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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.

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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-Infectious 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'[6], but only accepted as a new genus of viruses in 1975.[7] While the initial classification of the genus was mainly based on microscopic examination,[8] 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.[9] 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,[10,11] and can diffuse among mammals and humans.[12] This large genome confers them with high recombination rates by constantly developing transcription error and RNA-Dependent-RNA-polymerase (RdRP) jumps.[13] 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 assembly[14] (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

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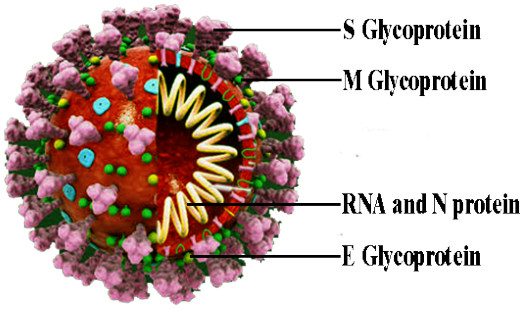


Figure 1: Representation of a typical coronavirus depicting essential structural proteins.

territory. This was reportedly caused by the CoV called SARS-CoV that caused significant epidemic claiming almost a thousand deaths and lasted till 2003.[15, 16] Generally, CoVs constitute a genus within the family Coronaviridae, order Nidovirales and subfamily Orthocoronavirinae.[17] 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.[18] 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.[19] 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.[20,21]

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.[17] 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.[22]

Generally, although, CoV infections are controllable, there remains the possibility of sporadic new cases if humans continue to encounter their animal hosts.[23, 24] 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.[25,26] While, ethnomedicinal plants have been shown to possess antiviral activity over the years, .[27-30] the demand for new antivirals continue to exist and increase given the increasing prevalence and emergence of novel viral infections like human immunodeficiency virus (HIV) and SARS-CoV. This article, therefore, 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 CoVs and the current global challenge of COVID-19.

MATERIALS AND METHODS

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.[14] 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.[31] 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.[32-34]

For CoVs, the S glycoprotein has two subunits (S1 and S2) and has been reportedly 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),

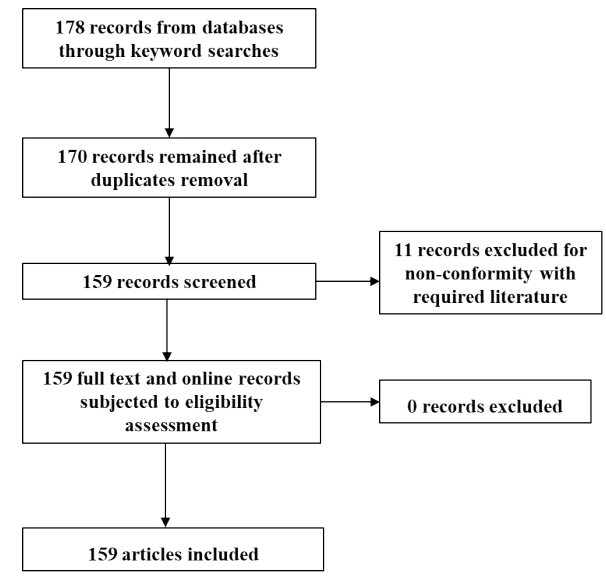


Figure 2: PRISMA flow chart showing total records, screened, included and excluded materials for this review.

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.[35] To facilitate entry, the S1-CTD of MERS-CoV and SARS-CoVs interact with dipeptidyl peptidase 4 (DPP4)[36] and angiotensin-converting enzyme 2 (ACE2), respectively.[37] 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.[36] 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.[38] 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′-UUUAAAC-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),[37] 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,[32] 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,[31] 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.[34] 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

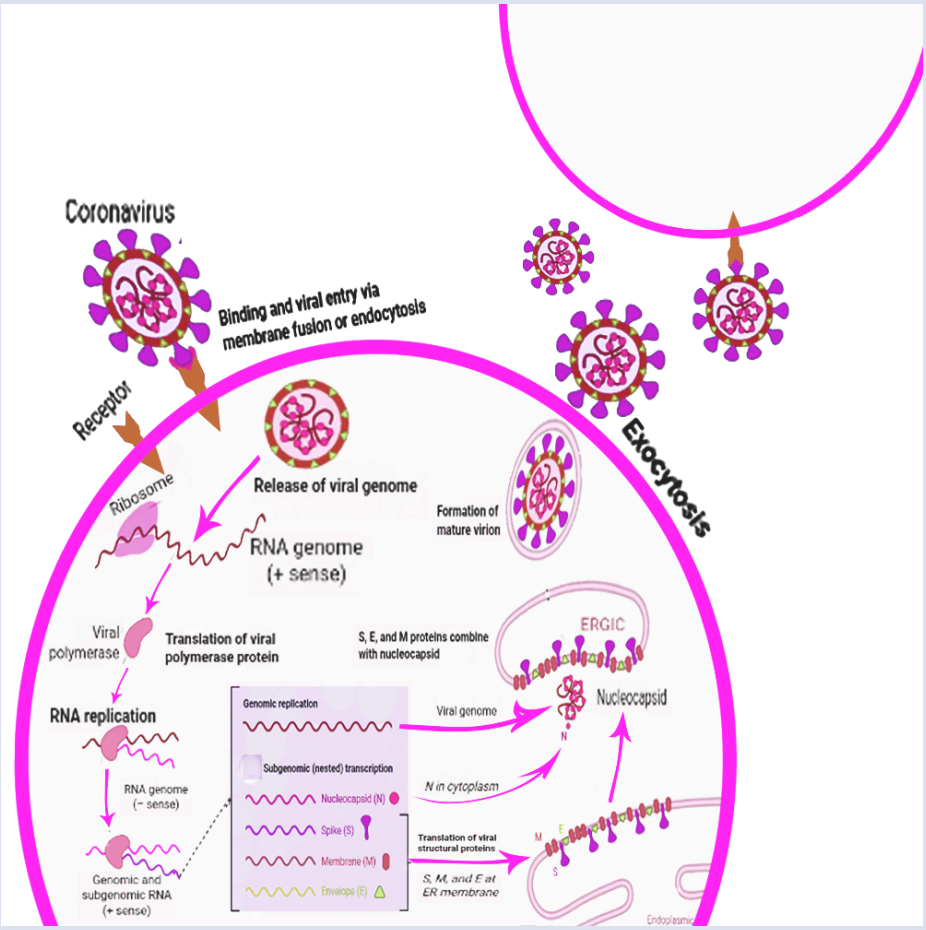


Figure 3: Schematic illustration of the mode of transmission and life cycle of representative HCoVs. The life cycle usually begins with viral entry initiated by interaction of S protein with specific host-cell receptor, and subsequent entry into the host's cell. This is succeeded by replicase protein expression and replication of the viral particles. Thereafter, the structural proteins (N, S, E, and M) are translated, inserted into the endoplasmic reticulum (ER) and subsequently moved to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). The new virion is assembled and then released by exocytosis to continue possible new cycle.

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 Civet	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

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.[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 to market probability. In addition, early drug developmental phases and drug-interaction properties from animal models used in pre-clinical trials are readily available.[41-42]

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.[19] Some notable examples of BSAAs include emetine (an antiprotozoal capable of inhibiting HCoV-OC43, Zika and Ebola viruses and HIV-1 infections), enoxacin (anti-Zika and anti-HIV-1),[43] amodiaquine (antimalarial and anti-Zika),[44] and niclosamide (anthelminthic and anti-Zika).[45-48] Several other BSAAs including chloroquine, azithromycin, cyclosporine, rapamycin, mycophenolic acid, ezetimibe and nitazoxanide are currently undergoing phase IV surveillance studies under this concept.[19] 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.[19]

Another therapeutic is the cyclooxygenase (COX) mediator/inhibitor, indomethacin. Indomethacin/indocin has been shown to be an effective inhibitor of SARS-CoV-2 *in vitro*.[49] It is a non-steroidal anti-inflammatory drug (NSAID) with good antiviral potential against canine CoV *in vivo*.[49] It also showed similar potential against human SARS-CoV.[16] In a study involving canine models, the faecal 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.[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 (3CLpro) 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 *in vitro* inhibition of SARS such as calpain inhibitors, valinomycin,[50] glycopeptide antibiotics, nelfinavir,[51] plant lectins, aurintricarboxylic acid and hesperetin[52] could be subjected to further studies targeting SARS-CoV-2. Other identified anti-SARS-CoV agents include HIV protease inhibitors,[53] anthraquinone-based compound,[54] carbohydrate-binding agents,[55] an antipsychotic[54] and a nucleoside analogue.[56] Hsieh et al.[57] further expanded the list from their report on the successful test of a combination therapy that involved nelfinavir and agglutinin from *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 *in vivo*[58] and its efficacy in SARS-CoV infection has been demonstrated since 2004.[53]

Agglutinin from *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.[59] 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.[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 future studies toward a new drug development target for the treatment of pathogenic HCoVs including SARS-CoVs.[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.[61,62] Another oral pill intervention being tested is favipiravir known as Avigan and is favoured over remdesivir which is intravenously injected.[63] Other promising antiviral drugs undergoing test and clinical trials include SPL7013 from Starpharm, an antiviral dendrimer,[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.[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.[66] With regards to vaccines for SARS-CoV-2, the National Institute of Allergy

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-CoV2 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.[69] 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.[69,71] Another antimalarial drug, artemisinin is obtained from *Artemisia annua*.[72] Again, while emetine, an amoebicidal drug is obtained from *Cephaelis ipecacuanha*, others such as quinidine, topotecan, taxol, morphine, aspirin, digitalis and colchicine are derived and developed from herbal plants.[69,73-75] Although, modern pharmaceuticals are effective for the management and treatment of various viral diseases, the emergence of antiviral-resistant mutants and occurrence of novel viral strains (e.g. SARS-CoV-2) with no known effective cure and vaccine, have undermined their applications.[38,76] Moreover, some antiviral drugs are expensive, toxic and not broad-spectrum based. Hence, there is a continuous demand for novel, highly potent, less toxic and cost-effective antivirals which could be proficiently fulfilled by medicinal plants.

