CoV activity of Lycorisin radiata (ethanolic extract), Artemisia annua (ethanolic extract), Pyrosis lingua (chloroform extract), and Lindera aggregata (ethanolic extract) with EC50 ranging from 2.4 ± 0.2 to 88.2 ± 7.7 µg/ml (Table 2). Further fractionation and purification of the alkaloid components of the most potent extract, Lycoris radiata (EC50: 2.4 ± 0.2 µg/ml) resulted in the isolation of the active ingredient of the herb, lycorine with EC50 of 15.7 ± 1.2 mM. Its remarkable SI value greater than 900 also makes it a great lead compound for future drug design.96

With the use of a Vero E6 cell-based cytopathogenic effect (CPE) assay, the anti-SARS-CoV potential of 221 compounds was determined by Wen and co-workers.97 The study demonstrated that ten diterpenoids which include ferruginol, dehydroabieta-7-one, sugiol, crypotojaponol, 8β-hydroxyabieta-9(11),13-dien-12-one, 7β-hydroxydeoxycryptojaponol, 6,7-dehydroroyleanone, 3β-,12-dehydroabieta-7-one (SI: 89.8), betulonic acid (SI: 180), and savinin (SI: >667) were the leading candidates for novel antiviral drug development. The highest potency was displayed by the 13-one (SI: >510), 7β-hydroxydeoxycryptojaponol (SI: 111), 3β-,12-dehydroabieta-7-one (SI: 76.3), 8β-hydroxyabieta-9(11),13-dien-12-one diterpenoids which include ferruginol, dehydroabieta-7-one, 7β-hydroxydeoxycryptojaponol, 6,7-dehydroroyleanone, 3β-,12-dehydroabieta-7-one, diacetoxyabieta-6,8,11,13-tetraene, pinusolidic acid, forskolin; two sesquiterpenoids viz., cedrene-3β,12-diol, α-cadinol; two triterpenoids namely betulinic acid, betulonic acid; five lignoids hinokinin, savinin, 4β-O-benzoylisolariciresinol, honokiol, magnolol; and a phenolic compound, curcumin had remarkable anti-SARS-CoV activity at concentrations between 3.3 and 10 µM. All of these phytocompounds, except sugiol and 4β-O-benzoylisolariciresinol markedly inhibited SARS-CoV replication. Moreover, the SI values of ferruginol (SI: 58.3), 1256 Jamiu, et al.: Phytotherapeutic Evidence Against Coronaviruses and Prospects for COVID-19
Pharmacognosy Journal, Vol 12, Issue 6, Nov-Dec, 2020
**Table 2: Medicinal plants with anti-coronaviral potential.**

