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Review

Potential natural candidates in the treatment of coronavirus infections

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ABSTRACT

Many viral infections do not have treatments or resistant to existing antiviral therapeutic interventions, and a novel strategy is required to combat virus-mediated fatalities. A novel coronavirus (coronavirus disease 2019 [COVID-19]) emerged in Wuhan, China, in late 2019 and rapidly spread across the globe. COVID-19 has impacted human society with life-threatening and unprecedented health, social, and economic issues, and it continues to affect millions of people. More than 5,800 clinical trials are in place worldwide to develop treatments to eradicate COVID-19. Historically, traditional medicine or natural products, such as medicinal plants, marine organisms and microbes, have been efficacious in treating viral infections. Nevertheless, important parameters for natural products, including clinical trial information, pharmacokinetic data, potency and toxicity profiles, *in vivo* and *in vitro* data, and product safety require validation. In this review article, an evaluation is performed of the potential application of natural product-based antiviral compounds, including crude extracts and bioactive chemical compounds obtained from medicinal plants, marine organisms, and microbes, to treat the viral infections COVID-19.

Contents

1. Introduction

Coronaviruses, a large family of viruses that include severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), SARS-CoV-2, and Middle East respiratory syndrome coronavirus (MERS-CoV), have had a significant detrimental effect on the social, health, and economic components of human society since 2000. The manifestation of SARS-CoV-2 as coronavirus disease 2019 (COVID-19) was initially transmitted to humans via bats and the latter has since become a global pandemic (Wong et al., 2019). This paper covers the epidemiological data pertaining to the coronavirus family, the genetic profile of COVID-19, current viral therapeutic interventions practiced in hospitals, ongoing clinical trials, coronavirus drug development, and combination therapy. The use of naturally occurring chemical constituents in research in the treatment of COVID-19, for example, the use of natural antiviral compounds from marine sources and microbes, bioactive phytoconstituents (in the treatment of MERS-CoV), drug repurposing

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in antiviral therapy, and current antiviral interventions, are also discussed. For several decades, natural products, including plants, marine sources, and microbes, have been considered important components in the development of drugs used as various treatments. However, several natural resources are yet to be explored, along with therapeutic compounds derived from phytoconstituents, to alleviate hazardous and life-threatening pandemic diseases, such as COVID-19. Viruses are resistant to and unaffected by antiviral therapy owing to gene mutation. In terms of the drug discovery paradigm for SARS-CoV-2, the principal goal is to protect the human population against coronavirus with the help of potent compounds or interventions. Viruses can affect humans, animals, plants, insects, fungi, and bacteria. It has been well documented that only 15% of nearly 300,000 plant species have been processed for the systematic investigation of biologically potent active substances. In particular, compounds from marine and microbial resources have yet to be exploited as a treatment in pandemic disease.

The term "virus" derives from Latin and means "poison" or "venom," and viruses are considered to be virulent in nature. Viruses were studied extensively by Louis Pasteur and other researchers at the end of the nineteenth century. Compared to bacteria, they were considered to be pathogens or tiny parasites (Gelderblom, 1996). Viruses have common characteristics; for example, they comprise a genome, DNA, or RNA central core enclosed by a protective protein shell. With viruses, the nucleic acid is double stranded in most cases; however, there are a few single-stranded DNA viruses (Gelderblom, 1996). The protective protein shell of viruses is enclosed within an envelope, referred to as a capsid, which holds proteins and lipids. The replication of the virus ensues once it enters the host's cells; without entry, reproduction cannot occur (Gelderblom, 1996). The contagious viral particle inside the host's cell is known as a virion, and it is dependent upon the energy-producing protein "machinery" in the host's cell (Gelderblom, 1996; Fields, 1983).

Research studies performed on genome sequence analysis have revealed that SARS, SARS-CoV-2 (which causes COVID-19), and MERS-CoV belong to the genus *Betacoronavirus* (Chen et al., 2020). Typically, the presentation of COVID-19 infection is mild when compared with other coronaviruses (Chen et al., 2020). With COVID-19, the genetic structure is identical to that of betacoronaviruses and comprises 14 open reading frames (ORFs) in total (i.e., 27 proteins). Of the ORFs, those numbered 1 and 2, found on the 5′- terminal region of the gene, encode a total of 15 non-structural proteins. The major proteins (envelope, membrane, nucleocapsid, and spike), together with eight accessory proteins, are encoded in the 3′-terminal regions (Chen et al., 2020).

Phylogenetic tree analysis was applied to SARS-CoV-2 to evaluate the genetic similarities and differences with other coronaviruses. The findings have shown that SARS-CoV-2 is more phylogenetically analogous to the bat SARS-like coronavirus, SARS-CoV; however, MERS-CoV and SARS-CoV share the same genetic family, with evidence of a distinctive viral evolution (i.e., SARS-CoV-2 versus MERS and SARS) (Benvenuto et al., 2020). Research work on the genomic link between SARS-CoV-2 and SARS family revealed that 380th amino acid substitutions, mostly in non-structural protein genes (Benvenuto et al., 2020). Twenty-seven mutations were observed in genes that encode the viral spike protein that is chiefly responsible for viral entry and receptor binding (Benvenuto et al., 2020; Chan et al., 2020a, 2020b; Lu et al., 2020; Paraskevis et al., 2020; Wu et al., 2020). Coronaviruses belong to the family *Coronaviridae* that comprises positive-strand RNA and enveloped viruses with the capacity to severely infect mammals, birds, and other vertebrates (Masters, 2006). Classification of the virus is based upon data obtained using sequence-based analysis (Snijder et al., 2003; van Boheemen et al., 2012). As per a contemporary classification developed by a *Coronaviridae* family study group, 39 species of coronavirus exist in 27 subgenera, two subfamilies, and five genera (Ziebuhr, 2019; Ziebuhr et al., 2018). In particular, coronaviruses belong to the order *Nidovirales,* subor-der *Cornidovirineae,* and realm *Riboviri* (Ziebuhr, 2019; Ziebuhr et al., 2018; Siddell et al., 2019).

