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REVIEW

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Natural products for COVID-19 prevention and treatment regarding to previous coronavirus infections and novel studies

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Recently, the novel life-threatening coronavirus infection (COVID-19) was reported at the end of 2019 in Wuhan, China, and spread throughout the world in little time. The effective antiviral activities of natural products have been proved in different studies. In this review, regarding the effective herbal treatments on other coronavirus infections, promising natural products for COVID-19 treatment are suggested. An extensive search in Google Scholar, Science Direct, PubMed, ISI, and Scopus was done with search words include coronavirus, COVID-19, SARS, MERS, natural product, herb, plant, and extract. The consumption of herbal medicine such as *Allium sativum*, *Camellia sinensis*, *Zingiber officinale*, *Nigella sativa*, *Echinacea* spp. *Hypericum perforatum*, and *Glycyrrhiza glabra*, *Scutellaria baicalensis* can improve the immune response. It seems that different types of terpenoids have promising effects in viral replication inhibition and could be introduced for future studies. Additionally, some alkaloid structures such as homoharringtonine, lycorine, and emetine have strong anti-coronavirus effects. Natural products can inhibit different coronavirus targets such as S protein (emodin, baicalin) and viral enzymes replication such as $3CL^{pro}$ (Iguesterin), PL^{pro} (Cryptotanshinone), helicase (Silvestrol), and RdRp (Sotetsuflavone). Based on previous studies, natural products can be introduced as preventive and therapeutic agents in the fight against coronavirus.

KEYWORDS
$3CL^{pro}$ inhibitors, ACE2, coronavirus, COVID-19, natural products, PL^{pro} inhibitors

1 | INTRODUCTION

Atypical pneumonia from coronavirus infections is a life-threatening disease in humans. Pervious outbreak coronavirus infection was the severe acute respiratory syndrome (SARS) in 2003 in China and Middle East respiratory syndrome (MERS) in 2012 in Saudi Arabia (Drosten et al., 2003). Recently, the novel coronavirus infection (COVID-19) was reported at end of 2019 in Wuhan, China, and spread throughout the world in little time. According to the World Health Organization (WHO) reports in 3 months COVID-19 became to pandemic disease. According to the reports from the Centers for Disease Control and Prevention (CDC), the COVID-19 symptoms have ranged from mild symptoms to severe illness and death. Based on the MERS-CoV infection, the incubation period of SARS-CoV-2 may between 2 and 14 days after exposure. COVID-19 symptoms include fever, coughing, sore throat, fatigue, and shortness of breath. The COVID-19 may present with mild and moderate disease (81% of cases), or severe disease (14% of cases). In 5% critical disease has occurred with respiratory failure, septic shock, multiple organ dysfunction, or multiple organ failure (Wu & McGoogan, 2020).

Because there is no specific vaccine and treatment for COVID-19, the first therapeutic strategy for patients is only supportive. Like

Abbreviations: $3CL^{pro}$, 3Clike protease; ACE2, angiotensin-converting enzyme 2; AT1R, angiotensin II type 1 receptor; CoVs, coronaviruses; E, envelope; HE, hemagglutinin–esterase; M, membrane; MERS, Middle East respiratory syndrome; N, nucleocapsid; PL^{pro}, papain-like protease; RAS, renin–angiotensin system; RDE, receptor-destroying enzyme; RdRp, RNA-dependent RNA polymerase; S, spike; SAR, structure–activity relationship; SARS, severe acute respiratory syndrome.

the previous CoV infection epidemics, preventive actions such as quarantine are important for all communities to reduced transmission virus. Furthermore, SARS-CoV-2 is sensitive to heats and UV rays and inactivated with disinfectants like ethanol (70%) and sodium hypochlorite so, frequently disinfection is effective in combat with SARS-CoV-2.

An extensive search between 1990 and 2020 in electronic databases (Google Scholar, Science Direct, PubMed, ISI, and Scopus) was done with search words include coronavirus, COVID-19, SARS, MERS, natural product, herb, plant, and extract.

In this review, regarding the previous herbal effective treatments for SARS and MERS, and other studies on coronavirus infection, the potential herbal treatments for COVID-19 are suggested.

2 | CLASSIFICATION OF CORONAVIRUS

Coronaviruses (CoVs) from subfamily the *Orthocoronavirinae* in *Coronaviridae* family are enveloped, single-stranded RNA viruses that have been known for more than five decades (Cheever, Daniels, Pappenheimer, & Bailey, 1949) and can infect different animal species and humans and cause respiratory and neurological diseases (Weiss & Leibowitz, 2011). Taxonomy studies show that CoVs are divided into four genera including α-coronavirus, β-coronavirus, δ-coronavirus, and γ-coronavirus. CoVs that cause mainly respiratory tract infections belong to the α-coronavirus and β-coronavirus groups. β-coronavirus group divided into four subgroups (a, b, c, and d). SARS-CoV and MERS-CoV are classified in b and c lineage, respectively (Chan et al., 2015). The SARS-CoV-2 sequence analysis showed that is classified belongs to the b lineage (Cascella, Rajnik, Cuomo, Dulebohn, & Napoli, 2020; Figure 1). Bioinformatics analysis of the SARS-CoV-2 genome has shown 89% similarity with bat SARS-like-CoVZXC21 and 82% similarity with that of human SARS-CoV (Chan et al., 2020).