| SN | Plant | Family | Plant part | Extract | Metabolite or extract (Dose) | EC₅₀ | Proposed mechanism | HCoV | Reference |
|----|-------|--------|------------|---------|-----------------------------|------|-------------------|------|-----------|
| 1  | Artemisia annua | Asteraceae | Whole plant | Ethanol | Artemisinin (10⁻⁷ - 10⁻⁴ mg/ml) | 34.5 ± 2.6 µg/ml | Unclear | SARS-CoV | 78 |
| 2  | Cassiae Semen extract (Cassia tora) | Fabaceae | Seed | n-hexane | Na (0 - 10 µg/ml) | 8.43 µg/ml | Inhibition of SARS-CoV 3CL protease activity | SARS-CoV | 96 |
| 3  | Dioscoreae Rhizoma extract (Dioscorea batatas) | Dioscoreaceae | Tuber | Methanol | Na (0 - 10 µg/ml) | 8.03 µg/ml | Inhibition of SARS-CoV 3CL protease activity | SARS-CoV | 96 |
| 4  | Gentianae Radix extract (Gentiana scabra) | Gentianaceae | Rhizome | n-hexane | Na (0 - 10 µg/ml) | 8.70 µg/ml | Inhibition of viral replication | SARS-CoV | 96 |
| 5  | Lindera aggregata | Lauraceae | Root | Ethanol | Na (10⁻¹ - 10⁻⁴ mg/ml) | 8.82 ± 7.7 µg/ml | Inhibition of viral replication | SARS-CoV | 96 |
| 6  | Loranthi Ramus extract (Taxillus chinensis) | Loranthaceae | Stem, leaf | n-hexane | Na (0 - 10 µg/ml) | 5.39 µg/ml | Inhibition of viral replication | SARS-CoV | 96 |
| 7  | Lycoris radiata | Amaryllidaceae | Stem | Ethanol | Lycorine (10⁻ⁱ - 10⁻⁷ mg/ml) | 2.4 ± 0.2 µg/ml | Unclear | HCoV-OC43, HCoV-NL63, MERS-CoV, MHV-A59 | 99 |
| 8  | Pyrosia lingua | Polypodiaceae | Leaf | Chloroform | Na (10⁻¹ - 10⁻⁴ mg/ml) | 43.2 ± 14.1 µg/ml | Unclear | SARS-CoV | 78 |
| 9  | Rhizoma Cibotii extracts (Cibotium barometz) | Cibotiaceae | Rhizome | Ethanol and methanol | Na (0 - 10 µg/ml) | 8.42 and >10 µg/ml | Inhibition of SARS-CoV 3CL protease activity | SARS-CoV | 92 |
| 10 | Strobilanthes cusia | Acanthaceae | Leaf | Methanol | Na (0 - 10 µg/ml) | 0.64 ± 0.43 µg/ml | Virucidal activity | HCoV-NL63 | 110 |
| 11 | Glycyrrhiza glabra L., Glycyrrhiza uralensis | Fabaceae | Root | Na | Glycyrrhizin (300 mg/L) | Na | Virucidal activity | SARS-CoV | 77, 101, 102 |
| 12 | Houttuynia cordata Thunb. | Saururaceae | Whole plant | Aqueous | Na | Na | Increase the activity CD4+ and CD8+ of T cells; inhibition of protease (3CLpro); RNA dependent RNA polymerase (RdRp) activity. | SARS-CoV | 103 |
| 13 | Toona sinensis Roem | Meliaceae | Leaf | Aqueous | Quercetin (Na) | Na | Unclear | SARS-CoV | 91, 95 |
| 14 | Pelargonium sidoides DC. | Geraniaceae | Root | Aqueous | Catechin and gallocatechin (Na) | Na | Inhibit replication of H1N1, H3N2 virus strains, respiratory syncytial virus, and human coronavirus Inhibited the interaction of SARS-CoV-3 protein and ACE2 | SARS-CoV | 95, 104 |
| 15 | Rheum officinale | Polygonaceae | Root tubers | Aqueous | Emodin (Na) | Na | Inhibited the interaction of SARS-CoV protein and ACE2 | SARS-CoV | 54 |
| 16 | Polygonum multiflorum Thunb. | Polygonaceae | Root and vine | Aqueous | Emodin (Na) | 200 µM | Inhibited the interaction of SARS-CoV protein and ACE2 | SARS-CoV | 54 |
| 17 | Polygonum aviculare | Polygonaceae | Root tuber | Aqueous | Juglanin (10 - 40 µM) | 2.3 µM | Inhibit the replication and expression of coronavirus and TRP gene | SARS-CoV | 88 |
| 18 | Anthemis hyaline DC. | Asteraceae | Flower and bud | Ethanol | Flavanoids. (Na) | Na | Inhibit the replication and expression of coronavirus and TRP gene | SARS-CoV | 98, 106 |
| 19 | Nigella sativa L. | Ranunculaceae | Seed | Ethanol | Thymoquinon, α- Hederin and Nigellidine (Na) | Na | Virucidal activity | SARS-CoV | 77, 101, 102 |
inhibited SARS-CoV in vitro, though the elicited mechanism is yet to be elucidated, its activity was attributed to the presence of quercetin, a known plant flavonol with reported antiviral activity against HIV-luc/SARS.\(^{70,71}\) Furthermore, a species from the family Geraniaceae in southern Africa that has been formulated into an herbal drug for the treatment of respiratory infection, *Pelargonium sidoides* was also found to hinder the replication of H1N1, H3N2 virus strains, respiratory syncytial virus, and HCoVs.\(^{94,95}\) Another study that involves the antiviral activity of six extracts from *Cassia tora*, with 50\% effective concentration (EC\(_{50}\)) values ranging from 5 to 10 µg/ml. While all the extracts showed good inhibitory activity against Vero E6 cells, the methanolic extracts of *Dioscorea batatas* and *Cibotium barometz* against Vero E6 cells, the methanolic extracts of *Dioscorea batatas* and *Cibotium barometz* demonstrated the highest antiviral potential for the first time in *E. neriifolia*. Of the triterpenoids, 3β-Friedelanol\(^{91}\) and 3β-Friedelanol \(\text{E. neriifolia}\) flavonoid glycoside, and thirteen of these compounds were identified for the first time in *E. neriifolia*. The ethanolic leaf extract of *E. neriifolia* is a potential new source of antiviral agents, and suggested that further assays aimed at tackling SAR-CoV-2 and other related viruses could be done on thistle, barley, sundew, and *Ficus sp.*\(^{116}\) Another study involving the antiviral activity of a traditional Chinese medicine, *Scrophularia coccinea* (IC\(_{50}\) : 0.64 µg/ml) has been reported. Its derivatives such as tanshinone IIa, N-cis feruloyltyramine and betulinic acid.\(^{17}\) Recently, the broad-spectrum inhibitory effects of phytocompounds such as lycorine, emetine, monensin sodium, and mycophenolic acid against a panel of HCoVs (HCoV-OC43, HCoV-NL63, MERS-CoV, and MHH-A59) have also been demonstrated.\(^{110}\) Moreover, while emetine and lycorine are potent inhibitors of dengue virus replication, lycorine has also been reported as a good inhibitor of replication in several viruses such as polioviruses, herpes simplex virus 1, Bunyamwera virus, and West Nile virus.\(^{110-112}\) Very recently, the anti-HCoV-NL63 activity of a traditional Chinese medicine, *Strobilanthus cusia* (IC\(_{50}\), 0.64 µg/ml) has also been demonstrated. Its derivatives such as lycorine has also been reported as a good inhibitor of replication in several viruses such as polioviruses, herpes simplex virus 1, Bunyamwera virus, and West Nile virus.\(^{110-112}\) Very recently, the anti-HCoV-NL63 activity of a traditional Chinese medicine, *Strobilanthus cusia* (IC\(_{50}\), 0.64 µg/ml) has been reported. Its derivatives such as tanshinone IIa, N-cis feruloyltyramine and betulinic acid.\(^{17}\) Euphorbia neriifolia L. and *Nigella sativa* in the management of HCoV infection. The compounds were sugiol, kaempferol, cryptotanshinone, mocopinamide, coumaroyltyramine, quercetin, dihomo-γ-linolenic acid, dihydrotanshinone, desmethoxyreserpine, lignan, tanshinone IIa, N-cis feruloyltyramine and betulinic acid.\(^{17}\)