2. Epidemiologic data

COVID-19 is an infectious respiratory disease caused by a novel coronavirus, SARS-CoV-2, which first emerged in Wuhan, China, in late December 2019 (Ksiazek et al., 2003; Peiris et al., 2003; Drosten et al., 2003). The World Health Organization (WHO) declared COVID-19 to be a public health disaster of global concern on January 30, 2020, and a pandemic in March 2020. By May 30, 2021, the total number of confirmed cases and deaths globally were more than 169 million and 3.5 million, respectively (WHO, 2021). The outbreak of COVID-19 cases is similar to those that occurred from 2002 to 2004 (SARS) and in 2012 (MERS) as there are no specific treatment guidelines for people who are infected with the COVID-19 virus and experiencing mild to moderate respiratory symptoms. The risk of acquiring COVID-19 is higher for the elderly and those with a chronic disease, including diabetes mellitus, chronic respiratory disease, cancer, and cardiovascular disease (Jordan et al., 2020). COVID-19 is transmitted via saliva droplets and the nasal discharge of infected individuals when they cough sneeze. Currently, there is no standardized specific therapeutic treatment for COVID-19, although several clinical trials are investigating potential medications (WHO, 2021). MERS-CoV utilizes dipeptidyl peptidase to gain access to the host's cells, and angiotensin-converting enzyme 2 (ACE2), a human cell receptor, is utilized by SARS-CoV and (Wan et al., 2020).

3. SARS-CoV-2

The SARS-CoV-2 virus particle is spherical, and the surface contains protruding projections (i.e. spike proteins). The virus uses these spikes to latch on to human cells. Subsequently, a structural change in the virus results in viral membrane fusion. Later, entry by the viral gene into the host cell takes place, which leads to the production of a large number of viruses. The spikes of SARS-CoV-2 bind to the human cell surface through the Angiotensin-converting enzyme 2 (ACE2) receptors (Lu et al., 2020). The pattern of viral attachment and binding to the host cell was similarly identified during the SARS outbreak that occurred in 2002 (Anthony et al., 2017). Coronaviruses belong to a single-stranded positive-sense RNA enveloped virus family. They are roughly 60–140 nm in diameter, and the virion has a crown-like morphology and club-shaped glycoprotein projections (Tyrrell and Myint, 1996; Singhal, 2020). Regarding the pathophysiology of COVID-19, the first phase comprises viral load and host cell infection, which triggers an inflammatory response in the target cells. Excessive stimulation of the innate immune system causes critical inflammatory tissue destruction, leading to acute respiratory distress syndrome, multiple types of dysfunction, and septic shock in the later phase of viral infection. Of all the steps in viral infection, researchers have focused on the virus' life cycle. The symptoms of COVID-19 include a fever, cough, influenza-like symptoms, night sweats, muscle stiffness, dizziness, diarrhea, nausea, loss of appetite, chills, and pain (WHO, 2021).

4. MERS-CoV

According to the World Health Organization and National Center for Immunization and Respiratory Diseases (NCIRD), MERS is a

viral respiratory infection caused by a novel respiratory coronavirus (MERS-CoV), which is identical to COVID-19. It was first identified in September 2012 in Saudi Arabia, subsequently spreading to 27 countries. Typically, people infected with MERS-CoV experience chronic respiratory illness, along with cough, fever, and shortness of breath. By March 2020, there have been 2,535 confirmed cases of MERS and 876 fatalities. Of these, 80% occurred in Saudi Arabia, with only two cases being recorded in the U.S.; both these cases recovered (NCIRD, 2019; WHO, 2020). In addition to acute respiratory distress syndrome and organ malfunction, MERS-CoV causes kidney and lung impairment through the induction of apoptosis via the upregulation of fibroblast growth factor 2 and SMAD family member 7 (Yeung et al., 2016). The most common clinical manifestations of MERS-CoV are pneumonia, diarrhea, cough, fever, and respiratory impairment, although some MERS-CoV cases are asymptomatic (Hwang et al., 2018). Camels are the major reservoir host for MERS-CoV. Currently, there is no definitive treatment for MERS-CoV, but numerous MERS-CoV vaccines are in the developmental stage (Hemida et al., 2020)

5. Anti-SARS-CoV phytoconstituents

Polyherbal formulations, comprising medicinal plants such as *Flos Chrysanthemi Indici*, *Herba Eupatorii, Fructus Tsaoko*, *Herba Houttuyniae*, and *Herba Artemisiae Scopariae*, have exhibited anticomplementary activity against SARS-CoV. Varius studies have isolated and purified different compounds that inhibited the activity of SARS-CoV. In one study, bioactivity-mediated fractionation and HPLC-DAD-ESI-MS were carried out to isolate 15 phytochemical constituents (Zhang and Chen, 2008). In particular, flavonoids, such as rutin, apigenin, apigenin-7,4′-dimethyl ether, hyperoside, acaciin, acacetin, luteolin, aristolactam, and quercitrin, were demonstrated to exert inhibitory potential on the classical and alternative pathways of the complementary system (Fig. 1). Of the flavonoids extracted from *Herba Artemisiae*, *Herba Houttuyniae*, and *Flos Chrysanthemi Indici*, it was found that luteolin had the most enhanced anticomplementary effect through the classical

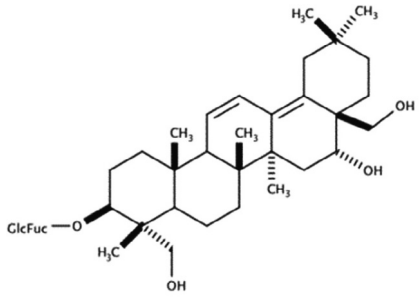

Fig. 2. Antiviral activity of saikosaponin B_2 (Cheng et al., 2006).

pathway (CH_{50}) and alternative pathway (AP_{50})(CH_{50} = 0.19 mM; AP_{50} = 0.17 mM) (Zhang and Chen, 2008).