3 | PREVENTION OF COVID-19 AND IMMUNE ENHANCERS

Like other viral diseases, the host immune response is one of the most important solutions for protection against viral infection. Herbal medicines can improve host antiviral immune response and increase the survival rate in COVID-19. Considering the immune enhancer activity of herbal medicines, some of the famous natural immune boosters are useful for COVID-19 prevention include *Allium sativum*, *Camellia sinensis*, *Zingiber officinale*, *Nigella sativa*, *Echinacea* spp. *Hypericum perforatum*, and *Glycyrrhiza glabra* (Sultan, Buttxs, Qayyum, & Suleria, 2014). Furthermore, based on historical data from previous coronavirus infection, natural medicine has a significant role in the prevention of infection, especially in high-risk patients. The most used herbs included *Astragalus membranaceus*, *Glycyrrhiza glabra* (Luo et al., 2020), *Scutellaria baicalensis*, *Gypsum fibrosum*, *Bupleurum chinense*, *Gardenia jasminoides* (Hsu et al., 2008). So, natural medicine has potential benefits in COVID-19 prevention and can be advised in high-risk patients with regarding the underlying medical conditions (Figure 2).

4 | TREATMENT STRATEGIES FOR COMBAT WITH COVID-19

Studies in SARS-CoV and MERS-CoV pathophysiology are limited but the pathogenesis mechanisms of viral infection are similar. Understanding the structure and virion particle of CoVs is important in the prevention and therapeutic interventions of COVID-19. The different parts of coronavirus include spike (S), envelope (E), membrane (M), nucleocapsid (N), and structural proteins and some also encode a hemagglutinin–esterase (HE) protein (Tseng et al., 2010).

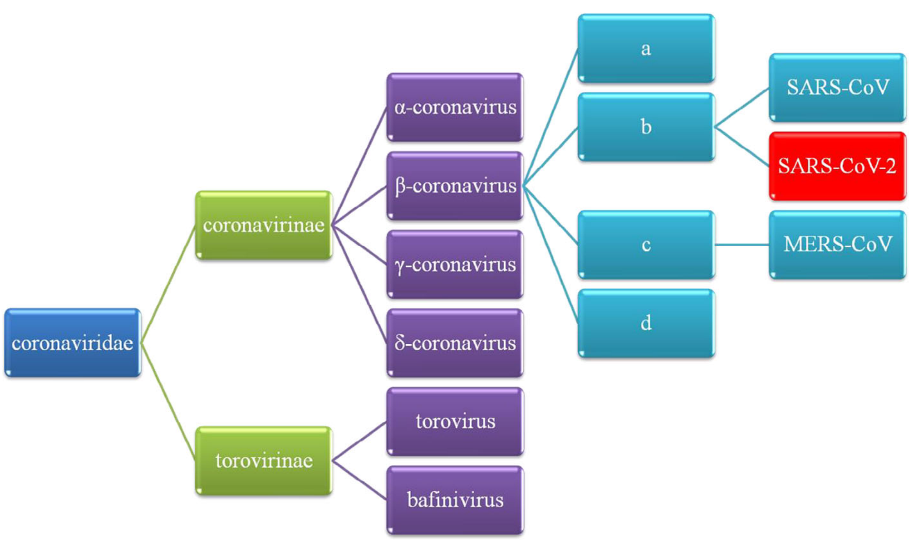

FIGURE 1 Classification of different types of coronavirus [Colour figure can be viewed at wileyonlinelibrary.com]