|   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|
| 19. | *Citrus sinensis* (L.) Osbeck | Rutaceae | Peel | Ethanol | Carvacrol and α-pinene (Na) | Na | Inhibit the replication and expression of coronavirus and TRP gene | SARS-CoV 88 |
| 20. | *Torrey mexicana* (L.) Siebold & Zucc. | Taxaceae | Leaf | Ethanol | Luteolin, Quercetin and Apigenin (Na) | 20.23.8 and 280.8 µM | Inhibition of 3CLpro | SARS-CoV 107 |
| 21. | *Euphorbia neriifolia* L. | Euphorbiaceae | Leaf | Ethanol | Triterpenoids (0 – 25 µM), flavonoid glycoside (Na). Hinokinin (0 – 10 µM) | Na | Virucidal activity | HCoV 97, 108 |
| 22. | *Isatidis indigotica* | Brassicaceae | Root | Aqueous | Snigirin, Indigo, β-sitosterol and Aloe-emodin (Na), Hesperetin (Na) | Na | anti-SARS-CoV 3CLpro | SARS-CoV 74, 79 |
| 23. | *Scrophularia scorodonia* | Scrophulariaceae | Na | Na | Saikosaponin A, B2, C and D (0 – 25 µM) | Na | Virucidal activity | HCoV 22E9 90 |
| 24. | *Panax Ginseng* | Araliaceae | Root | Na | Ginsenoside-Rh1. (Na), Aescin (0 – 20 µM), Ressonine (0 – 20 µM) | 100 µM | Inhibition of viral replication | SARS-CoV 50 |
| 25. | *Cinnamomum sp.* | Lauraceae | Cortex | Na | Procyanidin B1 (0 – 500 µM) | 41.3 ± 3.4 µM | Inhibition of pseudovirus infection | SARS-CoV 106 |
| 26. | *Curcuma longa* (Tumeric) | Zingiberaceae | Rhizome | Na | Curcumin (0 – 10 µM) | >10 µM | Viral replication inhibition | SARS-CoV 82 |

Na = Not available
Saposnikovia divaricata coumarins, phloroglucinols of Dryopteris crassirhizoma and oleane triterpenes derived from Camellia japonica flowers also demonstrated antiviral potential against porcine epidemic diarrhea virus (PEDV), a member of the Coronaviridae family.\textsuperscript{18,19} The replication pathway of PEDV is similar to human CoVs. In other words, vaccines for MERS and PEDV could be based on similar theory\textsuperscript{20, 121} such that the compounds reported in medicinal plant species studied by Yang et al.\textsuperscript{122} could become promising candidates for further research to better tackle fatal HCoVs. Also, anti-HCoV-229E potential of saikosaponin A, B2, C and D expressed from medicinal Scrophularia scrobana, Heteromorpha and Bupleurum species have been demonstrated to prevent viral attachment and penetration in vitro. These compounds could be repurposed for SARS-CoV-2.\textsuperscript{21} Other potential plants believed to fight viral respiratory infections include Peragonium soidoses (African geranium), Androgaphis paniculata (kalmegh) and fruit of Sambucus nigra (black elder).\textsuperscript{21} A list of prospective plants and their metabolites for COVID-19 are presented in Table 2.

**Plants and their metabolites as specific inhibitors of HCoV target proteins**

As earlier mentioned, the HCoVs encode proteins including the 3-chymotrypsin-like protease (3CL\textsuperscript{pro}) – a cysteine protease, which is important for viral replication, transcription and subsequent maturation; papain-like protease (PL\textsuperscript{pro}) – essential for translation and deubiquitination; and spike protein (S) – which is indispensable for host cell entry.\textsuperscript{122, 123} These proteins provide possible targets for drug development and screening of traditional medicines with anti-coronaviral potential. In fact, some structure-based analyses and high-throughput studies have highlighted plant metabolites as potent inhibitors of these proteins. Phytochemicals such as hesperetin, sinigrin, indigo, β-sitosterol, hirsutone, emodin, myricetin and tannic acid have been reported to exhibit anti-coronaviral properties through their modulatory effect on HCoV target proteins.\textsuperscript{91, 124}

A study by Lin and co-workers\textsuperscript{125} reported the anti-SARS-CoV 3CL\textsuperscript{pro} potential of aqueous extract of *Litchi indigotica*. The same study was further expanded to screen five major compounds of *L. indigotica* root extract (indigo, indirubin, indican, sinigrin, and β-sitosterol) and seven other plant-derived phenolic compounds including aloen-emodin, hesperetin, quercetin, naringenin, daidzein, emodin, and chrysophanol against the same protein. Although, hesperetin (a phenolic compound) was the most efficient in blocking the cleavage processing of the protein with 50% inhibitory concentration (IC\textsubscript{50}) of 8.3 µM, other compounds such as sinigrin, indigo, β-sitosterol, hirsutone, emodin, myricetin and chrysophanol (6) have been reported to exhibit anti-coronaviral properties through their modulatory effect on HCoV target proteins.\textsuperscript{91, 124}

In another study, the anti-SARS-CoV 3CL\textsuperscript{pro} activity of a phenolic compound, curcumin (IC\textsubscript{50} \(\approx 40\) µM); two triterpenoids, betulinic acid (IC\textsubscript{50} \(\approx 10\) µM), betulonic acid (IC\textsubscript{50} \(\approx 100\) µM); and two lignoids, hinokinin (IC\textsubscript{50} \(\approx 100\) µM), savinin (IC\textsubscript{50} \(\approx 25\) µM) has been demonstrated.\textsuperscript{92} Another phenolic compound, quercetin-3-β-galactoside and some of its derivatives have been identified as potent inhibitors of SARS-CoV 3CL\textsuperscript{pro} through a series of molecular docking and enzyme inhibition assays. The findings further demonstrated that although residue Gln189 of SARS-CoV 3CL\textsuperscript{pro} plays an indispensable role in its interaction with quercetin-3-β-galactoside, its mutation does not affect the enzymatic activity of the protease.\textsuperscript{127} Quercetin also possesses significant anti-murine coronaviral activity.\textsuperscript{93} Findings of Wen and co-workers\textsuperscript{94} have shown the anti-SARS-CoV 3CL\textsuperscript{pro} activity of extracts of *Citrobium barometz* (Rhizoma Cibotii) and *Dioscorea batatas* (Dioscoreaceae Rhizoma) with IC\textsubscript{50} values of 39 µg/ml and 44 µg/ml respectively. The aqueous extract of *Houttuynia cordata* have also been reported to possess significant anti-SARS-CoV 3CL\textsuperscript{pro} property as well as considerable immune-stimulatory effect via the increment of CD4\textsuperscript{+} and CD8\textsuperscript{+}.\textsuperscript{128}