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*, *Pyrrossia 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.[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, infectivity, reverse transcription, protein expression, assembly, release or host-specific interactions.[32,79]

Interestingly, traditional or herbal medicine has been previously employed to treats 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-workers[77] evaluated the antiviral potential of liquorice roots-derived compounds such as ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid 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 (EC_{50}) 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 theaflavin,[84] water soluble tannic acid and theaflavin3-gallate[85] which contribute to its antiviral function against rotavirus and SARS-CoV. *Eleutherococcus senticosus* containing theaflavin and catechin has also been shown to be effective against rotavirus and HCoVs.[84,86] Glycyrrhizin is also a good inhibitor of hepatitis B virus; it is capable of stimulating endogenous production of interferons and with remarkable antioxidant activity.[87] Similarly, a further study by Hoever and co-workers[88] 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.[88]

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 aescin and reserpine, with EC_{50} values of 6.0 μM and 3.4 μM, respectively.[50] Similarly, baicalin, a flavonoid from another traditional Chinese medicine, *Scutellaria baicalensis* has also been reported to possess anti-SARS-CoV activity.[89] Furthermore, the anti-HCoV-229E activity of glucosidic compounds, saikosaponins (A, B_2, C and D) has been shown. The strongest potency was displayed by saikosaponin B_2 and its mechanism of action was attributed to the interference of early stages of viral replication such as viral attachment, adsorption and penetration.[90] In another study by Yi and co-workers[91] that involved the screening of small molecules from 121 Chinese herbs extracts resulted in the identification of two molecules, tetra-O-galloyl-β-d-glucose (TGG) and luteolin from *Galla chinensis* and *Rhodiola kirilowii*, respectively with substantial effects on SARS-CoV. 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.[91] A high throughput screening of 200 Chinese medicinal herb extracts has demonstrated the significant anti-SARS-CoV activity of *Lycoris radiata* (ethanolic extract), *Artemisia annua* (ethanolic extract), *Pyrrosia lingua* (chloroform extract), and *Lindera aggregata* (ethanolic extract) with EC_{50} 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* (EC_{50}: 2.4 ± 0.2 μg/ml) resulted in the isolation of the active ingredient of the herb, lycorine with EC_{50} of 15.7 ± 1.2 mM. Its remarkable SI value greater than 900 also makes it a good lead compound for future drug design.[78]

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.[92] The study demonstrated that ten diterpenoids which include ferruginol, dehydroabieta-7-one, sugiol, cryptojaponol, 8β-hydroxyabieta-9(11),13-dien-12-one, 7β-hydroxydeoxycryptojaponol, 6,7-dehydroroyleanone, 3β-,12-diacetoxyabieta-6,8,11,13-tetraene, pinusolidic acid, forskolin; two sesquiterpenoids viz., cedrane-3β,12-diol, α-cadinol; two triterpenoids namely betulinic acid, betulonic acid; five lignoids hinokinin, savinin, 4,4′-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 4,4′-O-benzoylisolariciresinol markedly inhibited SARSCoV replication. Moreover, the SI values of ferruginol (SI: 58), dehydroabieta-7-one (SI: 76.3), 8β-hydroxyabieta-9(11),13-dien-12-one (SI: >510), 7β-hydroxydeoxycryptojaponol (SI: 111), 3β-,12-diacetoxyabieta-6,8,11,13-tetraene (SI: 193), pinusolidic acid (SI: >159), forskolin (SI: 89.8), betulonic acid (SI: 180), and savinin (SI: >667) were higher than that of the positive control (valinomycin, SI: 41.4) used in the study, thus highlighting their potential as good lead compounds.

In some study, an aqueous extract of the leaf of *Toona sinensis*

Table 2: Medicinal plants with anti-coronaviral potential.

SN	Plant	Family	Plant part	Extract	Metabolite or extract (Dose)	EC_{50}	Proposed mechanism	HCoV	Reference
1.	*Artemisia annua*	Asteraceae	Whole plant	Ethanol	Artemisinin (10^{-1} - 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)	88.2 ± 7.7 µg/ml	Unclear	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 cortex	Ethanol	Lycorine (10^{-1} - 10^{-4} mg/ml) Lycorine (0 – 20 µM)	2.4 ± 0.2 µg/ml 0.15 to 1.63 µM	Unclear	SARS-CoV HCoV-OC43, HCoV-NL63, MERS-CoV, MHV-A59	78 99
8.	*Pyrrosia 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	100
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, 93
14.	*Pelargonium sidoides* DC.	Geraniacea	Root	Na	Catechin and gallocatechin (Na)	Na	Inhibit replication of H1N1, H3N2 virus strains, respiratory syncytial virus, and human coronavirus	SARS-CoV	95, 104
15.	*Rheum officinale* Baill	Taxaceae	Root tubers	Aqueous	Emodin (Na)	Na	Inhibited the interaction of SARS-CoVS protein and ACE2	SARS-CoV	54
16.	*Polygonum multiflorum* Thunb. *Polygonum aviculare*	Polygonaceae	Root tuber and vine	Aqueous	Emodin (Na) Juglanin (10 - 40 µM)	200 µM 2.3 µM	Inhibited the interaction of SARS-CoVS protein and ACE2	SARS-CoV	54 105
17.	*Anthemis hyaline* DC.	Asteracaea	Flower and bud	Ethanol	Flavanoids. (Na)	Na	Inhibit the replication and expression of coronavirus and TRP gene	SARS-CoV	98
18.	*Nigella sativa* L.	Ranunculaceae,	Seed	Ethanol	Thymoquinon, α- Hederin and Nigellidine (Na)	Na	Inhibit the replication and expression of coronavirus and TRP gene	SARS-CoV	98, 106

19.	*Citrus sinensis* (L.) Osbeck	Rutacaea	Peel	Ethanol	Carvacrol and α-pinene (Na)	Na	Inhibit the replication and expression of coronavirus and TRP gene	SARS-CoV	[98]
20.	*Torreya nucifera* (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. *Phyllanthus urinaria*	Euphorbiaceae Phyllanthaceae	Leaf	Ethanol	Triterpenoids (0 - 25 μM), flavonoid glycoside (Na). Hinokinin (0 –-10 μM)	Na	Virucidal activity	HCoV	[97, 108] [92]
22.	*Isatidis indigotica*	Brassicaceae	Root	Aqueous	Sinigrin, Indigo, β-sitosterol and Aloe-emodin (Na), Hesperetin (Na)	Na	anti-SARS-CoV 3CLpro	SARS-CoV	[78, 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 *Aesculus hippocastanum* *Rauwolfia species*	Araliaceae	Root	Na	Ginsenoside-Rb1. (Na) Aescin (0 - 20 μM) Reserpine (0 - 20 μM)	100 μM 6.0 μM 3.4 μM	Inhibition of viral replication	SARS-CoV	[50]
25.	*Cinnamomum* sp.	Lauraceae	Cortex	Na	Procyanidin B1 (0 – 500 μM) Procyanidin A2 (0 – 500 μM) Cinnamtannin B1 (0 – 500 μM)	41.3 ± 3.4 μM 29.9 ± 3.3 μM 32.9 ± 3.9 μM	Inhibition of pseudovirus infection	SARS-CoV	[109]
26.	*Curcuma longa* (Tumeric)	Zingiberaceae	Rhizome	Na	Curcumin (0 – 10 μM)	>10 μM	Viral replication inhibition	SARS-CoV	[92]

Na = Not available

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.[91,93] 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 anti-SARS-CoV activities of more than 200 Chinese medicinal herbs' extracts was conducted by Wen and co-workers.[96] The study reported significant anti-SARS-CoV activity of six extracts from *Cassia tora, Cibotium barometz, Gentiana scabra*, *Dioscorea batatas,* and *Taxillus chinensis* 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 *Cibotium barometz* and *Dioscorea batatas* elicited the most significant effect and thus confirming their probable therapeutic potential in the treatment of SARS-COVs.

In 2012, Chang *et al*. reported the presence of triterpenoids in *Euphorbia neriifolia* L. and had anti-HCoV potential.[97] Found in Pingtung, Taiwan in the South-eastern region of Asia, the ethanolic leaf extract of *Euphorbia neriifolia* revealed the presence of 22 triterpenoids and a flavonoid glycoside, and thirteen of these compounds were identified for the first time in *E. neriifolia*. Of the triterpenoids, 3β-Friedelanol and friedelane derivatives demonstrated the highest antiviral potential against HCoV. The study concluded that, due to the structure-activity relationship, the friedelane skeleton could serve a potential scaffold in the evolution and synthesis of novel anti-HCoV-229E medications. Ulasli et al.[98] also reported the efficacy of *Anthemis hyalina*, *Citrus sinensis*, and *Nigella sativa* in the management of HCoV infection. The extracts from the three investigated plants inhibited the replication and expression of CoV and TRP gene, respectively.