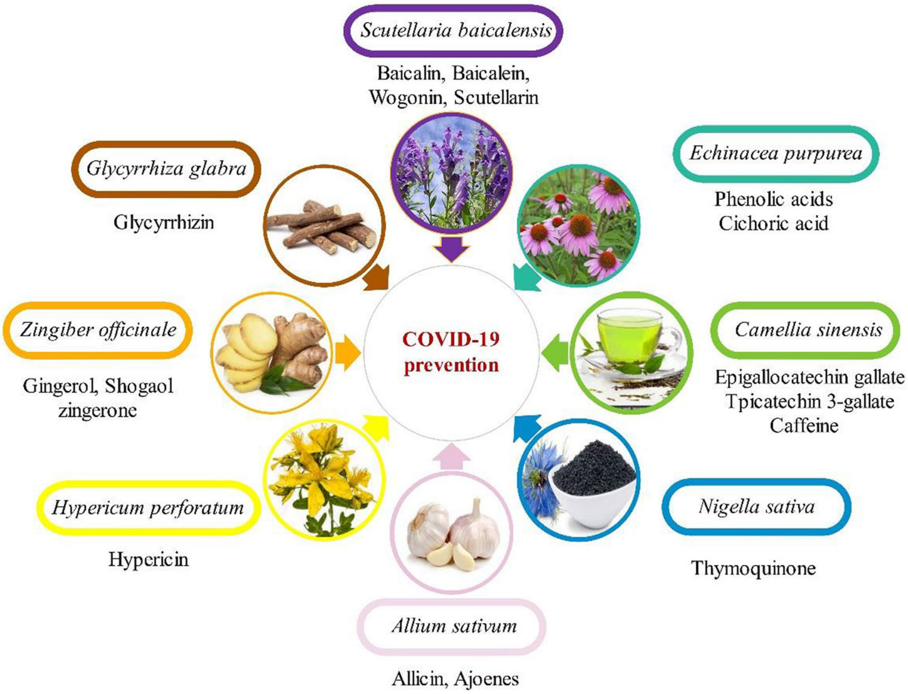

FIGURE 2 COVID-19 prevention with natural products [Colour figure can be viewed at wileyonlinelibrary.com]

4.1 | Viral attachment inhibition

The initial step in viral infection is the virus attachment to the appropriate host cells. One of the important mechanisms in viral attachment is viral glycoprotein to cell carbohydrate interaction such as sialic acid. The coronavirus glycoprotein is responsible for host cell recognition, virus fusion, and destroys the receptor. The receptor-destroying enzyme (RDE) activity is important for virus release (Mesecar & Ratia, 2008). In coronavirus, the HE glycoprotein is responsible for receptor binding and receptor-destroying activity. Spike (S) glycoprotein is involvement in host cell recognition and virus-host membrane fusion (Thiel, 2008).

S glycoprotein is cleaved by the host cell protease (e.g., TMPRSS2) into S1 and S2 subunits. S1 is responsible for binding to host cell surface receptors, and the S2 mediates the fusion of the virus to the host cell (Xia et al., 2014). S glycoprotein in subgroup b from β-coronaviruses recognizes and binds to angiotensin-converting enzyme 2 (ACE2). Therefore, ACE2 is a strong SARS-CoV receptor (Li et al., 2003) and also in SARS-CoV-2 (Hoffmann et al., 2020). Renin–angiotensin system (RAS) is involved in SARS-CoV infection and ACE2 expression is increased during SARS infection and following lung failure (Kuba et al., 2005). So, ACE2 inhibitors can be produced as a potential therapy for COVID-19 and other coronavirus infections.

A screening about medicinal plants that significantly interacted with S protein and ACE2 demonstrated that *Rheum officinale* and *Polygonum multiflorum* can be inhibited the ACE2 with IC_{50} values ranged from 1 to 10 μg/ml. Emodin with anthraquinone structure is an active ingredient in this genus and significantly blocked the S protein and ACE2 interaction in a dose-dependent manner. SAR analysis showed that the side chains of the anthraquinone skeleton have a great impact on the S protein and ACE2 binding (Ho, Wu, Chen, Li, & Hsiang, 2007). So, emodin could be suggested as a potential treatment for SARS-Cov2.

On the other hand, an imbalance between ACE2/Ang (1–7)/Mas receptor and ACE/Ang-II/AT1R pathway in the RAS leads to inflammation and severe pneumonia. SRAR-CoV-2 bind to ACE2 and the ACE2/Ang (1–7)/Mas receptor pathway was inhibited and an imbalance in RAS has occurred. This pathway inhibition was occurred in other severe respiratory diseases (Ji, Gao, Sun, Hao, & Liu, 2015; Khan et al., 2017; Yu et al., 2016). So, the activation of the ACE2/Ang (1–7)/Mas receptor pathway might reduce the pulmonary inflammatory response and mortality in COVID-19 (Brojakowska, Narula, Shimony, & Bander, 2020; Sun, Yang, Sun, & Su, 2020).

Sini decoction from Traditional Chinese Medicine consists of three different herbs: aconite (*Aconitum carmichaelii*), licorice (*Glycyrrhiza glabra*), and ginger rhizome (*Zingiber officinale*). Sini decoction significantly ameliorated *E. coli*-induced acute lung injury by reducing inflammatory factors in lung tissue and decrease the expression of ACE and angiotensin II type 1 receptor (AT1R). Furthermore, Sini decoction could activate the ACE2-Ang-(1–7)-Mas pathway (Liu et al., 2018). So, Sini decoction could be effective in COVID-19 treatment.

Baicalin a glycosylated flavonoid derived from the *S. baicalensis*, significantly reduced cell oxidative damage induced by Ang II and activated ACE2-Ang-(1–7)-Mas pathway. Baicalin can protect endothelial cells from oxidative stress and Ang-II dysfunction via PI3K/AKT/eNOS pathway upregulation and ACE2/Ang-(1–7)/Mas activation. Taken together, baicalin can be suggested as a potential treatment for COVID-19 treatment via ACE2/Ang-(1–7)/Mas activation (Wei et al., 2015).