Out of the 312 Chinese medicinal herbs screened by Ho and co-workers,\textsuperscript{34} only three herbs, *Rheum officinale* Baill. (root tuber), *Polygonum multiflorum* Thunb. (root tuber) and *P. multiflorum* Thunb. (vin) displayed considerable inhibition of SARS-CoV S protein and angiotensin converting enzyme type 2 (ACE2) interaction with IC\textsubscript{50} values ranging from 1 to 10 µg/ml. Furthermore, to confirm the phytochemical component responsible for the inhibitory effect, three previously characterised biomolecules of the plants were screened. Emodin, but not Rhein and chrysin significantly blocked SARS-CoV S-protein and ACE2 interaction in a dose-dependent fashion with IC\textsubscript{50} value of 200 µM. It is noteworthy that ACE2 is the entry receptor for SARS-CoV and blockage of its interaction with SARS-CoV S protein would prevent virus entry.\textsuperscript{34} The antiviral activity of emodin against enveloped viruses including influenza virus and varicella-zoster virus, via the disruption of lipid layer has been reported by an earlier study.\textsuperscript{129}

The anti-SARS-CoV 3CL\textsuperscript{pro} property of ethanol extract of *Torreya nucifera* leaves has been reported.\textsuperscript{95} A bioassay guided fractionation and purification led to the identification of eight diterpenoids (18-hydroxyferruginol (1), hinokiol (2), ferruginol (3), 18-oxoferruginol (4), O-acetyl-18-hydroxyferruginol (5), methyl dehydroabietate (6), isopimaric acid (7), and kaidyol (8)) and four biflavonoids (amentoflavone (9), bilobetin (10), ginkgetin (11), and sciadopitysin (12)) with anti-SARS-CoV 3CL\textsuperscript{pro} activity from the plant’s n-hexane and ethyl acetate fractions, respectively. Although the bioflavonoids were the most potent inhibitors of the protease with IC\textsubscript{50} values ranging from 8.3 to 72.3 µM, the diterpenoids also exerted considerable inhibitory effects with IC\textsubscript{50} values ranging from 49.6 to 283.5 µM. Three other flavonoids viz., luteolin, quercetin and apigenin anti-SARS-CoV 3CL\textsuperscript{pro} activity was also demonstrated with IC\textsubscript{50} values of 20.3 and 280.8 µM, respectively.\textsuperscript{130} In a similar study, four triterpenes from *Tripterygium regelii* namely celastrol, pristimerin, tingenone, and uigesterin inhibited 3CL\textsuperscript{pro} activity with IC\textsubscript{50} values of 10.3, 5.5, 9.9, and 2.6 µM, respectively.\textsuperscript{131} Similarly, a study by Yu and co-workers\textsuperscript{132} has reported the antiviral activity (via the inhibition of SARS-CoV helicase protein) of two flavonoids, myricetin and scutellarein with IC\textsubscript{50} values of 2.71 ± 0.19 µM and 0.86 ± 0.48 µM, respectively.

A bioactivity guided fractionation and spectroscopic analysis of the ethanolic extract of *Alnus japonica* led to the isolation of nine small diarylethylene's molecules (polyphenols). Six out of the polyphenolic compounds namely hisutonone, hisutanonol, orogonin, rubron, rubronaside B and rubronaside A exerted significant dose-dependent inhibitory effect against SARS-CoV PL\textsuperscript{pro}. It is worthwhile that the biological activity of these molecules was greatly impacted by their chemical structures with most remarkable effect (IC\textsubscript{50} \(\approx 4.1\) µM) exerted by hisutonone which contains an α, β-unsaturated carbonyl group with a catechol moiety.\textsuperscript{133} The remarkable interactions of natural myricetin and rubranoside B and rubranoside A with S-CoV S protein as well as considerable immune-stimulatory effect via the increment of CD4\textsuperscript{+} and CD8\textsuperscript{+}.\textsuperscript{134}

The replication pathway in PEDV are similar to human CoVs. In other words, vaccines for MERS and PEDV could be based on similar theory\textsuperscript{20, 121} such that the compounds reported in medicinal plant species studied by Yang et al.\textsuperscript{122} could become promising candidates for further research to better tackle fatal HCoVs. Also, anti-HCoV-229E potential of saikosaponin A, B2, C and D expressed from medicinal Scrophularia scrobana, Heteromorpha and Bupleurum species have been demonstrated to prevent viral attachment and penetration in vitro. These compounds could be repurposed for SARS-CoV-2.\textsuperscript{21} Other potential plants believed to fight viral respiratory infections include Peragonium soidoses (African geranium), Androgaphis paniculata (kalmegh) and fruit of Sambucus nigra (black elder).\textsuperscript{21} A list of prospective plants and their metabolites for COVID-19 are presented in Table 2.
host cells. It is worthwhile that the formula has also been reported to inhibit of viral replication and reduction of cytokines release from SARS-CoV-2 activity was through the deformation of viral morphology, and fruits such as kaempferol and daidzein, quercetin, puerarin, epigallocatechin, gallocatechin gallate, epigallocatechin gallate have shown anti-SARS-CoV 3CLpro activity. Phenolics in Isatis indigotica, and the aqueous extract of Houttuynia cordata also showed SARS-CoV 3CLpro inhibition. A recent study by Runfeng and coworkers noted the inhibitory activity of lianhuaqingwen, a traditional Chinese medicine formula composing of 13 herbs against the most recent SARS-CoV-2 with IC\textsubscript{50} value of 411.2 µg/ml. The exerted anti-SARS-CoV-2 activity was through the deformation of viral morphology, inhibition of viral replication and reduction of cytokines release from host cells. It is worthwhile that the formula has also been reported to exert broad-spectrum effects on influenza viruses via inhibition of viral propagation and immunomodulation.

Similarly, a study on medicinal plant metabolites such as diallyl disulfide from Allium sativum (garlic), capsaicin from Capsicum (pepper), limonene from Elettaria (cardamom), thymol from Mentha pulegium (pennyroyal), coumarin from liquorice, verbascoside from Stachys schischkelevi (hedge净tle), curcumin from Curcuma longa (tumeric) and glucuronic acid from Astraglus gossypinus (Tragacanth) was recently conducted to detect potential compounds with activity against SARS-CoV-2 using protease enzyme interaction. Of these compounds which showed good interaction, curcumin showed the highest protease inhibiting activity against SARS-CoV-2 and may be useful in antiprotease-based medication for treatment of COVID-19.