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 MHV-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 poliomyelitis virus, herpes simplex virus 1, Bunyamwera virus, and West Nile virus.[110-112] Very recently, the anti-HCoV-NL63 activity of a traditional Chinese medicine, *Strobilanthes cusia* (IC_{50}: 0.64 μg/ml) has been reported. Its derivatives such as tryptanthrin and indigodole B are also potent inhibitors of HCoV-NL63 replication with IC_{50} values of 1.52 and 2.60 μM, respectively.[100] The plant and its two derivatives also exhibited significant virucidal effects on HCoV-NL63. The mechanistic effects of tryptanthrin was via the alteration of spike proteins and inference with viral enzymes (e.g. RNA-dependent RNA polymerase, papain-like protease 2) that are involved in viral (HCoV-NL63) RNA genome synthesis, late stages of replication, and production of virus progeny.[100] Furthermore, this phytocompound has also been reported to possess remarkable anti-neuroinflammatory, hepatoprotective, antitumor (leukemia, breast and colon cancer cells), and antimicrobial properties.[113-115]

A recent meta-analysis study of medicinal plants has also lent credence and suggested that further assays aimed at tackling SAR-CoV-2 and other CoVs could be done on thistle, barley, sundew, and *Ficus* sp.[116] Another docking study showed the potential of *Citrus* sp., galangal (*G. nivalis*), sappan wood (*Biancaea sappan*), and *Curcuma* sp. for use in prophylaxis against SAR-CoV-2.[117] Also, *in silico* studies have further showed that 13 natural compounds from Chinese traditional medicine databases had anti-SARS-CoV-2 potential. The compounds were sugiol, kaempferol, cryptotanshinone, moupinamide, coumaroyltyramine, quercetin, dihomo-γ-linolenic acid, dihydrotanshinone, desmethoxyreserpine, lignan, tanshinone IIa, N-cis feruloyltyramine and betulinic acid.[17]

Saposhnikovia divaricata coumarins, phloroglucinols of *Dryoteris crassirhizoma* and oleanane triterpenes derived from *Camellia japonica* flowers also demonstrated antiviral potential against porcine epidemic diarrhoea virus (PEDV), a member of the Coronaviridae family.[118,119] The replication pathway in PEDV are similar to human CoVs. In other words, vaccines for MERS and PEDV could be based on similar theory[120, 121] such that the compounds reported in medicinal plant species studied by Yang et al.[119] could become promising candidates for further research to better tackle fatal HCoVs. Also, anti-HCoV-22E9 potential of saikosaponin A, B2, C and D expressed from medicinal *Scrophularia scorodonia*, *Heteromorpha* and *Bupleurum* species have been demonstrated to prevent viral attachment and penetration *in vitro*. These compounds could be repurposed for SARS-CoV-2.[90] Other potential plants believed to fight viral respiratory infections include *Pelargonium sidoides* (African geranium), *Andrographis paniculata* (kalmegh) and fruit of *Sambucus nigra* (black elder).[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^{pro}) – a cysteine protease, which is important for viral replication, transcription and subsequent maturation; papain-like protease (PL^{pro}) – essential for translation and deubiquitination; and spike protein (S) – which is indispensable for host cell entry.[122-125] 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. Phytocompounds such as hesperetin, sinigrin, indigo, β-sitosterol, hirsutenone, emodin, myricetin and tannic acid have been reported to exhibit anti-coronaviral properties through their modulatory effect on HCoV target proteins.[85,126]

A study by Lin and co-workers[126] reported the anti-SARS-CoV 3CL^{pro} potential of aqueous extract of *Isatidis indigotica*. The same study was further expanded to screen five major compounds of *I. indigotica* root extract (indigo, indirubin, indican, sinigrin, and β-sitosterol) and seven other plant-derived phenolic compounds including aloe-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_{50}) of 8.3 μM, other compounds such as sinigrin, indigo, β-sitosterol, and aloe-emodin also exerted remarkable inhibitory effects with IC_{50} values ranging from 217 to 1210 μM. Chen and co-workers[85] have also highlighted the anti-SARS CoV 3CL^{pro} properties of three phenolic compounds from black tea which include tannic acid, 3-isotheaflavin-3-gallate, and theaflavin-3,3'-digallate with IC_{50} values of 3, 7 and 9.5 μM, respectively. The study noted the better inhibitory effect of 3-isotheaflavin-3-gallate and theaflavin-3,3'-digallate against the protease than theaflavin; this observation was attributed to the absence of gallate group in theaflavin. Findings of this study also demonstrated the significant SARS CoV 3CL^{pro} inhibitory activity of black tea (IC_{50}: 70 μg/ml) and Puer tea (IC_{50}: 25 μg/ml) compared to oolong and green tea (IC_{50}: 125 μg/ml).[85]

In another study, the anti-SARS CoV 3CL^{pro} activity of a phenolic compound, curcumin (IC_{50}: 40 μM); two triterpenoids, betulinic acid (IC_{50}: 10 μM), betulonic acid (IC_{50}: >100 μM); and two lignoids, hinokinin (IC_{50}: >100 μM), savinin (IC_{50}: 25 μM) has been demonstrated.[92] Another phenolic compound, quercetin-3-β-galactoside and some of its derivatives have been identified as potent inhibitors of SARS-CoV 3CL^{pro} through a series of molecular docking and enzyme inhibition assays. The findings further demonstrated that although residue Gln189 of SARS-CoV 3CL^{pro} plays indispensable role in its interaction with quercetin-3-β-galactoside, its mutation does not affect the enzymatic activity of the protease.[127] Quercetin also possesses significant anti-murine coronaviral activity.[128] Findings of Wen and co-workers[96] have shown the anti-SARS CoV 3CL^{pro} activity of extracts of *Cibotium barometz* (Rhizoma Cibotii) and *Dioscorea batatas* (Dioscoreae Rhizoma) with IC_{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^{pro} property as well as considerable immune-stimulatory effect via the increment of $CD4^+$ and $CD8^+$.[103]

Out of the 312 Chinese medicinal herbs screened by Ho and co-workers,[54] only three herbs, *Rheum officinale* Baill. (root tuber), *Polygonum multiflorum* Thunb. (root tuber) and *P. multiflorum* Thunb. (vine) displayed considerable inhibition of SARS-CoV S protein and angiotensin converting enzyme type 2 (ACE2) interaction with IC_{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_{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.[54] 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.[129]

The anti-SARS-CoV 3CL^{pro} property of ethanol extract of *Torreya nucifera* leaves has been reported.[107] 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 kayadiol (8)] and four biflavonoids [amentoflavone (9), bilobetin (10), ginkgetin (11), and sciadopitysin (12)] with anti-SARS-CoV 3CL^{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_{50} values ranging from 8.3 to 72.3 μM, the diterpenoids also exerted considerable inhibitory effects with IC_{50} values ranging from 49.6 to 283.5 μM. Three other flavonoids viz., luteolin, quercetin and apigenin anti-SARS CoV 3CL^{pro} activity was also demonstrated with IC_{50} values of 20, 23.8 and 280.8 μM, respectively.[107] In a similar study, four triterpenes from *Tripterygium regelii* namely celastrol, pristimerin, tingenone, and iguesterin inhibited 3CL^{pro} activity with IC_{50} values of 10.3, 5.5, 9.9, and 2.6 μM, respectively.[130] Similarly, a study by Yu and co-workers[131] has reported the antiviral activity (via the inhibition of SARS-CoV helicase protein) of two flavonoids, myricetin and scutellarein with IC_{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 diarylheptanoid's molecules (polyphenols). Six out of the polyphenolic compounds namely hirsutenone, hirsutanonol, oregonin, rubranol, rubranoside B and rubranoside A exerted significant dose-dependent inhibitory effect against SARS-CoV PL^{pro}. It is worthwhile that the biological activity of these molecules was greatly impacted by their chemical structures with most remarkable effect (IC_{50}: 4.1 μM) exerted by hirsutenone which contains an α, β-unsaturated carbonyl group with a catechol moiety.[132] The remarkable interactions of natural myricetin and scutellarein flavonoids targeting viral helicase [SARS CoV (SCV) helicase-nsP13][133] could be seen as another promising lead for future anti-SARS-CoV medications.

A flavonoid scaffold of rhoifolin, herbacetin and pectolinarin have been shown to significantly inhibit the 3CLpro of SARS-CoV. Molecular

docking studies indicated that the flavonoids bind with the spike S1, S2 and S3' protein sites.[134] Antiviral flavonoids found in vegetables and fruits such as kaempferol[105, 135] and daidzein, quercetin, puerarin, epigallocatechin, gallocatechin gallate, epigallocatechin gallate[136] have shown anti-SARS-CoV 3CLpro activity. Phenolics in *Isatis indigotica*,[78, 79] and the aqueous extract of *Houttuynia cordata*[103] also showed SARS-CoV 3CLpro inhibition. A recent study by Runfeng and co-workers[137] noted the inhibitory activity of lianhuaqingwen, a traditional Chinese medicine formula composing of 13 herbs against the most recent SARS-CoV-2 with IC_{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.[137] 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.[138]

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 schtschegleevi* (hedge nettle), 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.[102] 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 infection.[102]

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, dimethylprotobioside. The latter is an anti-mitotic 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.[139] In another development with the recent advancement in bioinformatics, Salim and Noureddine[106] studied the molecular docking of the metabolites isolated from *Nigella sativa* as a potential COVID-19 inhibitor. They found out that α-hederin and nigellidine, 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, Fig. 4) and several other classes of phytonutrients 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^{50} or EC_{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 $3CL^{pro}$	SARS-CoV	77
3.	Reserpine (*Aesculus hippocastanum*)	Alkaloid	3.4 μM	May inhibit $3CL^{pro}$	SARS-CoV	50
4.	Aescin (*Rauwolfia* species)	Saponin	6.0 μM	May inhibit $3CL^{pro}$	SARS-CoV	50
5.	Lianhuaqingwen	Chinese medicine formula	411.2 μg/ml	May inhibit $3CL^{pro}$	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 $3CL^{pro}$	SARS-CoV	92
9.	Dehydroabieta-7-one (*Chamaecyparis obtusa* var. *formosana*)	Terpenoid	4.00 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
10.	Sugiol (*Chamaecyparis obtusa* var. *formosana*)	Terpenoid	-	-	SARS-CoV	92
11.	Cryptojaponol (*Cryptomeria japonica*)	Terpenoid	>10 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
12	8β-hydroxyabieta-9(11),13-dien-12-one (*Chamaecyparis obtusa* var. *formosana*)	Terpenoid	1.47 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
13.	7β-hydroxydeoxycryptojaponol (*Cryptomeria japonica*)	Terpenoid	1.15 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
14.	6,7-dehydroroyleanone (*Chamaecyparis obtusa* var. *formosana*)	Terpenoid	5.55 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
15.	3β-,12-diacetoxyabieta-6,8,11,13-tetraene (*Juniperus formosana*)	Terpenoid	1.57 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
16.	Pinusolidic acid (*Chamaecyparis obtusa* var. *formosana*)	Terpenoid	4.71 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
17.	Forskolin (*Coleus forskohlii*)	Terpenoid	7.5 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
18.	Cedrane-3β,12-diol (*Juniperus formosana*)	Terpenoid	>10 μM	May inhibit $3CL^{pro}$	SARS-CoV	92