The second glycoprotein that expresses on the surface of some coronavirus is HE with hemagglutination and acetylesterase function. In Influenza, A/B virus hemagglutinin (HA) is related to enzyme neuraminidase (NA) or sialidase. Neuraminidase inhibitors (such as oseltamivir or zanamivir) are a class of antiviral drugs with preventing the viral by budding from the host cell and viral reproduction. But HE glycoprotein from human CoV binds to sialic acid-9-O-acetylestrase that causing hemagglutination and acetylesterase function (De Groot, 2006).

4.2 | Genome replication inhibition

The important viral protease enzymes in SARS-CoV replication are 3Clike protease ($3CL^{pro}$) and papain-like protease (PL^{pro}). The other essential enzymes in SARS-CoV replication are helicase and RdRp. So inhibitors against these enzymes can be suggested as potential drugs for COVID-19 treatment.

4.2.1 | Chymotrypsin-like (3CLpro) inhibitors

The $3CL^{pro}$ enzyme (or main protease (M^{pro})) that encoded in CoVs is responsible for the proteolysis, viral replication, and infection process, thereby making it an ideal target for antiviral therapy. Table 1 is summarized the natural products with $3CL^{pro}$ inhibitory activity.

The most potential structure with SARS-CoV $3CL^{pro}$ inhibitory activity is iguesterin (IC_{50}: 2.6 μM) and pristimerin (IC_{50}: 5.5 μM) with quinone-methide triterpenes structure that isolated from *Tripterygium regelii* (Ryu, Park, et al., 2010b).

Another potential in vitro $3CL^{pro}$ inhibitor structure is tannins compounds. Among tannins structure, tannic acid (IC_{50}: 3 μM) and 3-Isotheaflavin-3 gallate (IC_{50}: 7 μM) that isolated from *Camellia sinensis* have more potent inhibitory activity against $3CL^{pro}$ (Chen, Lin, et al., 2005a).

TABLE 1 Natural products with $3CL^{pro}$ inhibitory activity

Plant	Active compound	Class of compounds	Additional data	Reference
Rheum palmatum extract	—	—	IC_{50}: 13.76 μg/ml	(Luo et al., 2009)
Salvia miltiorrhiza	Rosmariquinone	Abietane analog	IC_{50}: 21.1 μM	(Park et al., 2012b)
Salvia miltiorrhiza	Methyl tanshinonate	Abietane diterpen	IC_{50}: 21.1 μM	(Park, Kim, et al., 2012b)
Salvia miltiorrhiza	Dihydrotanshinone I	Abietane diterpen	IC_{50}: 14.4 μM	(Park, Kim, et al., 2012b)
Angelica keiskei	Xanthoangelol E	Alkylated chalcones	IC_{50}: 11.4 μM	(Park et al., 2016)
Angelica keiskei	Xanthoangelol B	Alkylated chalcones	IC_{50}: 22.2 μM	(Park et al., 2016)
Camellia sinensis black tea	Theaflavin-3,3′ digallate	Polyphenols (tannins)	IC_{50}: 9.5 μM	(Chen et al., 2005a)
Camellia sinensis	3-Isotheaflavin-3 gallate	Polyphenols (tannins)	IC_{50}: 7 μM	(Chen, Lin, et al., 2005a)
Camellia sinensis	Tannic acid	Polyphenols (tannins)	IC_{50}: 3 μM	(Chen, Lin, et al., 2005a)
Isatis indigotica	Hesperetin	Flavonoids	IC_{50}: 8.3 μM	(Lin et al., 2005)
Vegetables	Quercetin	Flavonoids	IC_{50}: 23.8 μM	(Ryu et al., 2010a)
Vegetables	Luteolin	Flavonoids	IC_{50}: 20.2 μM	(Ryu, Jeong, et al., 2010a)
Torreya nucifera	Amentoflavone	Bioflavonoids	IC_{50}: 8.3 μM	(Ryu, Jeong, et al., 2010a)
Torreya nucifera	Apigenin	Flavonoids	IC_{50}: 280.8 μM	(Ryu, Jeong, et al., 2010a)
Juniperus formosana	Betulinic acid	Terpenoids	IC_{50}: 10 μM Competitive inhibitor (K_i: 8.2 μM)	(Wen et al., 2007)
Chamaecyparis obtusa	Savinin	Lignoids	IC_{50}: 25 μM Competitive inhibitor (K_i: 9.1 μM)	(Wen et al., 2007)
Triterygium regelii	Celastrol	Terpenoids	IC_{50}: 10.3 μM Competitive inhibitor	(Ryu et al., 2010b)
Triterygium regelii	Pristimerin	Terpenoids	IC_{50}: 5.5 μM Competitive inhibitor	(Ryu, Park, et al., 2010b)
Triterygium regelii	Tingenone	Terpenoids	IC_{50}: 9.9 μM Competitive inhibitor	(Ryu, Park, et al., 2010b)
Triterygium regelii	Iguesterin	Terpenoids	IC_{50}: 2.6 μM Competitive inhibitor	(Ryu, Park, et al., 2010b)
Curcuma longa	Curcumin	Diaryl heptanoid	IC_{50}: 40 μM	(Wen et al., 2007)

4.2.2 | Papain-like protease (PLpro) inhibitors

Another CoV protease enzyme is a papain-like protease (PL^{pro}) that responsible for proteolysis, host's innate immunity antagonist, deubiquitination, and viral replication (Clementz et al., 2010), so make an important target for antiviral drugs. Table 2 is summarized the natural products with PL^{pro} inhibitory activity.