Worthy of mention is a CoV infection intervention (no. EP19990203128) put forward by Mas Pharmaceutical. The intervention includes the glucopyranoside analogues found in Ginseng Panax species, methylpanaxadiol and 1-protopanaxatriol, in combination with a protodioscin derivative associated with Dioscorea plant, dimethylprotopsiquamine. The latter is an anti-miticot agent and the former showed anti-mutagenic and pro-apoptotic activities. In combination, the intervention targets the total functional and structural destruction of the virus through their RNA-dependent RNA polymerase and DNA gyrase inhibitive characteristics. In another development with the recent advancement in bioinformatics, Salim and Noureddine studied the molecular docking of the metabolites isolated from Nigella sativa as a potential COVID-19 inhibitor. They found out that α-hederin and nигellidine, when compared with chloroquine, have better energy scores thus touting the metabolites as good candidates for the treatment of COVID-19. Table 3 presents some of the specific plant-derived inhibitors of HCoV target proteins.

Overall, an insight into recognition of the class of compounds studied so far against HCoVs revealed that, phenolics (31.78%) and terpenoids (28.04%) are the most investigated phytocompounds with flavonoids (13.08%) and alkaloids (12.15%) also finding some promising applications (Table 3, Figure 4). The seldom application of lignoids (6.54%), saponins (5.61%) and steroids (0.93%) (Table 3, Figure 4) and several other classes of phytoneutrants of therapeutic significance not even being studied against HCoVs is a further promising ground calling for in-depth research targeting the prime proteins of these viruses and especially the current SARS-CoV-2 posing significant global challenge.