A study was conducted by Cheng, Ng (Cheng et al., 2006) found that saikosaponins, such as A, B_2, C, and D, extracted from medicinal herbs, *Bupleurum* spp., *Heteromorpha* spp., and *Scrophularia scorodonia*, were shown to have antiviral activity using an XTT cell proliferation assay. The anticoronaviral activities of saikosaponins were reported as follows: saikosaponin A cytotoxic concentration (CC_{50} = 228.1 ± 3.8 μM; effective concentration (EC_{50}) = 8.6 ± 0.3 μM; selectivity index (SI) = 26.6), saikosaponin B_2 (CC_{50} = 383.3 ± 0.2 μM; EC_{50} = 1.7 ± 0.1 μM; SI = 221.9), saikosaponin C (CC_{50} = 121.5 ± 0.1 μM; EC_{50} = 19.9 ± 0.1 μM; SI = 19.2), and saikosaponin D (CC_{50} = 176.2 ± 0.2 μM; EC_{50} = 13.2 ± 0.3 μM; SI = 13.3). Of the four saikosaponins, saikosaponin B_2 was demonstrated to have the most significant antiviral activity on MRC5 cells, with no cytotoxic effects (Fig. 2). MRC5 cells treated with a 2.5 μM concentration of saikosaponin did not cause cytotoxicity. In addition, ≥ 60% of the cells were viable when treated with a 25 μM concentration of four different saikosaponins. Saikosaponin B_2 was found to disrupt the critical steps in the early stages of viral replication, viral

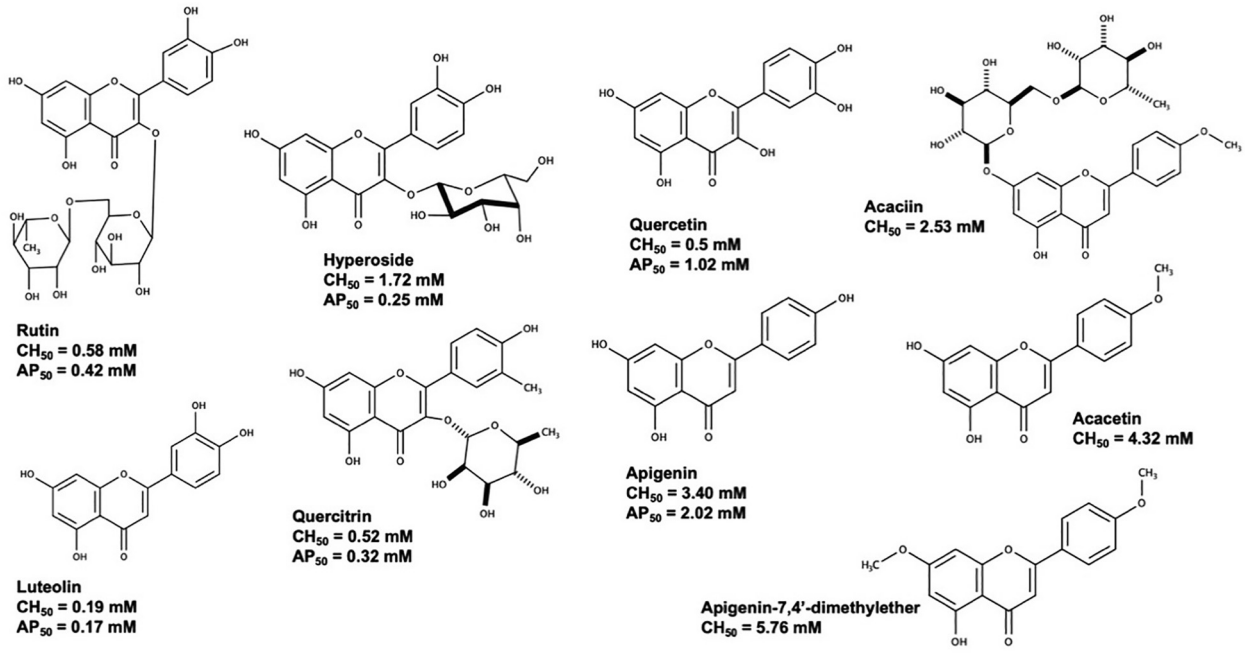

Fig. 1. Anticomplementary effects of flavonoids extracted from Herba Artemisiae, Herba Houttuyniae, and Flos Chrysanthemi Indici (Zhang and Chen, 2008).

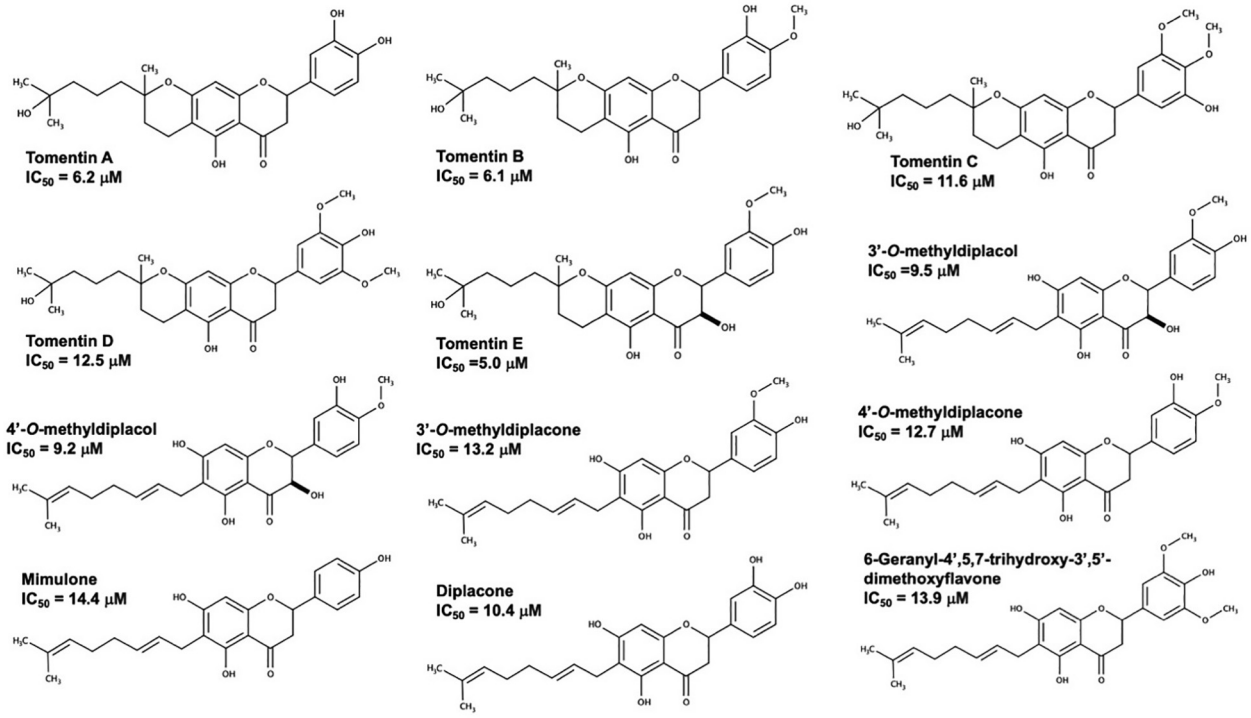

Fig. 3. The isolation of geranylated flavonoids from Paulownia tomentosa and its anti-PL^{pro} abilities (Cho et al., 2013).

attachment, and penetration; it also inhibited human coronavirus 229E (HCoV-229E) infection in (Cheng et al., 2006).