19.	α-cadinol (*Chamaecyparis obtusa* var. *formosana*)	Terpenoid	4.44 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
20.	Betulinic acid (*Betula pubescens*)	Terpenoid	>10 μM	May inhibit $3CL^{pro}$ and S protease	SARS-CoV	92
21.	Betulonic acid (*Juniperus formosana*)	Terpenoid	0.63 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
22.	Hinokinin (*Chamaecyparis obtusa* var. *formosana*)	Lignoid	>10 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
23.	Savinin (*Chamaecyparis obtusa* var. *formosana*)	Lignoid	1.13 μM	May inhibit $3CL^{pro}$ and S protease	SARS-CoV	92
24.	4,4′ -O-benzoylisolariciresinol (Synthetic liganoid)	Lignoid	-	-	SARS-CoV	92
25.	Honokiol (*Magnolia* spp.)	Lignoid	6.50 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
26.	Magnolol (*Magnolia* spp.)	Lignoid	3.80 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
27.	Curcumin (*Curcuma longa*)	Phenolic	>10 μM	May inhibit $3CL^{pro}$	SARS-CoV	92
28.	Baicalin (*Scutellaria baicalensis*)	Flavonoid	12.5 to 25 μg/ml	-	SARS-CoV	89
29.	Saikosaponin A (*Bupleurum* spp.)	Saponin	8.6 ± 0.3 μM	May inhibit $3CL^{pro}$	HCoV-229E	90
30.	Saikosaponin B_2 (*Bupleurum* spp.)	Saponin	1.7 ± 0.1 μM	May inhibit $3CL^{pro}$ and S protease	HCoV-229E	90
31	Saikosaponin C (*Bupleurum* spp.)	Saponin	19.9 ± 0.1 μM	May inhibit $3CL^{pro}$	HCoV-229E	90
32.	Saikosaponin D (*Bupleurum* spp.)	Saponin	13.2 ± 0.3 μM	May inhibit $3CL^{pro}$	HCoV-229E	90
33.	Lycorine (*Lycoris radiata*)	Alkaloid	0.15 to 1.63 μM	-	HCoV-OC43, HCoV-NL63, MERS-CoV, MHV-A59	110
34.	Emetine (*Cephaelis ipecacuanha*)	Alkaloid	0.12 to 1.43 μM	-	HCoV-OC43, HCoV-NL63, MERS-CoV, MHV-A59	110
35.	Berbamine (*Berberis* spp.)	Alkaloid	1.48 to 13.14 μM	-	HCoV-OC43, HCoV-NL63, MERS-CoV, MHV-A59	110
36.	Tetrandrine (*Stephania tetrandra*)	Alkaloid	0.29 to 12.68 μM	-	HCoV-OC43, HCoV-NL63, MERS-CoV, MHV-A59	110
37.	Pristimerin (*Tripterygium wilfordii*)	Terpenoid	1.63 to 13.87 μM	-	HCoV-OC43, HCoV-NL63, MERS-CoV, MHV-A59	110
38.	Harmine (*Peganum harmala*)	Alkaloid	1.90 to 13.77 μM	-	HCoV-OC43, HCoV-NL63, MERS-CoV, MHV-A59	110
39.	Conessine (*Holarrhena floribunda*)	Alkaloid	2.34 to 11.46 μM	-	HCoV-OC43, HCoV-NL63, MERS-CoV, MHV-A59	110
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	100
41.	Chrysin	Phenolic	200 μM	Inhibition of (S) protein and ACE2 interaction	SARS-CoV	54
42.	Indigodole B (*Strobilanthes cusia*)	Alkaloid	2.60 ± 0.11 μM	May inhibit $3CL^{pro}$	HCoV-NL63	100
43.	Tetrandrine (*Stephania tetrandra*)	Alkaloid	0.33 ± 0.03 μM	Inhibition of viral S and N protein	HCoV-OC43	140
44.	Fangchinoline (*Stephania tetrandra*)	Alkaloid	1.01 ± 0.07 μM	Inhibition of viral S and N protein	HCoV-OC43	140
45.	Cepharanthine (*Stephania tetrandra*)	Alkaloid	0.83 ± 0.07 μM	Suppression of viral replication; inhibition of viral S and N protein	HCoV-OC43	140
46.	Procyanidin B1 (Cinnamomi Cortex)	Flavonoid	41.3 ± 3.4 μM	Inhibition of pseudovirus infection	SARS-CoV	109

47.	Procyanidin A2 (Cinnamomi Cortex)	Flavonoid	29.9 ± 3.3 µM	Inhibition of pseudovirus infection	SARS-CoV	[109]
48.	Cinnamtannin B1 (*Cinnamomum verum*)	Flavonoid	32.9 ± 3.9 µM	Inhibition of pseudovirus infection	SARS-CoV	[109]
49.	Silvestrol (*Aglaia* spp.)	Phenolic	3 nM	Inhibition of cap-dependent viral mRNA translation	HCoV-229E	[141]
50.	Juglanin (*Polygonum aviculare*)	Phenolic	2.3 µM	Blockage of 3a channel	SARS-CoV	[105]
51.	Silvestrol (*Aglaia* spp.)	Phenolic	1.3 nM	Inhibition of cap-dependent viral mRNA translation	MERS-CoV	[141]
52.	Sinigrin (*Isatis indigotica*)	Glucoside	217 µM	SARS-CoV $3CL^{pro}$ inhibition	SARS-CoV	[126]
53.	Beta-sitosterol (*Isatis indigotica*)	steroid	1210 µM	SARS-CoV $3CL^{pro}$ inhibition	SARS-CoV	[126]
54.	Indigo (*Isatis indigotica*)		752 µM	SARS-CoV $3CL^{pro}$ inhibition	SARS-CoV	[126]
55.	Aloe-emodin	Phenolic	366 µM	SARS-CoV $3CL^{pro}$ inhibition	SARS-CoV	[126]
56.	Hesperetin	Phenolic	8.3 µM	SARS-CoV $3CL^{pro}$ inhibition	SARS-CoV	[126]
57.	Kazinol A	Phenolic	66.2–88.5 µM	Inhibition of $3CL^{pro}$ and PL^{pro}	SARS-CoV and MERS-CoV	[142]
58.	Emodin (*Rheum* and *Polygonum* genera)	Phenolic	200 µM	Inhibition of SARS-CoV S protein and ACE2 interaction	SARS-CoV	[54]
59.	Myricetin	Flavonoid	2.71 ± 0.19 µM	Inhibition of SARS-CoV helicase	SARS-CoV	[131]
60.	Scultellarein	Flavonoid	0.86 ± 0.48 µM	Inhibition of SARS-CoV helicase	SARS-CoV	[131]
61.	Hirsutenone (*Alnus japonica*)	Phenolic	4.1 ± 0.3 µM	Inhibition of SARS-CoV PL^{pro}	SARS-CoV	[132]
62.	Hirsutanonol (*Alnus japonica*)	Phenolic	7.8 ± 1.7 µM	Inhibition of SARS-CoV PL^{pro}	SARS-CoV	[132]
63.	Oregonin (*Alnus japonica*)	Phenolic	20.1 ± 2.2 µM	Inhibition of SARS-CoV PL^{pro}	SARS-CoV	[132]
64.	Rubranol (*Alnus japonica*)	Phenolic	12.3 ± 0.9 µM	Inhibition of SARS-CoV PL^{pro}	SARS-CoV	[132]
65.	Rubranoside B (*Alnus japonica*)	Phenolic	8.0 ± 0.2 µM	Inhibition of SARS-CoV PL^{pro}	SARS-CoV	[132]
66.	Rubranoside A (*Alnus japonica*)	Phenolic	9.1 ± 1.0 µM	Inhibition of SARS-CoV PL^{pro}	SARS-CoV	[132]
67.	Quercetin-3-β-galactoside	Flavonoid	42.79 ± 4.97 µM	Competitive inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[127]
68.	Quercetin	Flavonoid	23.8 ± 1.9 µM	Inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
69.	Betulinic acid	Terpenoid	10 µM	Competitive inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[92]
70.	Betulonic acid	Terpenoid	>100 µM	Inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[92]
71.	Hinokinin	Lignoid	>100 µM	SARS-CoV $3CL^{pro}$ inhibition	SARS-CoV	[92]
72.	Savinin	Lignoid	25 µM	Competitive inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[92]
73.	Curcumin	Phenolic	40 µM	SARS-CoV $3CL^{pro}$ inhibition	SARS-CoV	[92]
74.	Broussochalcone B	Phenolic	11.6–112.9 µM	Inhibition of $3CL^{pro}$ and PL^{pro}	SARS-CoV and MERS-CoV	[142]
75.	Broussochalcone A	Phenolic	9.2–88.1 µM	Inhibition of $3CL^{pro}$ and PL^{pro}	SARS-CoV and MERS-CoV	[142]
76.	4-hydroxyisolonchocarpin	Phenolic	35.4–202.7 µM	Inhibition of $3CL^{pro}$ and PL^{pro}	SARS-CoV and MERS-CoV	[142]
77.	Papyriflavonol A	Phenolic	3.7–112.5 µM	Inhibition of $3CL^{pro}$ and PL^{pro}	SARS-CoV and MERS-CoV	[142]
78.	Tannic acid	Phenolic	3 µM	SARS-CoV $3CL^{pro}$ inhibition	SARS-CoV	[85]
79.	3-isotheaflavin-3-gallate	Phenolic	7 µM	SARS-CoV $3CL^{pro}$ inhibition	SARS-CoV	[85]
80.	Theaflavin-3,3'-digallate	Phenolic	9.5 µM	SARS-CoV $3CL^{pro}$ inhibition	SARS-CoV	[85]
81.	Theaflavin	Phenolic	56 µM	SARS-CoV $3CL^{pro}$ inhibition	SARS-CoV	[85]
82.	Theaflavin-3-gallate and Theaflavin-3'-gallate	Phenolics	43 µM	SARS-CoV $3CL^{pro}$ inhibition	SARS-CoV	[85]
83.	Apigenin	Phenolic	280.8 ± 21.4 µM	Inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
84.	Kazinol J	Phenolic	15.2–109.2 µM	Inhibition of $3CL^{pro}$ and PL^{pro}	SARS-CoV and MERS-CoV	[142]