### Table 3: Plant-derived specific inhibitors of HCoVs.

| SN | Compound                                      | Type                        | IC\textsubscript{50} or EC\textsubscript{50} | Proposed mechanism of action | HCoV          | Reference |
|----|----------------------------------------------|-----------------------------|---------------------------------------------|-----------------------------|--------------|-----------|
| 1  | Lycorine (Lycoris radiata)                   | Alkaloid                    | 15.7 ± 1.2 nM                               | Unclear                     | SARS-CoV     | 78        |
| 2  | Glycyrrhizin (Glycyrrhiza glabra) (licorice root) | Saponin                    | 300 mg/L                                   | May inhibit 3CL\textsuperscript{50} | SARS-CoV     | 77        |
| 3  | Reserpine (Aesculus hippocastanum)           | Alkaloid                    | 3.4 µM                                     | May inhibit 3CL\textsuperscript{50} | SARS-CoV     | 58        |
| 4  | Aescin (Rauwolfia species)                   | Saponin                     | 6.0 µM                                     | May inhibit 3CL\textsuperscript{50} | SARS-CoV     | 58        |
| 5  | Lianhuaqingwen                               | Chinese medicine formula    | 411.2 µg/ml                                 | May inhibit 3CL\textsuperscript{50} | SARS-CoV-2   | 137       |
| 6  | Tetra-O-galloyl-β-d-glucose (Galla chinensis) | Phenolic                    | 4.5 µM                                     | May inhibit S protein        | SARS-CoV     | 91        |
| 7  | Luteolin (Rhodiola kirilowii)                | Flavonoid                   | 10.6 µM                                    | May inhibit S protein        | SARS-CoV     | 91        |
| 8  | Ferruginol (Chamaecyparis obtusa var. formosana) | Terpenoid                  | 1.39 µM                                    | May inhibit 3CL\textsuperscript{50} | SARS-CoV     | 92        |
| 9  | Dehydroabieta-7-one (Chamaecyparis obtusa var. formosana) | Terpenoid                  | 4.00 µM                                    | May inhibit 3CL\textsuperscript{50} | SARS-CoV     | 92        |
| 10 | Sugiol (Chamaecyparis obtusa var. formosana) | Terpenoid                   | -                                          | -                           | SARS-CoV     | 92        |
| 11 | Cryptotauponol (Cryptomeria japonica) 8β-hydroxyabieta-9(11),13-dien-12-one (Chamaecyparis obtusa var. formosana) | Terpenoid                  | >10 µM                                     | May inhibit 3CL\textsuperscript{50} | SARS-CoV     | 92        |
| 12 | Cryptotauponol (Cryptomeria japonica) 8β-hydroxyabieta-9(11),13-dien-12-one (Chamaecyparis obtusa var. formosana) | Terpenoid                  | 1.47 µM                                    | May inhibit 3CL\textsuperscript{50} | SARS-CoV     | 92        |
| 13 | 7β-hydroxydeoxyabieta-pseudojaponol (Cryptomeria japonica) | Terpenoid                  | 1.15 µM                                    | May inhibit 3CL\textsuperscript{50} | SARS-CoV     | 92        |
| 14 | 6,7-dehydroxyabieta-pseudojaponol (Chamaecyparis obtusa var. formosana) | Terpenoid                  | 5.55 µM                                    | May inhibit 3CL\textsuperscript{50} | SARS-CoV     | 92        |
| 15 | 3β-,12-diaceocioxyabieta-6,8,11,13-tetraene (Juniperus formosana) | Terpenoid                  | 1.57 µM                                    | May inhibit 3CL\textsuperscript{50} | SARS-CoV     | 92        |
| 16 | Pinusolidic acid (Chamaecyparis obtusa var. formosana) | Terpenoid                  | 4.71 µM                                    | May inhibit 3CL\textsuperscript{50} | SARS-CoV     | 92        |
| 17 | Forskolin (Coleus forskohlii)                | Terpenoid                   | 7.5 µM                                     | May inhibit 3CL\textsuperscript{50} | SARS-CoV     | 92        |
| 18 | Cedrane-3β,12-diol (Juniperus formosana)     | Terpenoid                   | >10 µM                                     | May inhibit 3CL\textsuperscript{50} | SARS-CoV     | 92        |
| No. | Compound Description | Type | Concentration | Effect | Virus (Reference) |
|-----|---------------------|------|---------------|--------|------------------|
| 19. | α-cadinol (Chamaecyparis obtusa var. formosana) | Terpenoid | 4.44 µM | May inhibit 3CLpro | SARS-CoV |
| 20. | Betulinic acid (Betula pubescens) | Terpenoid | >10 µM | May inhibit 3CLpro and S protease | SARS-CoV |
| 21. | Betulonic acid (Juniperus formosana) | Terpenoid | 0.63 µM | May inhibit 3CLpro | SARS-CoV |
| 22. | Hinokinin (Chamaecyparis obtusa var. formosana) | Lignoid | >10 µM | May inhibit 3CLpro | SARS-CoV |
| 23. | Savinin (Chamaecyparis obtusa var. formosana) | Lignoid | 1.13 µM | May inhibit 3CLpro and S protease | SARS-CoV |
| 24. | 4,4′-O-benzoylisolariciresinol (Synthetic lignan) | Lignoid | - | - | - |
| 25. | Honokiol (Magnolia spp.) | Lignoid | 6.50 µM | May inhibit 3CLpro | SARS-CoV |
| 26. | Magnolol (Magnolia spp.) | Lignoid | 3.80 µM | May inhibit 3CLpro | SARS-CoV |
| 27. | Curcumin (Curcuma longa) | Phenolic | >10 µM | May inhibit 3CLpro | SARS-CoV |
| 28. | Baicalin (Scutellaria baicalensis) | Flavonoid | 12.5 to 25 µg/ml | May inhibit 3CLpro | SARS-CoV |
| 29. | Saikosaponin A (Bupleurum spp.) | Saponin | 8.6 ± 0.3 µM | May inhibit 3CLpro | HCoV-229E |
| 30. | Saikosaponin B2 (Bupleurum spp.) | Saponin | 1.7 ± 0.1 µM | May inhibit 3CLpro and S protease | HCoV-229E |
| 31. | Saikosaponin C (Bupleurum spp.) | Saponin | 19.9 ± 0.1 µM | May inhibit 3CLpro | HCoV-229E |
| 32. | Saikosaponin D (Bupleurum spp.) | Saponin | 13.2 ± 0.3 µM | May inhibit 3CLpro | HCoV-229E |
| 33. | Lycorine (Lycoris radiata) | Alkaloid | 0.15 to 1.63 µM | - | - |
| 34. | Emetine (Cephaelis ipecacuanha) | Alkaloid | 0.12 to 1.43 µM | - | - |
| 35. | Berbamine (Berberis spp.) | Alkaloid | 1.48 to 13.14 µM | - | - |
| 36. | Tetrandrine (Stephania tetrandra) | Alkaloid | 0.29 to 12.68 µM | - | - |
| 37. | Pristimerin (Tripterygium wilfordii) | Terpenoid | 1.63 to 13.87 µM | - | - |
| 38. | Harmine (Peganum harmala) | Alkaloid | 1.90 to 13.77 µM | - | - |
| 39. | Conessine (Holarrhena floribunda) | Alkaloid | 2.34 to 11.46 µM | - | - |
| 40. | Tryptanthrin (Strobilanthes cusia) | Alkaloid | 1.52 ± 0.13 µM | Alteration of spike proteins; Inhibition of RNA-dependent RNA polymerase; papain-like protease 2 inhibition; inhibition of viral replication | HCoV-NL63 |
| 41. | Chrysin | Phenolic | 200 µM | Inhibition of (S) protein and ACE2 interaction | SARS-CoV |
| 42. | Indigotin B (Strobilanthes cusia) | Alkaloid | 2.60 ± 0.11 µM | May inhibit 3CLpro | HCoV-NL63 |
| 43. | Tetrandrine (Stephania tetrandra) | Alkaloid | 0.33 ± 0.03 µM | Inhibition of viral S and N protein | HCoV-OC43 |
| 44. | Fangchinolone (Stephania tetrandra) | Alkaloid | 1.01 ± 0.07 µM | Inhibition of viral S and N protein | HCoV-OC43 |
| 45. | Cepharanthine (Stephania tetrandra) | Alkaloid | 0.83 ± 0.07 µM | Suppression of viral replication; inhibition of viral S and N protein | HCoV-OC43 |
| 46. | Procyanidin B1 (Cinnamomi Cortex) | Flavonoid | 41.3 ± 3.4 µM | Inhibition of pseudovirus infection | SARS-CoV |
| No. | Compound Description | Chemical Class | IC₅₀ Value | Assay Details | Virus Target |