Geranylated flavonoids, such as tomentin A, tomentin B, tomentin C, tomentin D, and tomentin E, together with seven other compounds containing 3,4-dihydro-2H-pyran scaffold (Fig. 3), were isolated from the fruits of *Paulownia tomentosa* and observed to inhibit SARS-CoV papain-like protease (PL^{pro}) (inhibitory concentration (IC_{50}) = 5–14 μM) in a dose-dependent manner (Cho et al., 2013).

The leaf extract of *Toona sinensis* Roem was assessed for antiviral efficacy and an *in vitro* anticoronaviral effect (SI = 12–17) (Chen et al., 2008). The antiviral activities of glycyrrhizin, ribavirin, mycophenolic acid, pyrazofurin, and 6-azauridine against coronavirus clinical isolates, FEM-1 and FEM-2, were evaluated. Glycyrrhizin was found to have an antiviral effect as it obstructed the replication stage of the SARS virus (Cinatl et al., 2003). The anti-SARS-CoV efficacy of the extracts of ≥ 200 Chinese medicinal herbs was determined using an *in vitro* Vero E6 cell-based assay, which assessed the SARS–CoV- triggered cytopathogenic effect. Of these extracts, six extracts from *Gentianae radix* (SI = > 57.5), *Dioscoreae rhizome* (SI = > 62.1), *Cassiae semen* (SI = > 59.4), *Loranthi ramus* (SI = > 92.9), and one extracts from *Rhizoma cibotii* (SI = > 59.4), were reported to have significant anti-SARS-CoV effects (Wen et al., 2011). The six extracts inhibited the SARS-CoV virus at concentrations ranging from 25 to 200 μg/ml. In particular, extracts from *Rhizoma cibotii* (IC_{50} = 39 μg/ml) and *Dioscoreae rhizome* (IC_{50} = 44 μg/ml) demonstrated potent anti-SARS-CoV 3C-like protase ($3CL^{pro}$) efficacy (Wen et al., 2011).

Baicalin, chlorogenic acid, and glycyrrhizin, along with several commercially available antiviral agents, were evaluated for their anti-SARS-CoV activity against 10 clinical isolates of the SARS coronavirus (Chen et al., 2004). Notably, baicalin, chlorogenic acid, and glycyrrhizin did not display anti-SARS-CoV activities in the fRhK-4 cell line. The neutralization assay revealed that glycyrrhizin was more active against the Vero E6 cell line at 72 h, whereas the plaque reduction assay revealed that baicalin had efficacious anti-coronaviral activity in the Vero cell lines (EC_{50} = 11 μg/ml) (Chen et al., 2004). The antiviral activity of extracts obtained from 200 medicinal plants against SARS-CoV was determined using an 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium inner salt assay (Li et al., 2005). Of these extracts, only four of them, *Lycoris radiata*, *Artemisia annua*, *Pyrrosia lingua*, and *Lindera aggregate,* displayed significant inhibitory virus-induced cytopathic effects (CPEs) (EC_{50} = 2.4–88.2 μg/ml). Of these four plants, *Lycoris radiata* was shown to have the strongest antiviral activity. Lycorine was isolated to identify novel phytochemical constituents (Fig. 4), and it was shown to have strong anti-coronaviral activity (EC_{50} = 15.7 nM; CC_{50} = 14980 nM; SI = > 900) (Li et al., 2005).

Lin et al. (2005) conducted a study to evaluate root extract, five compounds, and seven phenolic compounds of *Isatis indigotica* and their anti-SARS-CoV $3CL^{pro}$ effects. $3CL^{pro}$ is involved in the proteolytic conversion of replicase polypeptides 1a and 1ab to active proteins; therefore, it is considered to be a key discovery in drug development. Root extracts, indigo, sinigrin, aloe emodin, and hesperetin showed strong anti-$3CL^{pro}$ activity using a cleavage assay (IC_{50} values of micromolar concentrations) (Fig. 5). In this regard,

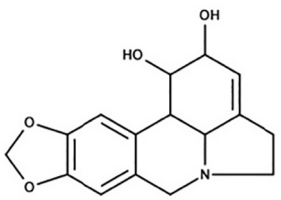

Fig. 4. The anti-SARS-CoV activity of lycorine isolated from Lycoris radiata (Li et al., 2005).

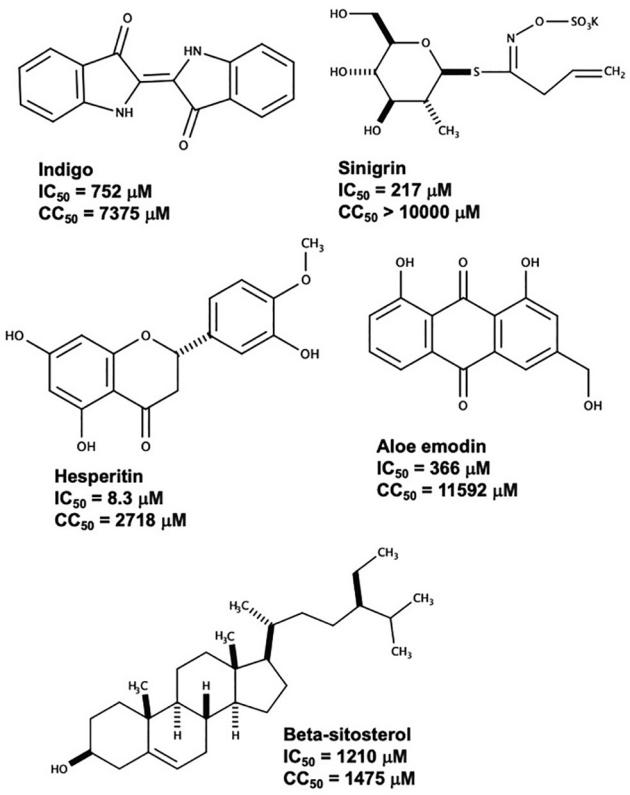

Fig. 5. Anti-PL^{pro} activity of natural compounds extracted from Isatis indigotica (Lin et al., 2005).

of these compounds, sinigrin (IC_{50} = 217 μM) was more potent than the other compounds (indigo, IC_{50} = 752 μM; β-sitosterol, IC_{50} = 1210 μM). The dose-dependent inhibition of cleavage activity was observed for phenolic molecules, aloe emodin (IC_{50} = 366-μM) and hesperetin (IC_{50} = 8.3 μM) using a 3CL^{pro} cell-based assay (Lin et al., 2005).