85.	18-hydroxyferruginol	Terpenoid	220.8 ± 10.4 µM	Inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
86.	Hinokiol	Terpenoid	233.4 ± 22.2 µM	Inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
87.	Ferruginol	Terpenoid	49.6 ± 1.5 µM	Inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
88.	18-oxoferruginol	Terpenoid	163.2 ± 13.8 µM	Inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
89.	O-acetyl-18-hydroxyferruginol	Terpenoid	128.9 ± 25.2 µM	Inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
90.	Methyl dehydroabietate	Terpenoid	207.0 ± 14.3 µM	Inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
91.	Isopimaric acid	Terpenoid	283.5 ± 18.4 µM	Inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
92.	Kayadiol	Terpenoid	137.7 ± 12.5 µM	Inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
93.	Amentoflavone	Flavonoid	8.3 ± 1.2 µM	Non-competitive inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
94.	Bilobetin	Flavonoid	72.3 ± 4.5 µM	Non-competitive inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
95.	Ginkgetin	Flavonoid	32.0 ± 1.7 µM	Non-competitive inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
96.	Sciadopitysin	Flavonoid	38.4 ± 0.2 µM	Non-competitive inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
97.	Abietic acid	Terpenoid	189.1 ± 15.5 µM	Inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
98.	Kazinol F	Phenolic	39.5–135.0 µM	Inhibition of $3CL^{pro}$ and PL^{pro}	SARS-CoV and MERS-CoV	[142]
99.	Luteolin	Flavonoid	20.0 ± 2.2 µM	Inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[107]
100.	Kazinol B	Phenolic	31.4– 233.3 µM	Inhibition of $3CL^{pro}$ and PL^{pro}	SARS-CoV and MERS-CoV	[142]
101.	Broussoflavan A	Phenolic	49.1– 125.7 µM	Inhibition of $3CL^{pro}$ and PL^{pro}	SARS-CoV and MERS-CoV	[142]
102.	Celastrol	Terpenoid	10.3 ± 0.2 µM	Competitive inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[130]
103.	Pristimerin	Terpenoid	5.5 ± 0.7 µM	Competitive inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[130]
104.	Tingenone	Terpenoid	9.9 ± 0.1 µM	Competitive inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[130]
105.	Iguesterin	Terpenoid	2.6 ± 0.3 µM	Competitive inhibition of SARS-CoV $3CL^{pro}$	SARS-CoV	[130]
106.	3'-(3-methylbut-2-enyl)-3',4,7-trihydroxyflavane	Phenolic	30.2–48.8 µM	Inhibition of $3CL^{pro}$ and PL^{pro}	SARS-CoV and MERS-CoV	[142]
107.	Corylifol	Phenolic	32.3 ± 3.2 µM	Inhibition of PL^{pro}	SARS-CoV	[143]

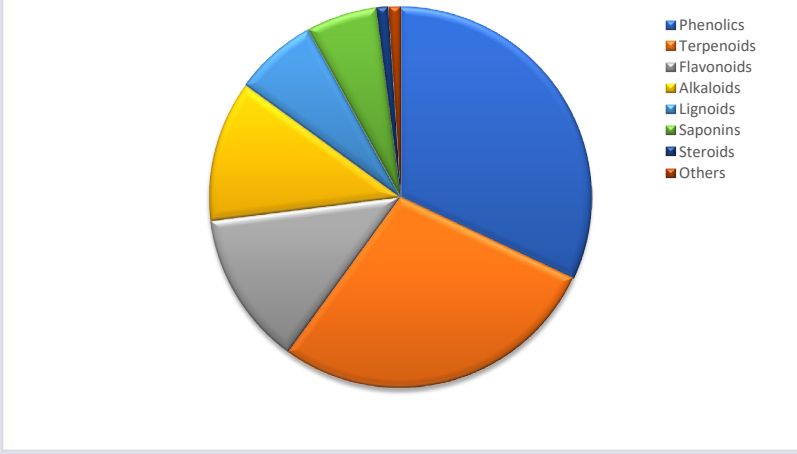


Figure 4: Class of phytocompounds studied against HcoVs.

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,[144] 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[145] 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*, *Burchellia bubalina*, *Crinium moorei*, *Cymbopogon validus*, *Euclea natalensis*, *Polygala virgate*, *Polygonum hystriculum*, *Salix mucronate*, *Scadoxus puniceus*, *Schotia brachypetala*, *Tropaeolum majus*, *Vitellariopsis marginata*, and *Zanthoxylum capense*.[146-157] 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.

REFERENCES

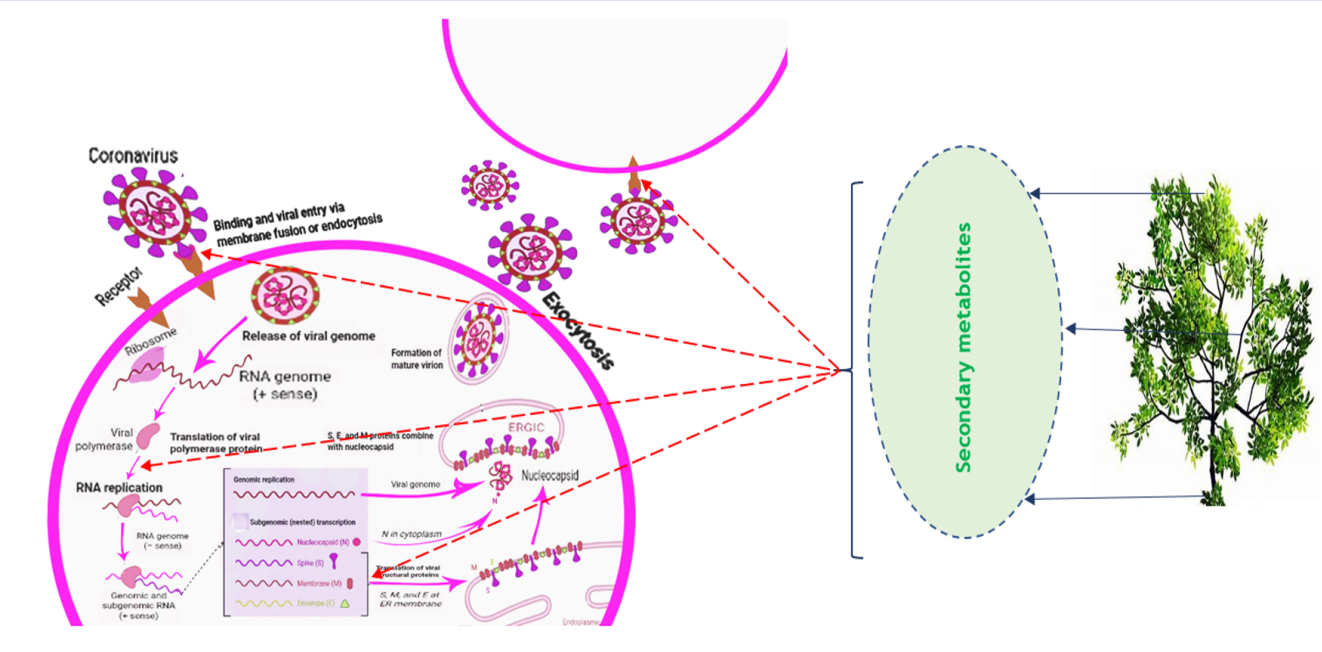
1. World Health Organization. WHO publishes list of top emerging diseases likely to cause major epidemics. 2015. Available at: http://www.who.int/medicines/ebola-treatment/WHO-list-of-top-emerging-diseases/en/.
2. James SL, Abate D, Abate KH, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392: 1789-1858.
3. De Clercq E, Li G. Approved antiviral drugs over the past 50 years. Clin Microbiol Rev. 2016; 29: 695-747.
4. Zhou P, Yang XL, Wang XG, *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020; 579: 270-273.
5. Schalk AS, Hawn MH. An apparently new respiratory disease of baby chicks. J Am Vet Med A. 1931; 78: 413-422.
6. Kahn JS, McIntosh K. History and recent advances in coronavirus discovery. Pediatr Infect Dis J. 2005; 24: S223.
7. Weiner LP. Coronaviruses: a historical perspective. Coronaviruses. 1987: 1-5.
8. Tyrrell DAJ, Almeida JD, Cunningham CH, *et al.* Coronaviridae. Intervirology. 1975; 5: 76-82.
9. Woo PCY, Huang Y, Lau SKP, Yuen K-Y. Coronavirus genomics and bioinformatics analysis. Viruses. 2010; 2: 1804-1820.
10. Dijkman R, van der Hoek L. Human coronaviruses 229E and NL63: Close yet still so far. J Formos Med Assoc. 2009; 108: 270-279.
11. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020; doi:10.1016/j.jare.2020.03.005.
12. Lai MMC, Holmes KV. Coronaviridae: the viruses and their replication. In: Knipe DM, Howley P, Eds. Field's Virology. 4th ed. Philadelphia (USA): Williams & Wilkin 2001; pp. 1163-1185.
13. Sahin AR. 2019 Novel coronavirus (COVID-19) outbreak: a review of the current literature. Eurasian J Med Investigation. 2020; doi:10.14744/ejmo.2020.12220.
14. Li F. Structure, function, and evolution of coronavirus spike proteins. Annu Rev Virol. 2016; 3: 237-61.
15. Drosten C, Günther S, Preiser W, *et al.* Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med. 2003; 348: 1967-1976.
16. Amici C, Di Coro A, Ciucci A, *et al.* Indomethacin has a potent antiviral activity against SARS coronavirus. Antiviral Ther. 2006; 11: 1021.
17. Alamanou MT. Anti-coronavirus natural products and *In silico* screening. Medium. 2020 March 28; [cited 2020 March 30]; [about 14 screens]. Available from: https://towardsdatascience.com/anti-coronavirus-natural-products-and-in-silico-screening-54d9f03b7daf.
18. Taxonomy. International Committee on Taxonomy of Viruses (ICTV) 2019. Available from: https://talk.ictvonline.org/taxonomy/.
19. Andersen PI, Ianevski A, Lysvand H, Vitkauskiene A, Oksenych V, Bjørås M, Telling K, Lutsar I, Dampis U, Irie Y, Tenson T. Discovery and development of safe-in-man broad-spectrum antiviral agents. Int J Infect Dis. 2020; 93: 268-276.
20. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017; 39: 529-539.
21. Yarnell E. Herbs for viral respiratory infections. Altern Compl Ther., 2018; 24(1). https://doi.org/10.1089/act.2017.29150.eya
22. Wrapp D, Wang N, Corbett KS, *et al.* Cryo-EM Structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020; 367: 1260-1263.
23. Peiris JSM, Guan Y, Yuen KY. Severe acute respiratory syndrome. Nat Med. 2004; 10: 588-597.
24. Skowronski DM, Astell C, Brunham RC, *et al.* Severe acute respiratory syndrome (SARS): a year in review. Annu Rev Med. 2005; 56: 357-381.
25. Serkedjieva J. Influenza virus variants with reduced susceptibility to inhibition by a polyphenol extract from *Geranium sanguineum* L. Die Pharmazie. 2003; 58: 53-57.
26. Tolo FM, Rukunga GM, Muli FW, *et al.* Anti-viral activity of the extracts of a Kenyan medicinal plant Carissa edulis against herpes simplex virus. J Ethnopharmacol. 2006; 104: 92-99.
27. Newman DJ, Cragg GM, Snader KM. The influence of natural product upon drug discovery. Nat Prod Rep. 2000; 17: 215-234.
28. De Clercq E. Antivirals and antiviral strategies. Nat Rev Microbiol. 2004; 2: 704-720.
29. Chattopadhyay D, Naik TN. Antivirals of ethnomedicinal origin: Structure-activity relationship and scope. Mini Rev Med Chem. 2007; 7: 275-301.
30. Naithani R, Huma LC, Holland LE, *et al.* Antiviral activity of phytochemicals: a comprehensive review. Mini Revs Med Chem. 2008; 8: 1106-1133.
31. Masters PS. The molecular biology of coronaviruses. Adv Virus Res. 2006; 66: 193-292.
32. Vellingiri B, Jayaramayya K, Iyer M, *et al.* COVID-19: A promising cure for the global panic. Sci Tot Environ. 2020; 725: 138277.
33. Chan JFW, Lau SKP, To KKW, Cheng VCC, Woo PCY, Yuen K-Y. Middle East Respiratory Syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clin Microbiol Rev. 2015; 28: 465-522.
34. Tu Y-F, Chien C-S, Yarmishyn AA, *et al.* A review of SARS-CoV-2 and the ongoing clinical trials. Int J Mol Sci. 2020; 21: 2657.
35. de Wilde AH, Snijder EJ, Kikkert M, van Hemert MJ. Host factors in coronavirus replication. In: Roles of host gene and non-coding RNA expression in virus infection. Curr Top Microbiol Immunol. 2017; (pp. 1-42). Springer, Cham.

36. Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? Clin Microbiol Infect. 2020; doi:10.1016/j.cmi.2020.03.026.
37. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nat Rev Microbiol. 2009; 7: 439-50.
38. Ahmad A, Rehman MU, Alkharfy KM. An alternative approach to minimize the risk of coronavirus (Covid-19) and similar infections. Eur Rev Med Pharmacol Sci. 2020; 24: 4030-4034.
39. Pushpakom S, Iorio F, Eyers PA, *et al.* Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov. 2019; 18: 41-58.
40. Rosa S, Santos W. Clinical trials on drug repositioning for COVID-19 treatment. Rev. Panam. Salud Públ. 2020; 44: 1-13.
41. Zheng W, Sun W, Simeonov A. Drug repurposing screens and synergistic drug combinations for infectious diseases. Br J Pharmacol. 2018: 175: 181-191.
42. Ianevski A, Andersen PI, Merits A, Bjoras M, Kainov D. Expanding the activity spectrum of antiviral agents. Drug Discov Today. 2019; 24: 1224-1228.
43. Young DD, Connelly CM, Grohmann C, Deiters A. Small molecule modifiers of microRNA miR-122 function for the treatment of hepatitis C virus infection and hepatocellular carcinoma. J Am Chem Soc. 2010; 132: 7976-7981.
44. Hulseberg CE, Feneant L, Szymanska-de Wijs KM, *et al.* Arbidol and other low-molecular-weight drugs that inhibit lassa and Ebola viruses. J Virol. 2019; 93: e02185-18.
45. Mazzon M, Ortega-Prieto AM, Imrie D, *et al.* Identification of broad spectrum antiviral compounds by targeting viral entry. Viruses. 2019; 11(2): 176.
46. Cairns DM, Boorgu D, Levin M, Kaplan DL. Niclosamide rescues microcephaly in a humanized *in vivo* model of Zika infection using human induced neural stem cells. Biol Open. 2018; 2018: 7.
47. Stachulski AV, Pidathala C, Row EC, *et al.* Thiazolides as novel antiviral agents. 2. Inhibition of hepatitis C virus replication. J Med Chem. 2011; 54: 8670-8680.
48. Wang YM, Lu JW, Lin CC, *et al.* Antiviral activities of niclosamide and nitazoxanide against chikungunya virus entry and transmission. Antiviral Res. 2016; 135: 81-90.
49. Xu T, Gao X, Wu Z, Selinger DW, Zhou Z. Indomethacin has a potent antiviral activity against SARS CoV-2 *in vitro* and canine coronavirus *in vivo*. BioRxiv. Prepr. doi: https://doi.org/10.1101/2020.04.01.017624. 2020.
50. Wu CY, Jan JT, Ma SH, *et al.* Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci USA. 2004; 6: 10012-10017.
51. Khaerunnisa S, Kurniawan H, Awaluddin R, Suhartati S, Soetjipto S. Potential inhibitor of COVID-19 Main protease (Mpro) from several medicinal plant compounds by molecular docking study. Prepr. doi: 10. 20944/preprints202003.0226. 2020; v1: 1-4.
52. De Clercq E. Potential antivirals and antiviral strategies against SARS coronavirus infections. Expert Rev Anti-infect Ther. 2006; 4: 291-302.
53. Yamamoto N, Yang R, Yoshinaka Y, *et al.* HIV protease inhibitor nelfinavir inhibits replication of SARS-associated coronavirus. Biochem Biophys Res Commun. 2004; 318: 719-725.
54. Ho TY, Wu SL, Chen JC, Li CC, Hsiang CY. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antiviral Res. 2007; 74: 92-101.
55. Keyaerts E, Vijgen L, Pannecouque C, *et al.* Plant lectins are potent inhibitors of coronaviruses by interfering with two targets in the viral replication cycle. Antiviral Res. 2007; 75: 179-187.
56. Tan EL, Ooi EE, Lin CY, *et al.* Inhibition of SARS coronavirus infection *in vitro* with clinically approved antiviral drugs. Emerg Infect Dis. 2004; 10: 581-586.
57. Hsieh LE, Lin CN, Su BL, *et al.* Synergistic antiviral effect of *Galanthus nivalis* agglutinin and nelfinavir against feline coronavirus. Antiviral Res. 2010; 88: 25-30.
58. Lewis 2nd JS, Terriff CM, Coulston DR, Garrison MW. Protease inhibitors: a therapeutic breakthrough for the treatment of patients with human immunodeficiency virus. Clin Ther. 1997; 19: 187-214.
59. van der Meer FJ, de Haan CA, Schuurman NM, *et al.* The carbohydrate-binding plant lectins and the non-peptidic antibiotic pradimicin A target the glycans of the coronavirus envelope glycoproteins. J Antimicrob Chemother. 2007; 60: 741-749.
60. Lundin A, Dijkman R, Bergstro¨m T, *et al.* Targeting membrane bound viral RNA synthesis reveals potent inhibition of diverse coronaviruses including the Middle East Respiratory Syndrome Virus. PLoS Pathog. 2014; 10: e1004166.
61. Pagliarulo N. A closer look at the Ebola drug that's become the top hope for a coronavirus treatment. BioPharma Dive. 2020 March 5. [cited 2020 April 15]; [about 7 screens]. Available from: https://www.biopharmadive.com/news/coronavirus-remdesivir-gilead-antiviral-drug-covid-19/573261/.
62. Preidt R. Why remdesivir might be a good bet against COVID-19. Health News-US News. 2020 April 16. [cited 2020 April 27]; [about 6 screens]. https://www.usnews.com/news/health-news/articles/2020-04-16/why-remdesivir-might-be-a-good-bet-against-covid-19
63. Hussein S. Avigan: Antiviral being tested for coronavirus patients - Barron's. Agence France-Presse. 2020 April 17; [cited 2020 April 20]; [about 4 screens]. Available from: https://www.barrons.com/news/avigan-antiviral-being-tested-for-coronavirus-patients-01587102905?refsec=afp-news.
64. Wilson R, Chan A. Starpharma's SPL7013 shows significant activity against SARS-CoV-2 (coronavirus). Business Wire. 2020 April 16; [cited 2020 April 27]; [about 5 screens]. Available from: https://finance.yahoo.com/news/starpharma-spl7013-shows-significant-activity-131100623.html.
65. Jeffay N. Israeli firm hopeful as it starts treating COVID-19 patients with placenta cells. The Times of Israel. 2020 April 16; [cited 2020 April 21]; [about 3 screens]. Available from: https://www.timesofisrael.com/israeli-company-hopes-to-treat-coronavirus-patients-with-placenta-cells/.
66. National Institute of Health: National Institute of Allergy and Infectious Diseases. Developing therapeutics and vaccines for coronaviruses. 2020a April 6; [cited 2020 April 25]; [about 1 screen]. Available from: https://www.niaid.nih.gov/diseases-conditions/coronaviruses-therapeutics-vaccines.
67. National Institute of Health: National Institute of Allergy and Infectious Diseases. Atlanta site added to NIH clinical trial of a vaccine for COVID-19. NIH:NIAID. 2020b March 27; [cited 2020 April 23]; [about 2 screens]. Available from: https://www.niaid.nih.gov/news-events/atlanta-site-added-nih-clinical-trial-vaccine-covid-19.
68. Kim E, Erdos G, Huang S, *et al.* Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development. EBioMedicine. 2020 Apr 2: 102743.
69. Ganjhu RK, Mudgal PP, Maity H, *et al.* Herbal plants and plant preparations as remedial approach for viral diseases. Virusdisease. 2015; 26: 225-236.
70. Rates SM. Plants as source of drugs. Toxicon. 2001; 39: 603-613.
71. Redeploying plant defences. Nature Plants Editorial. 2020; 6: 177-177. Available from: http://www.nature.com/natureplants.
72. Weathers PJ, Towler M, Hassanali A, Lutgen P, Engeu PO. Dried-leaf *Artemisia annua*: a practical malaria therapeutic for developing countries? World J Pharmacol. 2014; 3: 39-55.
73. Patrono C. Aspirin: new cardiovascular uses for an old drug. Am J Med. 2001; 110: S62-S65.
74. Yang F, Hanon S, Lam P, Schweitzer P. Quinidine revisited. Am J Med. 2009; 122: 317-321.
75. Weaver BA. How taxol/paclitaxel kills cancer cells. Mol Biol Cell. 2014; 25: 2677-2681.
76. Nii-Trebi NI. Emerging and neglected infectious diseases: insights, advances, and challenges. BioMed Res Int. 2017: 1-15.
77. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet. 2003; 361(9374): 2045-6.
78. Li SY, Chen C, Zhang HQ, *et al.* Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antiviral Res. 2005; 67: 18-23.
79. Lin LT, Hsu WC, Lin CC. Antiviral natural products and herbal medicines. J Tradit Compl Med. 2014; 4: 24-35.
80. Islam MT, Sarkar C, El-Kersh DM, et al. Natural products and their derivatives against coronavirus: A review of the non-clinical and pre-clinical data. Phytother Res. 2020; doi: 10.1002/ptr.6700
81. Zhao CH, Guo YB, Wu H, *et al.* 2003. Clinical manifestation, treatment, and outcome ofsevere acute respiratory syndrome: analysis of 108 cases in Beijing. Zhonghua Yi Xue Za Zhi. 2003; 83: 897-901.
82. Zhong NS, Zeng GQ. Our strategies for fighting severe acute respiratory syndrome (SARS). Am J Respir Crit Care Med. 2003; 168: 7-9.
83. Lin YL, Huang YL, Ma SH, *et al.* Inhibition of Japanese encephalitis virus infection by nitric oxide: antiviral effect of nitric oxide on RNA virus replication. J Virol. 1997; 71: 5227-35.
84. Clark KJ, Grant PG, Sarr AB, *et al.* An *in vitro* study of theaflavins extracted from black tea to neutralize bovine rotavirus and bovine coronavirus infections. Vet Microbiol. 1998; 63: 147-157.
85. Chen C-N, Lin Coney PC, Huang KK, *et al.* Inhibition of SARS-CoV 3C-like protease activity by theaflavin-3,3-digallate (TF3). Evid.-Based Compl Altern Med. 2005; 2: 209-215.
86. Turan K, Nagata K, Kuru A. Antiviral effect of *Sanicula europaea* L. leaves extract on influenza virus-infected cells. Biochem Biophys Res Commun. 1996; 225: 22-26.
87. Ghosh N, Ghosh R, Mandal V, Mandal SC. Recent advances in herbal medicine for treatment of liver diseases. Pharm Biol. 2011; 49: 970-988.
88. Hoever G, Baltina L, Michaelis M, *et al.* Antiviral activity of glycyrrhizic acid derivatives against SARS–coronavirus. J Med Chem. 2005; 48: 1256-1259.
89. Chen F, Chan K, Jiang Y, *et al. In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol. 2004; 31: 69-75.