One of the most potential PL^{pro} inhibitory compounds is tanshinones with an abietane diterpene structure that isolated from *Salvia miltiorrhiza*. Tanshinone is good inhibitors of both $3CL^{pro}$ and PL^{pro}. However, their activity against PL^{pro} was much stronger than $3CL^{pro}$. IC_{50} values of Cryptotanshinone, Tanshinone IIA, and Dihydrotanshinone I were 0.8, 1.6, and 4.9 μM, respectively. The other structure with PL^{pro} inhibitory activity is diarylheptanoids such as Hirsutenone from *Alnus japonica* and showed more potent inhibitory activity against PL^{pro} (IC_{50}: 4.1 μM) and curcumin from *Curcuma longa* (IC_{50}: 5.7 μM; Park, Jeong, et al., 2012a). Also, prenylated chalcones such as xanthoangelol E and xanthoangelol F that isolated from *Angelica keiskei* have strong noncompetitive inhibition against PL^{pro} with IC_{50} range 1.2 and 5.6 μM, respectively (Park et al., 2016).

4.2.3 | RNA-dependent RNA polymerase (RdRp) inhibitors

RdRp is essential for viral replication and transcription of positive-strand RNA viruses (Chan et al., 2015). Antiviral drugs with RNA polymerase inhibitory activity are a good candidate for coronavirus treatment.

TABLE 2 Natural products with PL^{pro} inhibitory activity

Plant	Active compound	Class of compounds	Additional data	Reference
Salvia miltiorrhiza	Tanshinone I	Abietane diterpen	IC_{50}: 8.8 μM	(Park, Kim, et al., 2012b)
Salvia miltiorrhiza	Tanshinone IIA	Abietane diterpen	IC_{50}: 1.6 μM	(Park, Kim, et al., 2012b)
Salvia miltiorrhiza	Cryptotanshinone	Abietane diterpen	IC_{50}: 0.8 μM	(Park, Kim, et al., 2012b)
Salvia miltiorrhiza	Dihydrotanshinone I	Abietane diterpen	IC_{50}: 4.9 μM	(Park, Kim, et al., 2012b)
Paulownia tomentosa	Tomentin A	Prenylated flavonoids	IC_{50}: 6.2 μM competitive inhibitor (K_i: 4.8)	(Cho et al., 2013)
Paulownia tomentosa	Tomentin B	Prenylated flavonoids	IC_{50}: 6.1 μM competitive inhibitor (K_i: 3.5)	(Cho et al., 2013)
Paulownia tomentosa	Tomentin C	Prenylated flavonoids	IC_{50}: 11.6 μM competitive inhibitor (K_i: 5.0)	(Cho et al., 2013)
Paulownia tomentosa	Tomentin D	Prenylated flavonoids	IC_{50}: 12.5 μM competitive inhibitor (K_i: 13.0)	(Cho et al., 2013)
Paulownia tomentosa	Tomentin E	Prenylated flavonoids	IC_{50}: 5.0 μM competitive inhibitor (K_i: 3.7)	(Cho et al., 2013)
Paulownia tomentosa	3′-O-methyldiplacol	Prenylated flavonoids	IC_{50}: 9.5 μM competitive inhibitor (K_i: 6.6)	(Cho et al., 2013)
Paulownia tomentosa	4′-O-methyldiplacol	Prenylated flavonoids	IC_{50}: 9.2 μM competitive inhibitor (K_i: 6.3)	(Cho et al., 2013)
Paulownia tomentosa	3′-O-methyldiplacone	Prenylated flavonoids	IC_{50}: 13.2 μM competitive inhibitor (K_i: 7.1)	(Cho et al., 2013)
Paulownia tomentosa	4′-O-methyldiplacone	Prenylated flavonoids	IC_{50}: 12.7 μM competitive inhibitor (K_i: 6.9)	(Cho et al., 2013)
Paulownia tomentosa	Mimulone	Prenylated flavonoids	IC_{50}: 14.4 μM competitive inhibitor (K_i: 7.8)	(Cho et al., 2013)
Paulownia tomentosa	Diplacone	Prenylated flavonoids	IC_{50}: 10.4 μM competitive inhibitor (K_i: 5.1)	(Cho et al., 2013)
Paulownia tomentosa	6-Geranyl-4′,5,7-trihydroxy-3′, 5′-dimethoxyflavanone	Prenylated flavonoids	IC_{50}: 13.9 μM competitive inhibitor (K_i: 8.4)	(Cho et al., 2013)
Alnus japonica	Hirsutenone	Diaryl heptanoid	IC_{50}: 4.1 μM	(Park et al., 2012a)
Curcuma longa	Curcumin	Diaryl heptanoid	IC_{50}: 5.7 μM	(Park, Jeong, et al., 2012a)
Angelica keiskei	Xanthoangelol E	Alkylated chalcones	IC_{50}: 1.2 μM	(Park et al., 2016)
Angelica keiskei	Xanthoangelol F	Alkylated chalcones	IC_{50}: 5.6 μM	(Park et al., 2016)
Angelica keiskei	Xanthoangelol	Alkylated chalcones	IC_{50}: 11.7 μM	(Park et al., 2016)
Angelica keiskei	Xanthoangelol B	Alkylated chalcones	IC_{50}: 11.7 μM	(Park et al., 2016)
Angelica keiskei	Isobavachalcone	Alkylated chalcones	IC_{50}: 13.0 μM	(Park et al., 2016)
Psoralea corylifolia	Bavachinin	Prenylated flavonoids	IC_{50}: 38.4 μM	(Kim et al., 2014).
Psoralea corylifolia	Corylifol A	Prenylated isoflavonoids	IC_{50}: 32.3 μM	(Kim et al., 2014)
Psoralea corylifolia	Isobavachalcone	Alkylated chalcones	IC_{50}:18.3 μM	(Kim et al., 2014)
Psoralea corylifolia	4′-O-methylbavachalcone	Alkylated chalcones	IC_{50}: 10.1 μM	(Kim et al., 2014)
Psoralea corylifolia	Neobavaisoflavone	Prenylated isoflavonoids	IC_{50}: 18.3 μM	(Kim et al., 2014)
Psoralea corylifolia	Psoralidin	Polyphenols	IC_{50}: 4.2 μM	(Kim et al., 2014)