In another study, the ethanolic extract of *Torreya nucifera* demonstrated antiviral activity against 3CL^{pro}, leading to the isolation of diterpenoids, flavones, and bioflavonoids (Ryu et al., 2010). Of the isolated compounds (18-hydroxyferruginol, hinokiol, ferruginol, 18-oxoferruginol, O-acetyl-18-hydroxyferruginol, methyl dehydroabietate, isopimaric acid, kayadiol, amentoflavone, bilobetin, ginkgetin, and sciadopitysin), amentoflavone (IC_{50} = 8.3 μM), apigenin (IC_{50} = 280.8 μM), luteolin (IC_{50} = 20.2 μM), and quercetin (IC_{50} = 23.8 μM) were associated with significant antiviral activity (Fig. 6). Molecular docking studies carried out in this research corroborated the results obtained from enzymatic assays. In addition, the presence of an apigenin moiety led to inhibitory activity against 3CL^{pro} (Ryu et al., 2010).

Glycyrrhizin and its derivatives were assessed for inhibitory activities against SARS-CoV *in vitro* (Fig. 7) (Hoever et al., 2005). Notably, the modification of the glycyrrhizin parent compound, following the inclusion of 2-acetamido-β-D-glucopyranosylamine with the glycoside residue of glycyrrhizin, led to a 10-fold improvement in anti-coronaviral activity when compared with the parent molecule.

Amide derivatives, two amino acid residues conjugated to the parent compound, along with free 30-COOH, had 70-fold greater antiviral effects against SARS-CoV compared to glycyrrhizin; nevertheless, cytotoxicity was increased, which meant a reduction in the SI (Hoever et al., 2005). Tanshinones, such as tanshinone I, tanshinone IIA, tanshinone IIB, dihydrotanshinone I, rosmariquinone,

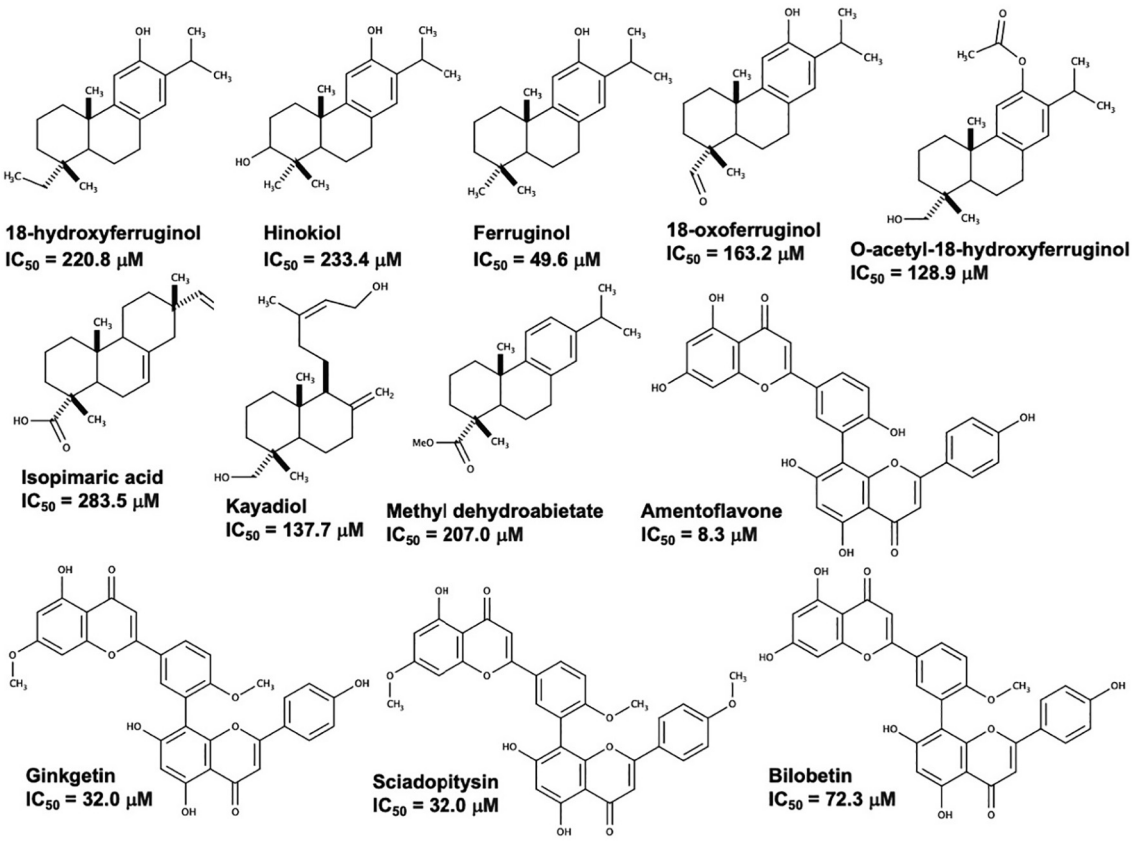

Fig. 6. The isolation of anti-3CL^{pro} natural products from Torreya nucifera (Ryu et al., 2010).