|-----|----------------------|----------------|------------|---------------|--------------|
| 47. | Procyanidin A2 (Cinnamomi Cortex) Flavonoid | Flavonoid | 29.9 ± 3.3 μM | Inhibition of pseudovirus infection | SARS-CoV |
| 48. | Cinnamomattin B1 (Cinnamomum verum) Flavonoid | Flavonoid | 32.9 ± 3.9 μM | Inhibition of pseudovirus infection | SARS-CoV |
| 49. | Silvestrol (Aglaia spp.) Phenolic | Phenolic | 3 nM | Inhibition of caps-dependent viral mRNA translation | SARS-CoV |
| 50. | Juglanin (Polygonum aviculare) Phenolic | Phenolic | 2.3 μM | Blockage of 3a channel | SARS-CoV |
| 51. | Silvestrol (Aglaia spp.) Phenolic | Phenolic | 1.3 nM | Inhibition of caps-dependent viral mRNA translation | MERS-CoV |
| 52. | Sinigrin (Isatis indigotica) Glucoside | Glucoside | 217 μM | SARS-CoV 3CLpro inhibition | SARS-CoV |
| 53. | Beta-sitosterol (Isatis indigotica) Steroid | Steroid | 1210 μM | SARS-CoV 3CLpro inhibition | SARS-CoV |
| 54. | Indigo (Isatis indigotica) Phenolic | Phenolic | 3 nM | Inhibition of cap-dependent viral mRNA translation | HCoV-229E |
| 55. | Aloe-emodin Phenolic | Phenolic | 2.3 μM | Blockage of 3a channel | SARS-CoV |
| 56. | Hesperetin Phenolic | Phenolic | 8.3 μM | SARS-CoV 3CLpro inhibition | SARS-CoV |
| 57. | Kazinol A Phenolic | Phenolic | 66.2–88.5 μM | Inhibition of 3CLpro and PLpro | SARS-CoV and MERS-CoV |
| 58. | Emodin (Rheum and Polygonum genera) Phenolic | Phenolic | 200 μM | Inhibition of SARS-CoV S protein and ACE2 interaction | SARS-CoV |
| 59. | Myricetin Flavonoid | Flavonoid | 2.71 ± 0.19 μM | Inhibition of SARS-CoV helicase | SARS-CoV |
| 60. | Scultellarein Flavonoid | Flavonoid | 0.86 ± 0.48 μM | Inhibition of SARS-CoV helicase | SARS-CoV |
| 61. | Hirsutoneone (Alnus japonica) Phenolic | Phenolic | 4.1 ± 0.3 μM | Inhibition of SARS-CoV PLpro | SARS-CoV |
| 62. | Hirsutanonol (Alnus japonica) Phenolic | Phenolic | 7.8 ± 1.7 μM | Inhibition of SARS-CoV PLpro | SARS-CoV |
| 63. | Oregonin (Alnus japonica) Phenolic | Phenolic | 20.1 ± 2.2 μM | Inhibition of SARS-CoV PLpro | SARS-CoV |
| 64. | Rubralin (Alnus japonica) Phenolic | Phenolic | 12.3 ± 0.9 μM | Inhibition of SARS-CoV PLpro | SARS-CoV |
| 65. | Rubranoside B (Alnus japonica) Phenolic | Phenolic | 8.0 ± 0.2 μM | Inhibition of SARS-CoV PLpro | SARS-CoV |
| 66. | Rubranoside A (Alnus japonica) Phenolic | Phenolic | 9.1 ± 1.0 μM | Inhibition of SARS-CoV PLpro | SARS-CoV |
| 67. | Quercetin-3-β-galactoside Flavonoid | Flavonoid | 42.79 ± 4.97 μM | Competitive inhibition of SARS-CoV 3CLpro | SARS-CoV |
| 68. | Quercetin Flavonoid | Flavonoid | 23.8 ± 1.9 μM | Inhibition of SARS-CoV 3CLpro | SARS-CoV |
| 69. | Betulinic acid Terpenoid | Terpenoid | 10 μM | Competitive inhibition of SARS-CoV 3CLpro | SARS-CoV |
| 70. | Betulonic acid Terpenoid | Terpenoid | >100 μM | Inhibition of SARS-CoV 3CLpro | SARS-CoV |
| 71. | Hinokinin Lignoid | Lignoid | >100 μM | Inhibition of SARS-CoV 3CLpro | SARS-CoV |
| 72. | Savinin Lignoid | Lignoid | 25 μM | Competitive inhibition of SARS-CoV 3CLpro | SARS-CoV |
| 73. | Curcumin Phenolic | Phenolic | 40 μM | SARS-CoV 3CLpro inhibition | SARS-CoV |
| 74. | Broussochalcone B Phenolic | Phenolic | 11.6–112.9 μM | Inhibition of 3CLpro and PLpro | SARS-CoV and MERS-CoV |
| 75. | Broussochalcone A Phenolic | Phenolic | 9.2–88.1 μM | Inhibition of 3CLpro and PLpro | SARS-CoV and MERS-CoV |
| 76. | 4-hydroxyisolonchocarpin Phenolic | Phenolic | 35.4–202.7 μM | Inhibition of 3CLpro and PLpro | SARS-CoV and MERS-CoV |
| 77. | Papyriflavonol A Phenolic | Phenolic | 3.7–112.5 μM | Inhibition of 3CLpro and PLpro | SARS-CoV and MERS-CoV |
| 78. | Tannic acid Phenolic | Phenolic | 3 μM | SARS-CoV 3CLpro inhibition | SARS-CoV |
| 79. | 3-isotheaflavin-3-gallate Phenolic | Phenolic | 7 μM | SARS-CoV 3CLpro inhibition | SARS-CoV |
| 80. | Theaflavin-3,3'-digallate Phenolic | Phenolic | 9.5 μM | SARS-CoV 3CLpro inhibition | SARS-CoV |
| 81. | Theaflavin Phenolic | Phenolic | 56 μM | SARS-CoV 3CLpro inhibition | SARS-CoV |
| 82. | Theaflavin-3-gallate and Theaflavin-3'-gallate Phenolics | Phenolics | 43 μM | SARS-CoV 3CLpro inhibition | SARS-CoV |
| 83. | Apigenin Phenolic | Phenolic | 280.8 ± 21.4 μM | Inhibition of SARS-CoV 3CLpro | SARS-CoV |
| 84. | Kazinol J Phenolic | Phenolic | 15.2–109.2 μM | Inhibition of 3CLpro and PLpro | SARS-CoV and MERS-CoV |
| No. | Compound                        | Class   | IC₅₀ (µM) | Activity                          |
|-----|--------------------------------|---------|-----------|----------------------------------|
| 85  | 18-hydroxyferruginol           | Terpenoid| 220.8 ± 10.4 | Inhibition of SARS-CoV 3CL<sup>107</sup> |
| 86  | Hinokiol                       | Terpenoid| 233.4 ± 22.2 | Inhibition of SARS-CoV 3CL<sup>107</sup> |
| 87  | Ferruginol                     | Terpenoid| 49.6 ± 1.5   | Inhibition of SARS-CoV 3CL<sup>107</sup> |
| 88  | 18-oxoferruginol               | Terpenoid| 163.2 ± 13.8 | Inhibition of SARS-CoV 3CL<sup>107</sup> |
| 89  | O-acetyl-18-hydroxyferruginol  | Terpenoid| 128.9 ± 25.2 | Inhibition of SARS-CoV 3CL<sup>107</sup> |
| 90  | Methyl dehydroabietate         | Terpenoid| 207.0 ± 14.3 | Inhibition of SARS-CoV 3CL<sup>107</sup> |
| 91  | Isopimaric acid                | Terpenoid| 283.5 ± 18.4 | Inhibition of SARS-CoV 3CL<sup>107</sup> |
| 92  | Kayadiol                       | Terpenoid| 137.7 ± 12.5 | Inhibition of SARS-CoV 3CL<sup>107</sup> |
| 93  | Amentoflavone                  | Flavonoid| 8.3 ± 1.2   | Non-competitive inhibition of SARS-CoV 3CL<sup>107</sup> |
| 94  | Bilobetin                      | Flavonoid| 72.3 ± 4.5   | Non-competitive inhibition of SARS-CoV 3CL<sup>107</sup> |
| 95  | Ginkgetin                      | Flavonoid| 32.0 ± 1.7   | Non-competitive inhibition of SARS-CoV 3CL<sup>107</sup> |
| 96  | Sciadopitysin                  | Flavonoid| 38.4 ± 0.2   | Non-competitive inhibition of SARS-CoV 3CL<sup>107</sup> |
| 97  | Abietic acid                   | Terpenoid| 189.1 ± 15.5 | Inhibition of SARS-CoV 3CL<sup>107</sup> |
| 98  | Kazinol F                      | Phenolic | 39.5–135.0 µM | Inhibition of 3CL<sup>107</sup> and PL<sup>142</sup> |
| 99  | Luteolin                       | Flavonoid| 20.0 ± 2.2   | Inhibition of SARS-CoV 3CL<sup>107</sup> |
| 100 | Kazinol B                      | Phenolic | 31.4–233.3 µM | Inhibition of 3CL<sup>107</sup> and PL<sup>142</sup> |
| 101 | Broussosflavan A               | Phenolic | 49.1–125.7 µM | Inhibition of 3CL<sup>107</sup> and PL<sup>142</sup> |
| 102 | Celastrol                      | Terpenoid| 10.3 ± 0.2   | Competitive inhibition of SARS-CoV 3CL<sup>130</sup> |
| 103 | Pristimerin                    | Terpenoid| 5.5 ± 0.7    | Competitive inhibition of SARS-CoV 3CL<sup>130</sup> |
| 104 | Tingenone                      | Terpenoid| 9.9 ± 0.1    | Competitive inhibition of SARS-CoV 3CL<sup>130</sup> |
| 105 | Iguesterin                     | Terpenoid| 2.6 ± 0.3    | Competitive inhibition of SARS-CoV 3CL<sup>130</sup> |
| 106 | 3’-(3-methylbut-2-enyl)-3’,4,7- | Phenolic | 30.2–48.8 µM | Inhibition of 3CL<sup>142</sup> and PL<sup>142</sup> |
| 107 | Corylifol                      | Phenolic | 32.3 ± 3.2 µM | Inhibition of PL<sup>143</sup> |