90. Cheng PW, Ng LT, Chiang LC, Lin CC. Antiviral effects of saikosaponins on human coronavirus 229E *in vitro*. Clin Exp Pharmacol Physiol. 2006; 33: 612-616.
91. Yi L, Li Z, Yuan K, *et al.* Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J Virol. 2004; 78: 11334-11339.
92. Wen CC, Kuo YH, Jan JT, *et al.* Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. J Med Chem. 2007; 50: 4087-4095.
93. Chen CJ, Michaelis M, Hsu HK, *et al. Toona sinensis* Roem tender leaf extract inhibits SARS coronavirus replication. J Ethnopharmacol. 2008; 120(1): 108-111.
94. Brendler T, van Wyk BE. A historical, scientific and commercial perspective on the medicinal use of *Pelargonium sidoides* (Geraniaceae). J Ethnopharmacol. 2008; 119: 420-433
95. Michaelis M, Doerr HW, Cinatl Jr J. Investigation of the influence of EPs® 7630, a herbal drug preparation from *Pelargonium sidoides*, on replication of a broad panel of respiratory viruses. Phytomedicine. 2011; 18(5): 384-386.
96. Wen CC, Shyur LF, Jan JT, *et al.* Traditional Chinese medicine herbal extracts of *Cibotium barometz, Gentiana scabra, Dioscorea batatas*, *Cassia tora*, and *Taxillus chinensis* inhibit SARS-CoV replication. J Trad Complem Med. 2011; 1(1): 41-50.
97. Chang FR, Yen CT, Ei-Shazly M, *et al.* Anti-human coronavirus (anti-HCoV) triterpenoids from the leaves of *Euphorbia neriifolia*. Nat Prod Comm. 2012; 7(11): 1934578X1200701103.
98. Ulasli M, Gurses SA, Bayraktar R, *et al.* The effects of *Nigella sativa* (Ns), *Anthemis hyalina* (Ah) and *Citrus sinensis* (Cs) extracts on the replication of coronavirus and the expression of TRP genes family. Mol Biol Rep. 2014; 41(3): 1703-1711.
99. Shen JW, Ruan Y, Ren W, Ma BJ, Wang XL, Zheng CF. Lycorine: a potential broad-spectrum agent against crop pathogenic fungi. J Microbiol Biotechnol. 2014; 24(3): 354-358.
100. Tsai Y-C, Lee C-L, Yen H-R, *et al.* Antiviral action of tryptanthrin isolated from *Strobilanthes cusia* leaf against human coronavirus NL63. Biomolecules. 2020; 10(3): 366.
101. Wang L, Yang R, Yuan B, Liu Y, Liu C. The antiviral and antimicrobial activities of licorice, a widely used Chinese herb. Acta Pharm Sin B. 2015; 5(4): 310-315.
102. Mohammadi N, Shaghaghi, N. Inhibitory effect of eight secondary metabolites from conventional medicinal plants on COVID_19 virus protease by molecular docking analysis. ChemRxiv. Prepr. doi: https://doi.org/10.26434/chemrxiv.11987475. 2020; v1.
103. Lau KM, Lee KM, Koon CM, *et al.* Immunomodulatory and anti-SARS activities of *Houttuynia cordata*. J Ethnopharmacol. 2008; 118: 79-85.
104. Kolodziej H, Schulz V. EPs 7630: From traditional application to modern phytodrug. Dtsch Apoth Ztg. 2003; 143: 55-64.
105. Schwarz S, Sauter D, Wang K, *et al.* Kaempferol derivatives as antiviral drugs against the 3a channel protein of coronavirus. Planta Med. 2014; 80: 177-182.
106. Salim B, Noureddine M. Identification of compounds from *Nigella sativa* as new potential inhibitors of 2019 novel coronavirus (Covid-19): molecular docking study. ChemRxiv. Prepr. https://doi.org/10.26434/chemrxiv.12055716.v1
107. Ryu YB, Jeong HJ, Kim JH, *et al.* Bioflavonoids from *Torreya nucifera* displaying SARS-CoV 3CL(pro) inhibition. Bioorg Med Chem. 2010a; 18: 7940-7947.
108. Chang C, Lien Y, Liu KCSC, Li S.-S. Lignans from *Phyllanthus urinaria*. Phytochemistry. 2003; 63: 825-833.
109. Zhuang M, Jiang H, Suzuki Y, *et al.* Procyanidins and butanol extract of *Cinnamomi* cortex inhibit SARS-CoV infection. Antiviral Res. 2009; 82: 73-81.
110. Shen L, Niu J, Wang C, *et al.* High-throughput screening and identification of potent broad-spectrum inhibitors of coronaviruses. J Virol. 2019; 15; 93(12): e00023-19.
111. Hwang YC, Chu JJ, Yang PL, Chen W, Yates MV. Rapid identification of inhibitors that interfere with poliovirus replication using a cell-based assay. Antiviral Res. 2008; 77: 232-236.
112. Khandelwal N, Chander Y, Rawat KD, *et al.* Emetine inhibits replication of RNA and DNA viruses without generating drug-resistant virus variants. Antiviral Res. 2017; 144: 196-204.
113. Kataoka M, Hirata K, Kunikata T, *et al.* Antibacterial action of tryptanthrin and kaempferol, isolated from the indigo plant (*Polygonum tinctorium* Lour.), against *Helicobacter pylori*-infected Mongolian gerbils. J Gastroenterol. 2001; 36: 5-9.
114. Miao S, Shi X, Zhang H, *et al.* Proliferation-attenuating and apoptosis-inducing effects of tryptanthrin on human chronic myeloid leukemia K562 cell line *in vitro*. Int J Mol Sci. 2011; 12: 3831-45.
115. Lee S, Kim DC, Baek HY, Lee KD, Kim YC, Oh H. Anti-neuroinflammatory effects of tryptanthrin from *Polygonum tinctorium* Lour. in lipopolysaccharide-stimulated BV2 microglial cells. Arch Pharm Res. 2018; 41: 419-30.
116. Sawikowska A. Meta-analysis of flavonoids with antiviral potential against coronavirus. Biometrical Lett. 2020 Mar 5; 1 (ahead-of-print).
117. Utomo RY, Ikawati R, Meiyanto E. Revealing the potency of *Citrus* and galangal constituents to Halt SARS-CoV-2 Infection. Prepr. doi:10.20944/preprints202003.0214. 2020; v1, 1-8.
118. Yang CW, Lee YZ, Kang lJ, *et al.* Identification of phenanthroindolizines and phenanthroquinolizidines as novel potent anti-coronaviral agents for porcine enteropathogenic coronavirus transmissible gastroenteritis virus and human severe acute respiratory syndrome coronavirus. Antiviral Res. 2010; 88(2): 160-168.
119. Yang JL, Ha TKQ, Oh WK. Discovery of inhibitory materials against PEDV corona virus from medicinal plants. Jpn J Vet Res. 2016; 64: S53-S63.
120. Enjuanes L, DeDiego ML, Álvarez E, Deming D, Sheahan T, Baric R. Vaccines to prevent severe acute respiratory syndrome coronavirus induced disease. Virus Res. 2008; 133: 45-62.
121. Rota PA, Oberste MS, Monroe SS, *et al.* Characterization of a novel coronavirus associated with severe acute respiratory syndrome. Science. 2003; 300: 1394-1394.
122. Li W, Moore MJ, Vasilieva N, *et al.* Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003; 426: 450-454.
123. Isaacson MK, Ploegh HL. Ubiquitination, Ubiquitin-like Modifiers, and Deubiquitination in Viral Infection. Cell Host Microbe. 2009; 5: 559-570.
124. Mukherjee P, Shah F, Desai P, Avery M. Inhibitors of SARS-3CLpro: virtual screening, biological evaluation, and molecular dynamics simulation studies. J Chem Inf Model. 2011; 51: 1376-92.
125. Zhang DH, Wu KL, Zhang X, Deng SQ, Peng B. *In silico* screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. J Integr Med. 2020; 18: 152-8.
126. Lin CW, Tsai FJ, Tsai CH, *et al.* Anti-SARS coronavirus 3C-like protease effects of *Isatis indigotica* root and plant-derived phenolic compounds. Antiviral Res. 2005; 68: 36-42.
127. Chen L, Li J, Luo C, *et al* Binding interaction of quercetin-3-β-galactoside and its synthetic derivatives with SARS-CoV 3CLpro: structure–activity relationship studies reveal salient pharmacophore features. Bioorg Med Chem. 2006; 14: 8295-8306.
128. Chiow KH, Phoon MC, Putti T, *et al.* Evaluation of antiviral activities of *Houttuynia cordata* Thunb. extract, quercetin, quercetrin and cinanserin on murine coronavirus and dengue virus infection. Asian Pac J Trop Med. 2016; 9: 1-7.
129. Sydiskis RJ, Owen DG, Lohr JL, Rosler KH, Blomster RN. Inactivation of enveloped viruses by anthraquinones extracted from plants. Antimicrob Agents Chemother. 1991; 35: 2463-2466.
130. Ryu YB, Park S-J, Kim YM, *et al.* SARS-CoV 3CLpro inhibitory effects of quinone-methide triterpenes from *Tripterygium regelii*. Bioorg Med Chem Lett. 2010b; 20: 1873-1876.
131. Yu MS, Lee J, Lee JM, *et al.* Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. Bioorg Med Chem Lett. 2012; 22(12): 4049-4054.
132. Park J-Y, Jeong HJ, Kim JH, *et al.* Diarylheptanoids from *Alnus japonica* inhibit papain-like protease of severe acute respiratory syndrome coronavirus. Biol Pharm Bull. 2012; 35: 2036-2042.
133. Keum YS, Jeong YJ. Development of chemical inhibitors of the SARS coronavirus: viral helicase as a potential target. Biochem Pharmacol. 2012; 84: 1351-1358.
134. Jo S, Kim S, Shin DH, Kim MS. Inhibition of SARS-CoV 3CL protease by flavonoids. J Enzyme Inhib Med Chem. 2020; 35: 145-151.
135. Zakaryan H, Arabyan E, Oo A, Zandi K. Flavonoids: promising natural compounds against viral infections. Arch Virol. 2017; 162: 2539-2551.
136. Nguyen TT, Woo HJ, Kang HK, *et al.* Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in *Pichia pastoris*. Biotechnol Lett. 2012; 34: 831-838.
137. Runfeng L, Yunlong H, Jicheng H, *et al.* Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). Pharmacol Res. 2020; 156: 104761.
138. Ding Y, Zeng L, Li R, *et al.* The Chinese prescription lianhuaqingwen capsule exerts anti-influenza activity through the inhibition of viral propagation and impacts immune function. BMC Complement Altern Med. 2017; 17(1): 130.
139. Mas Pharmaceutical. An antiviral formulation with DNA gyrase and RNA dependent RNA polymerase suppressive features as an adjunct treatment for coronaviral infections. European Commission. 2020 April 2; [cited 2020 April 22]; [about 2 screens]. Available from: https://cordis.europa.eu/article/id/415531-an-antiviral-formulation-with-dna-gyrase-and rnadependent-rna-polymerase-suppressive-feature/en