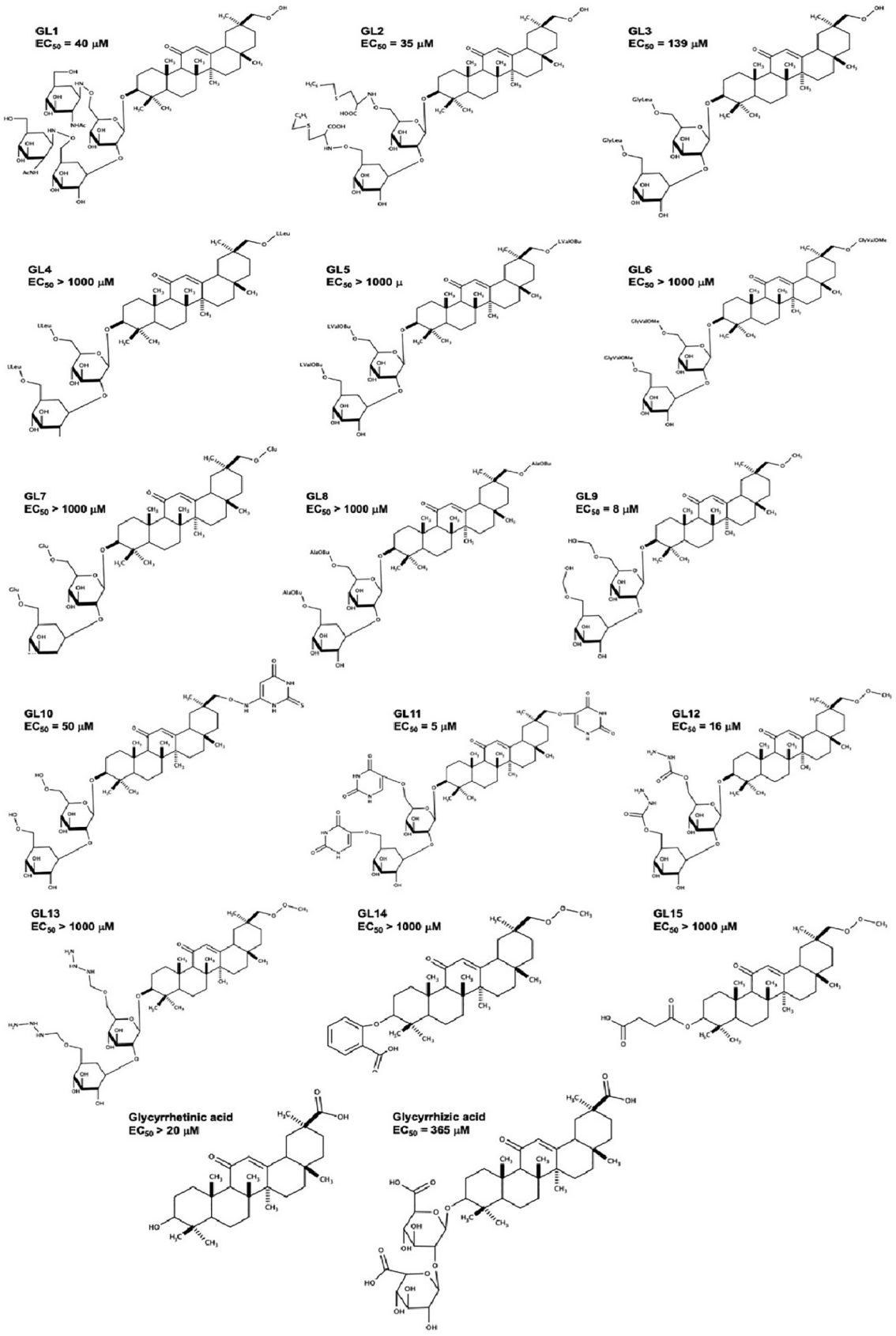

Fig. 7. Anti-SARS-CoV activity of glycyrrhizin and its derivatives (Hoever et al., 2005).

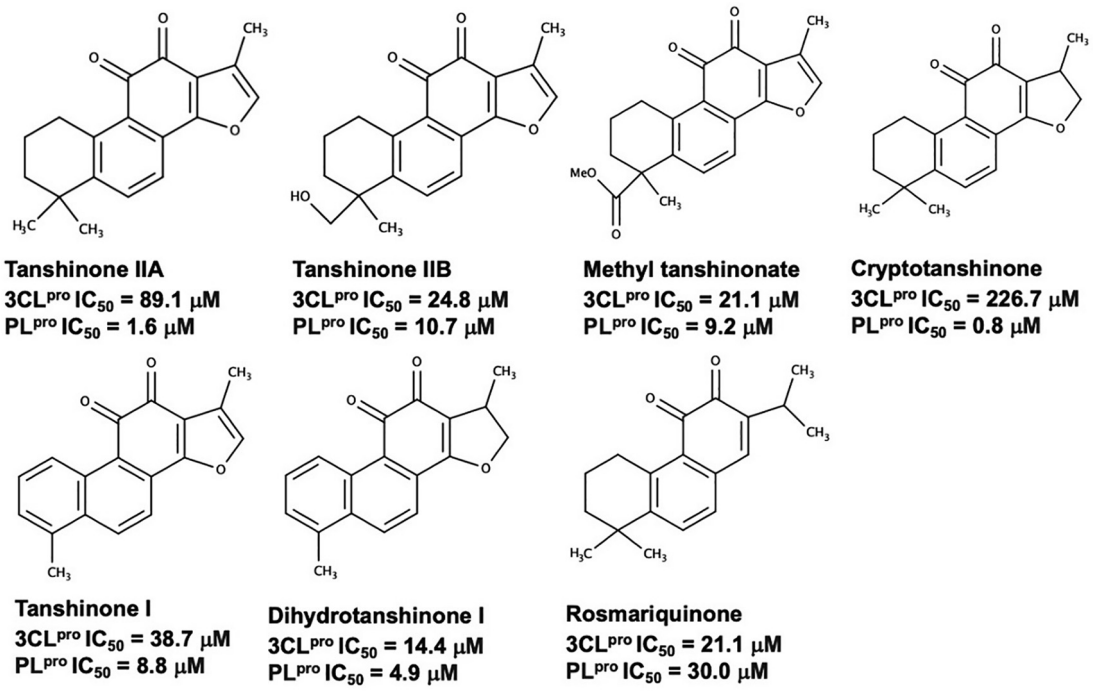

Fig. 8. Anti-PL^{pro} and anti-3CL^{pro} activity of tanshinone derivatives from Salvia miltiorrhiza (Park et al., 2012).

methyl tanshinonate, and cryptotanshinone, isolated from *Salvia miltiorrhiza,* inhibited SARS-CoV papain-like protease (PL^{pro}) and 3CL^{pro} (Park et al., 2012). Excepting rosmariquinone, these compounds were noncompetitive enzyme isomerization inhibitors. Importantly, all tanshinone derivatives inhibited PL^{pro} time dependently (Fig. 8); however, compounds pre-treated with 3CL^{pro} did not show enhanced inhibitory activity. Of the tanshinones, tanshinone I was found to be the most effective in inhibiting the deubiquitylation process (Park et al., 2012).