According to the literature, the biflavonoid skeleton is a potential RdRp inhibitor especially amentoflavone and robustaflavone are the most promising ones. Sotetsuflavone with bioflavonoid structure that isolated from *Dacrydium araucarioides*. in vitro study showed that sotetsuflavone is the strongest inhibitor of the RdRp of Dengue virus with IC_{50} = 0.16 μM. SAR analyses demonstrate that the C3′–C6″ linkage is important for inhibitory activity. Furthermore, the number and position of methylation groups modulated the activity (Coulerie et al., 2013).

4.2.4 | Helicase inhibitors

Helicase is a multifunctional protein and necessary for viral replication, therefore helicase inhibitors can introduce as antiviral drugs for coronavirus treatment.

Silvestrol belongs to the flavaglines with cyclopenta[b]benzofuran skeleton can be isolated from plants of the genus Aglaia, especially *Aglaia silvestris* and *Aglaia foveolata* (Pan, Woodard, Lucas, Fuchs, & Kinghorn, 2014). Silvestrol can inhibit RNA helicase eIF4A and show potent antiviral activity in Ebola virus-infected human macrophages. Silvestrol has a potent antiviral effect by inhibiting eIF4A-dependent viral mRNA translation (Müller et al., 2018), so it can be introduced as a good treatment against SARS-CoV-2.

5 | DIFFERENT CLASSES OF NATURAL PRODUCTS FOR COVID-19 TREATMENT

Some of pervious in vitro studies about SARS treatment were shown the potential efficacy of natural products for the development of COVID-19 treatment. According to the literature, the structure of effective natural products in COVID-19 treatment is discussed following.

5.1 | Terpenoid derivatives

Glycyrrhiza glabra (Leguminosae family) and active component, glycyrrhizin with saponin structure exert antiviral activity toward several viruses, including hepatitis A, B, C, varicella-zoster, HIV, herpes simplex type-1, and cytomegalovirus (Nassiri-Asl & Hosseinzadeh, 2007). In 2003, a clinical trial showed the potential antiviral activity of glycyrrhizin against two clinical isolates of coronavirus (FFM-1 and FFM-2) from patients. Glycyrrhizin inhibited SARS-associated virus replication and should be suggested for the treatment of SARS (Cinatl et al., 2003). Furthermore, in vitro study showed the antiviral effect of glycyrrhizin against SARS infection (Chen et al., 2004).

Quinone-methide triterpenes are a class of terpenoids that occur only in plants of the celastraceae family such as *Tripterygium regelii*. These compounds showed moderate inhibitory activity against $3CL^{pro}$ with IC_{50} about 2.6–10.3 μM. According to SAR analysis, the presence of a quinone-methide moiety has a significant role in $3CL^{pro}$ inhibition (Ryu, Park, et al., 2010b).

Tanshinones with abietane diterpene structure are isolated from *S. miltiorrhiza*. Tanshinones have different biological activities such as anti-inflammatory activity, cardiovascular effects, and antitumor activity. These compounds show selective inhibition against the SARS-CoV $3CL^{pro}$ and PL^{pro} and their activity is dependent on the type of enzymes. Different tanshinones show a more significant inhibitory effect against PL^{pro} (IC_{50} between 0.8 and 30.0 μM) (Park, Kim, et al., 2012b).