140. Kim DE, Min JS, Jang MS, *et al.* Natural bis-benzylisoquinoline alkaloids-tetrandrine, fangchinoline, and cepharanthine, inhibit human coronavirus OC43 infection of MRC-5 human lung cells. Biomolecules. 2019; 9: 696.
141. Müller C, Schulte FW, Lange-Grünweller K, *et al.* Broad-spectrum antiviral activity of the eIF4A inhibitor silvestrol against corona- and picornaviruses. Antiviral Res. 2018; 150: 123-129.
142. Park J-Y, Yuk HJ, Ryu HW, *et al.* Evaluation of polyphenols from *Broussonetia papyrifera* as coronavirus protease inhibitors. J Enzyme Inhib Med Chem. 2017; 32: 504-512.
143. Kim DW, Seo KH, Curtis-Long MJ, *et al.* Phenolic phytochemical displaying SARS-CoV papain-like protease inhibition from the seeds of *Psoralea corylifolia*. J Enzyme Inhib Med Chem. 2014; 29(1): 59-63.
144. Wenzhong L, Hualan L. COVID-19: Attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. ChemRxiv. Prepr. doi: 10.26434/chemrxiv.11938173. v8.
145. Van Vuuren S, Frank L. Southern African medicinal plants used as blood purifiers. J Ethnopharmacol. 2020; 249: p.112434.
146. Nwaehujor CO, Udeh NE. Screening of ethyl acetate extract of *Bridelia micrantha* for hepatoprotective and anti-oxidant activities on Wistar rats. Asian Pac J Trop Med. 2011; 4(10): 796-798.
147. Jäger AK, Hutchings A, van Staden J. Screening of Zulu medicinal plants for prostaglandin-synthesis inhibitors. J Ethnopharmacol. 1996; 52(2): 95-100.
148. Amoo SO, Ndhlala AR, Finnie JF, van Staden J. Antibacterial, antifungal and anti-inflammatory properties of *Burchellia bubalina*. South Afr J Bot. 2009; 75(1): 60-63.
149. Rungqu, P., Oyedeji, O., Nkeh-Chungag, B., Songca, S., Oluwafemi, O., Oyedeji, A. Anti-inflammatory activity of the essential oils *of Cymbopogon validus* (Stapf) Stapfex Burtt Davy from Eastern Cape, South Africa. Asian Pac J Trop Med. 2016; 9(5): 426-431.
150. Lall N, Meyer J, Taylor M, van Staden J. Anti-HSV-1 activity of *Euclea natalensis*. South Afr J Bot. 2005; 71: 444-446.
151. Beuscher N, Bodinet C, Neumann-Haefelin D, Marston A, Hostettmann K. Antiviral activity of African medicinal plants. J Ethnopharmacol. 1994; 42(2): 101-109.
152. Adewusi EA, Steenkamp V. *In vitro* screening for acetylcholinesterase inhibition and antioxidant activity of medicinal plants from southern Africa. Asian Pac J Trop Med. 2011; 4(10): 829-835.
153. Du K, Marston A, van Vuuren SF, van Zyl RL, van der Westhuizen JH. Flavonolacyl glucosides from the aril of *Schotia brachypetala* Sond. and their antioxidant, antibacterial and antimalarial activities. Phytochem Lett. 2014; doi: 10 cxxiii-cxxviii.
154. Bazylko A, Granica S, Filipek A, *et al.* Comparison of antioxidant, anti-inflammatory, antimicrobial activity and chemical composition of aqueous and hydroethanolic extracts of the herb of *Tropaeolum majus* L. Ind Crops Prod. 2013; 50: 88-94.
155. Ndhlala A, Finnie J, van Staden J. Plant composition, pharmacological properties and mutagenic evaluation of a commercial Zulu herbal mixture: *Imbiza ephuzwato*. J Ethnopharmacol. 2011; 133(2): 663-674.
156. Adebayo SA, Dzoyem JP, Shai LJ, Eloff JN. The anti-inflammatory and antioxidant activity of 25 plant species used traditionally to treat pain in southern African. BMC Complement Altern Med. 2015; 15(1): 159.
157. Eldeen I, Elgorashi E, van Staden J. Antibacterial, anti-inflammatory, anticholinesterase and mutagenic effects of extracts obtained from some trees used in South African traditional medicine. J Ethnopharmacol. 2005; 102(3): 457-464.

GRAPHICAL ABSTRACT



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