Lectins from 33 plants were assessed for anti-SARS-CoV potential and demonstrated significant antiviral effects against the coronavirus at non-toxic concentrations of 50–100 μg/ml (Keyaerts et al., 2007). Remarkable antiviral efficacy was attributed to mannose-binding lectins, while antiviral effects were also achieved by carbohydrate-binding lectins (i.e., glucose, galactose, galactose, N-acetylgalactosamine, and N-acetylaglucosamine). In this study, the natural lectins acted via two targets, the first of which appeared to be a viral attachment in the early phase of the replication cycle and the second of which was the final phase in the infectious cycle (Keyaerts et al., 2007). SARS-CoV spike protein, a type 1 membrane-bound protein, plays a critical role in the process of viral attachment to the host's cells via ACE2. Of 312 herbal plants, only three belonging to the Polygonaceae family interrupted the interaction between ACE2 and the SARS-CoV S protein, thus displaying antiviral activities. The root tubers collected from *Polygonum multiflorum* Thunb and *Rheum officinale* Baill and the vines from *Polygonum multiflorum* Thunb were shown to have anti-SARS-CoV S protein and ACE2 effects (IC$_{50}$ = 1–10 μg/ml). The dose-dependent inhibition of SARS-CoV S protein and ACE2 was achieved by emodin, an antiviral anthraquinone phytoconstituent extracted from two genera, Rheum and Polygonum. In addition, emodin abolished S protein-pseudotyped retrovirus-mediated infection in Vero E6 cells (Ho et al., 2007).

Houttuynia cordata, used as a component in a heat reduction and detoxification formulae, was also assessed for its anti-SARS-CoV efficacy. Research into the water extract of *Houttuynia cordata* revealed that the extract might trigger the significant and dose-dependent proliferation of mouse spleen lymphocytes. In addition, there was an increase in the levels of interleukin (IL)-2 and IL-10 and the CD4^{+} and CD8^{+}T cell count. In particular, the water extract contained anti-SARS-CoV 3CL^{pro} and RNA-dependent RNA polymerase. An extract of *Houttuynia cordata,* administered orally at 16 g/kg to animals in an acute oral toxicity study, was not associated with toxic effects (Lau et al., 2008).

The extract of *Rheum palmatum* had a significant anti-SARS-CoV 3CL^{pro} effect (IC$_{50}$ = 13.76 μg/ml, a 96% inhibition rate) (Luo et al., 2009). ORF-3a in SARS-CoV and human coronavirus OC43 (HCoV-OC43) codes the ion-permeable channel (the cation-selective channel, in particular) in infected cells, and this plays a key role in viral release. In another study, emodin blocked the release of the virus from infected cells and the 3a ion channel found in SARS-CoV and HCoV-OC43 (Schwarz et al., 2014). Flavonol derivatives, kaempferol, acylated kaempferol glucoside, and kaempferol glycosides, were also evaluated for their ability to suppress viral release in the 3a channel (Schwarz et al., 2014). Juglanin (IC$_{50}$ = 2.3 μM), an arabinose moiety, was shown to be a strong inhibitor of the 3a channel. Aside from juglanin, kaempferol derivatives with rhamnose moiety exhibited moderate anti-SARS-CoV activity via blocking of the 3a channel, therefore, inhibit virus release (Schwarz et al., 2014). The anti-SARS-CoV 3CL^{pro} potential of flavonoids, quercetin, epigallocatechin gallate, gallocatechin gallate, daidzein, epigallocatechin, ampelopsin, and puerarin, was analyzed. Epigallocatechin gallate (73 μM), quercetin (73 μM), and gallocatechin gallate (47 μM) had a significant inhibitory activity of 3CL^{pro} (Nguyen et al., 2012).

An ethanolic extract of *Euphorbia neriifolia* yielded 22 triterpenoids and one flavonoid glycoside (Chang et al., 2012). Of the isolated natural compounds, 3-beta friedelanol displayed strong antiviral activity when compared with the positive control, actinomycin D, in this study. These research findings provide support for the inclusion of friedelanol-containing triterpenoids in the development of drugs containing novel anti-SARS-CoV-229E molecules (Chang et al., 2012). Three novel pyranoxanthones, namely blancoxanthone, acetyl blancoxanthone, and

3-hydroxyblancoxanthone, and well-known pyranoxanthones, pyranojacaeubin and caloxanthone, were isolated from the roots of *Calophyllum blanco.* Of the pyranoxanthones, pyranojacareubin (15 μg/ml) and blancoxanthone (3 μg/ml) demonstrated the highest anti-SARS-CoV inhibitory activity against virus-induced cytopathic toxicity (Shen et al., 2005).

6. Natural compounds as agents against MERS-CoV

Lin et al. (2017) reported that resveratrol had antiviral activities against MERS-CoV, significantly suppressed MERS-CoV, and extended the cell viability of MERS-infected Vero E6 cells. In addition, a reduction in the nucleocapsid protein expression levels critical for MERS-CoV replication and the downregulation of apoptosis were observed in the cells after treatment with resveratrol. Eventually, a reduction in the resveratrol dose concertation was achieved by consecutive administration without reducing the inhibitory effect against MESR-CoV (Lin et al., 2017). Silvestrol, a phytoconstituent from *Aglaia* spp., inhibited MERS-CoV (EC_{50} = 1.3 nM), and potent antiviral activity was observed in peripheral blood mononuclear cells. Silvestrol was seen to have antiviral potential via the inhibition of RNA helicase eIF4A and CoV protein expression and specifically targeted viral replication in MERS-CoV (Müller et al., 2018).