Figure 4: Class of phytocompounds studied against HCoVs.
CONCLUSION AND PERSPECTIVES

Quite an array of plants, either whole, extract or plant metabolites, have shown great potential as antiviral agents and moieties. Potent antiviral phytochemical groups identified include saponins, tannins, lignans, alkaloids, flavonoids, lectins, coumarins, terpenoids, peptides and proteins. It therefore seems reasonable to suggest that the world should look to plants for novel natural compounds and antivirals. In addition to the possibility of harnessing natural phytochemicals for new pharmaceuticals development, plant metabolites could also become more efficacious when utilized in form of combination therapies with existing drug interventions. Increased research into plants and in-depth characterization of their metabolites could uncover more interesting results that would benefit humanity in its fight against emerging and re-emerging viral coronavirus infections such as the current COVID-19. Even though some promising compounds remain under clinical trials, the use of medicinal plants as prophylaxis or treatment interventions in viral respiratory infections should not be undermined. Also, with the recent speculation that, some of the target proteins of SARS-CoV-2 bind to and displaces oxygen from β-chain of the hemoglobin which subsequently results in hemotoxicity and inflammation of the alveolar macrophages, it could be logically suggested that blood purifiers including those of plant origin may offer complementary benefits against COVID-19. This speculation could support the touted efficacy of chloroquine for COVID-19 as it could compete for binding on the porphyrin of the hemoglobin in a manner that may prevent SARS-CoV-2 protein from binding. While this calls for further submission to substantiate the claim, metabolites with the ability to purify the blood and inhibit inflammation and oxidative stress could also be possible interventions for the prevention of COVID-19. Of recent, Van Vuuren and Frank reported Southern African medicinal plants that can be used for blood purifications. Interestingly, some of the plants reported have also been validated for antiviral, inflammatory, and antioxidant activities which make them probable candidates for the management of COVID-19. Some of the plants are Bridelia micrantha, Bulbine latifolia var. latifolia, Burchella bubalina, Crinum moorei, Cymbopogon validus, Eleuca natalensis, Polygona virginia, Polygnum hystriculium, Salix mucronate, Scadoxus puniceus, Schotia brachypetala, Tropaeolum majus, Vitellarioopsis marginata, and Zanthoxylum capscums. Overall, given the current body of evidence on the potential development of phytodrugs or phytomedicines for COVID-19, fears need to be allayed while clinical trials continue. The lockdown and other preventive measures which have been implemented in most parts of the world should be humanely exercised and supported with palliatives to ensure effectiveness and compliance. Increased awareness and update on developments should also be engaged in through all possible and genuine media. However, after aligning with all possible measures, one can only hope for the best possible outcome in a not-so-distant future. But will the world ever remain the same again? Time will tell.

CONFLICTS OF INTEREST

No conflict of interest exists among authors.

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