In 2012, the anti HCoV activity of triterpenoids that isolated from *Euphorbia neriifolia* leaves was evaluated in vitro. 3β-Friedelanol with a triterpenoid structure exhibited more potent antiviral activity and increased the cellular viability after incubation with HCoV (Chang et al., 2012). The structure of effective terpenoids structure in COVID-19 treatment is shown in Figure 3.

5.2 | Polyphenols and flavonoid derivatives

Polyphenols are an important class of natural products that have antiviral effects, especially they can block virus entry and prevent viral infection in the early stage.

Resveratrol is a stilbenoid that expressed in different plants such as *Vitis vinifera*, *Vaccinium macrocarpon*, and *Polygonum cuspidatum*. Resveratrol shows different pharmacological and therapeutic effects such as hepatoprotective, cardioprotective, neuroprotective, anti-inflammatory, and antimicrobial activities (Nassiri-Asl & Hosseinzadeh, 2009). Resveratrol significantly inhibited MERS-CoV infection and decreased MERS-CoV replication in vitro. Therefore, resveratrol is a potent anti-MERS agent and can be a promising antiviral agent against SARS-CoV2 (Lin et al., 2017).

Luteolin is a common flavonoid in medicinal plants. Luteolin binds to the surface spike protein of SARS-CoV (EC_{50} 10.6 μM) and interferes with the virus entry to the host cells, so luteolin is an effective antiviral drug against SARS-CoV-2 (Yi et al., 2004).

SAR study about quercetin-3-β-galactoside and its synthetic derivatives shows that four OH groups on the quercetin moiety are important for biological activity, removal the 7-OH decrease the $3CL^{pro}$ inhibitory activity, the sugar moiety is important for activity and change in sugar does not affect inhibitor potency (Chen et al., 2006). Therefore, glycosylated luteolin and quercetin derivatives are potential antiviral drugs against COVID-19.

Baicalin is a glycosylated flavonoid from *S. baicalensis* that shows antiviral activity against SARS (EC_{50} 12.5 μg/ml) against the prototype virus grown in fRhK-4 cell line (Chen et al., 2004).

Another in vitro SAR study about SARS-CoV PL^{pro} inhibition demonstrated that dihydro-2H-pyran group existence in flavonoid structure showed better inhibitory activity than other flavonoids (Cho et al., 2013).

Alkylated chalcones with C-5 prenyl unit that isolated from *Angelica keiskei* are types of polyphenols that show in vitro potent inhibitory activity against $3CL^{pro}$ and PL^{pro}. Alkylated chalcones demonstrated noncompetitive inhibition against PL^{pro} and the most potent compounds are xanthoangelol E (IC_{50}: 1.2 μM) and xanthoangelol F (IC_{50}: 5.6 μM). SAR analysis shows that perhydroxyl group is alkylated chalcone and has more inhibitory activity (Park et al., 2016).

Diarylheptanoids are a class of polyphenols, isolated from different species such as *Alpinia*, *Zingiber*, *Curcuma*, and *Alnus*. Hirsutenone is a diarylheptanoid that isolated from *A. japonica* and showed a more potent inhibitory activity against PL^{pro} (IC_{50}: 4.1 μM; Park, Jeong, et al., 2012a). Curcumin is another diarylheptanoid from *Curcuma longa* with different therapeutic activities such as anti-inflammatory, antihyperlipidemic, and antimicrobial activities (Soleimani, Sahebkar, & Hosseinzadeh, 2018). Curcumin shows potential inhibitory activity against PL^{pro} (IC_{50}: 5.7 μM). SAR analysis shows that α,β-unsaturated carbonyl moiety are essential for inhibitory activity (Park, Jeong, et al., 2012a). The structure of effective polyphenols structure in COVID-19 treatment is shown in Figure 4.