A basic characteristic of the enveloped surface found in coronaviruses is the presence of spike proteins on their surface, which are critical to viral entry into the host's cells (O'Keefe et al., 2010). Elevated levels of glycosylated spike proteins constitute a good target for the class of lectins in drug development. Two key functions of spike proteins are to help bind the virus to the target cells and facilitate the fusion of the target cell membrane with the virus envelope (Millet et al., 2016). Lectins are considered promising anti-coronaviral drug molecules, which primarily bind with spike proteins. Griffithsin, isolated from Griffithsia, a red marine algae species, is a natural lectin compound that consists of carbohydrate-binding sites (Millet et al., 2016). Griffithsin interacts with the MERS-CoV spike protein via glycans residue, thereby preventing viral attachment to the host's cells (Millet et al., 2016). An *in vitro* study of griffithsin showed anti-MERS-CoV effects (EC_{50} = 0.125 μM) (Millet et al., 2016). In another study, the anti-SARS-CoV activity of griffithsin was examined *in vitro* and *in vivo* experiments (O'Keefe et al., 2010). The inhibition of entry by the virus into the target organism was achieved via binding by griffithsin with the spike proteins located in SARS-CoV (O'Keefe et al., 2010). Griffithsin has also been shown to be potent against coronaviruses in birds and mammals. In a study that evaluated SARS-CoV infection in a mouse model, it had a significant positive impact on morbidity and mortality (O'Keefe et al., 2010). In addition, the unwanted adverse effects of the immunological response by the host's cells to SARS-CoV pathogenesis were inhibited by griffithsin (O'Keefe et al., 2010; Millet et al., 2016).

7. Drug repurposing methodology in the treatment of SARS-CoV

Niclosamide has been prescribed as an anthelminthic drug for several years and was found to hinder the replication stage of SARS-CoV; it also effectively abolished the synthesis of viral antigens (at a concentration of 1.56 μM) (Wu et al., 2004). Docking approaches, such as homology modelling, involving a crystallographic structure that shows the binding pocket of the $3CL^{pro}$ enzyme, were carried out to determine whether potent molecules would strongly bind with $3CL^{pro}$. Cinanserin, a serotonin antagonist, was isolated and underwent various bioassays, including a replicon system-based assay to evaluate HCoV-229E and a quantitative assay to assess infective SARS-CoV and HCoV-229E (Chen et al., 2005). Cinanserin achieved effective inhibition in the replication stage without any toxicity (IC_{50} = 19–34 μM) (Chen et al., 2005).

Numerous drug compounds (n = 2,406) were screened for their antiviral potential and were shown to have a mediating cytopathic effect (CPE) on viral infection in the 2019-n-CoVr and Vero E6 cell line models (Fan et al., 2020). A portion of each tested molecule (10 μM) was included in the experiments, and the cells were assessed at a 72-hour timepoint. At this juncture, three bioactive candidates, cepharanthine, mefloquine hydrochloride, and selamectin, were added to the infected cells (Fan et al., 2020). Inhibitory CPEs were observed. The levels of viral RNA after treatment with 10 μM of cepharanthine were 15,393-fold less than those of the control infected cells (Fan et al., 2020). Studies on viral RNA quantification revealed that cepharanthine, mefloquine hydrochloride and selamectin, considerably reduced viral replication. Of the three compounds, cepharanthine had a remarkable antiviral effect (EC_{50} = 0.98 μM; CC_{50} = 39.30 μM; SI = 39.91) (Fan et al., 2020). Past results of past research on the antiviral potential of cepharanthine in relation to HCoV-OC43 and SARS-CoV was in agreement with the findings of this study (Kim et al., 2019). The inhibiting potential of cepharanthine on viral entry and post entry processes was evaluated, and it was shown to have potent antiviral activity by preventing infection with coronavirus at these different stages (Fan et al., 2020).

8. Conclusion and future perspectives

The discovery and development of novel antiviral drugs are challenging owing to virus latency and high rates of mutation, while the deleterious adverse effects of antiviral compounds seriously hinder drug development furthered by the discovery of antiviral molecules. Notably, more than 5,800 clinical trials on COVID-19 have been reported in ClinicalTrials.

SARS-CoV-1, first identified in 2002, spread across the globe, and a new variant, SARS-CoV-2, which first emerged in 2019, is currently responsible for millions of fatalities worldwide. In 2002, 916 people died due to respiratory and immune system complications (Peiris et al., 2003) The complement activation in the pathogenesis of post-viral complications is considered to be very important; therefore, researchers have carried out work to identify antiviral agents that act on the complementary process with a view to using them as an effective option in the treatment of SARS (Zhang and Chen, 2008; Chen et al., 2008; Abe, 2006; Sarma et al., 2006; Sahu and Lambris, 2000). As the replication of SARS-CoV-2 occurs in the cytoplasm of virus-infected cells, targeting the replication phase of a particular virus is also considered to be a way of controlling COVID-19. The coronavirus proteases-dependent activities of replicase polyprotein mediate the replication process, and translation of the RNA replicase occurs in the viral genome. Protease found in the replicase, such as PL^{pro} and $3CL^{pro}$, facilitates its own liberation and the release of other non-structural proteins. PL^{pro} essentially has two key functions, which are to process the viral polyprotein and affect the cleavage of ubiquitin chains, followed by deISGylation, which makes PL^{pro} a viable focus for the development of antiviral drugs (Lenschow et al., 2007).

To summarize, traditional medicine has been an invaluable resource in the discovery of natural antiviral natural compounds for drug development, and it has numerous advantages, including abundant availability (i.e., of herbal and marine resources), minimal side-effects, robust resistance against viruses, cost-effectiveness, chemical diversity, and chemical novelty (Dhama et al., 2018; Huang et al., 2014; Mukhtar et al., 2008; Pushpa et al., 2013). In this review, several effective compounds are

mentioned that have an inhibition effect against the coronavirus. Compounds that have the lowest inhibition concentration are considered the most effective, including luteolin, saikosaponin B2, silvestrol, griffithsin and cepharanthine.

Natural products also have limitations such asperforming an assay of a natural product requires high-throughput screening and robust techniques as it is difficult to determine their mechanism of action and potential activity (Li and Vederas, 2009). The chemical structures of bioactive substances are also complex in nature. In addition, the isolation, purification, characterization and accessibility of natural products is time consuming and expensive (Harvey, 2000). Lastly, legislation governing biological resources is perplexing (Newman and Cragg, 2016; Strohl, 2000). Many drug molecules present in the market have been inspired by natural products and traditional medicines. Therefore, hopefully, natural products will be found to provide a treatment solution to COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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