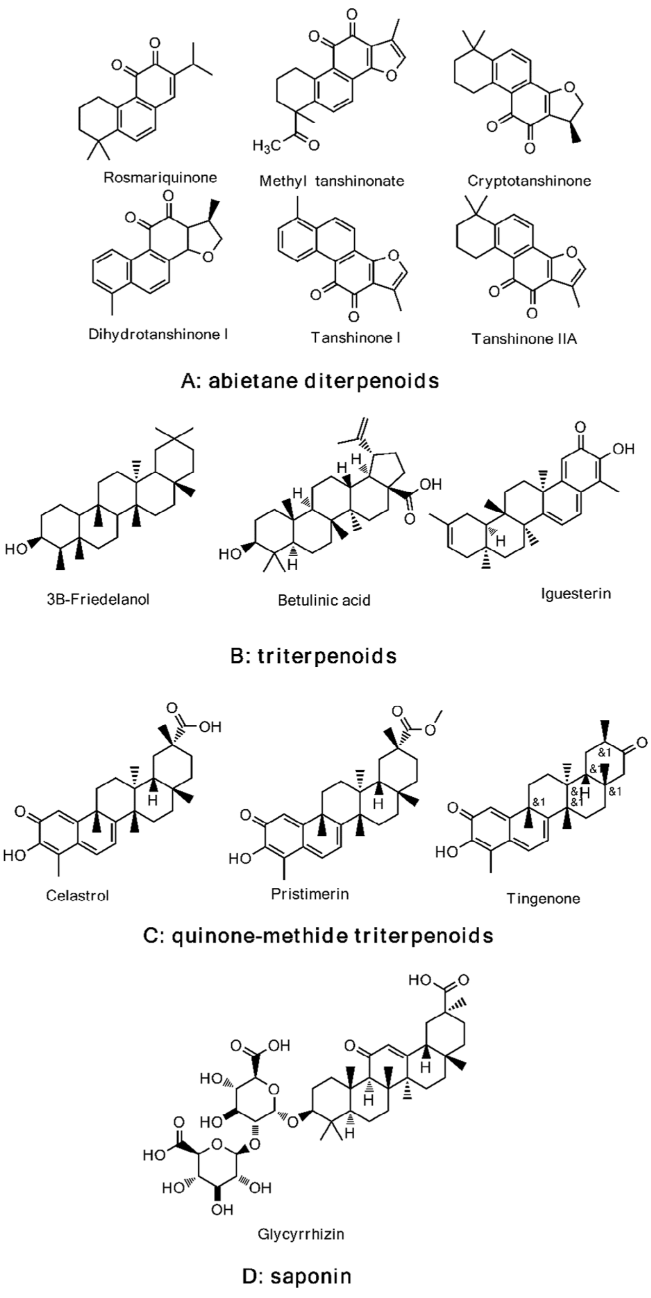

FIGURE 3 Chemical structures of terpenoids for SARS-CoV-2 treatment

5.3 | Alkaloids derivatives

In 2005, using MTS assay for the virus-induced cytopathic effect it was shown that *Lycoris radiata* extract (Amaryllidaceae family) has potent antiviral activity against SARS-CoV. The active compound of this extract is lycorine with an alkaloid structure that shows effective antiviral activity with an EC_{50} value of 15.7 ± 1.2 nM. These results demonstrated that lycorine is a good candidate for the development of new antiviral medicine (Li et al., 2005). Another study exhibit the potential in vitro inhibitory activity of lycorine against coronavirus replication such as HCoV-OC43 (EC_{50}: 0.15 μM), MERS-CoV (EC_{50}: 1.63 μM), and HCoV-NL63 (EC_{50}: 0.47 μM). Additionally, lycorine can decrease the viral load in the central nervous system of BALB/c mice and protect against HCoV-OC43-induced lethality (Shen et al., 2019).

Emetine with alkaloid structure is the main active ingredient of *Carapichea ipecacuanha* roots (Rubiaceae family) with anti-protozoal activity and vomiting agents. Emetine showed strong in vitro inhibition against different coronavirus replication such as HCoV-OC43 (EC_{50}: 0.30 μM), MERS-CoV (EC50: 0.34 μM), and HCoV-NL63 (EC50: 1.43 μM). Furthermore, emetine can block MERS-CoV entry to host cells (Shen et al., 2019).

Tylophorine and similar analogs with phenanthroindolizidine alkaloid structure, isolated from *Tylophora indica* (Asclepiadaceae). Tylophorine (IC_{50}: 58 nM) and 7-methoxycryptopleurine (IC_{50}: 20 nM) have potent coronavirus replication inhibitory effects (Yang et al., 2010). In another study, tylophorine at nanomolar concentration was also found to target viral RNA replication and cellular JAK2 mediated dominant NF-κB activation that is a common pro-inflammatory response of host cells to viral infection in CoV (Yang et al., 2017).

Bisbenzylisoquinoline alkaloids from the roots of *Stephania tetrandra* (Menispermaceae family) have different biological activity include anticancer, anti-inflammatory, and antioxidant (Weber & Opatz, 2019). The main active *S. tetrandra* alkaloids include tetrandrine (IC_{50}: 14.51 μM), fangchinoline (IC_{50}: 12.40 μM), and cepharanthine (IC_{50}: 10.54 μM) show potential antiviral activity against HCoV-OC43 infection and suppressed viral replication (Kim et al., 2019).

Homoharringtonine (omacetaxine mepesuccinate) is a cytotoxic alkaloid originally isolated from the *Cephalotaxus hainanensis* (Taxaceae family). It has been approved by the FDA for resistance to chronic myeloid leukemia treatment. Homoharringtonine demonstrates significant antiviral activity against diverse species of human and animal coronaviruses with the lowest IC_{50} (12 nM; Cao, Forrest, & Zhang, 2015).

Isatin (1H-indole-2,3-dione), an oxidized indole derivative that isolated from plants like *Strobilanthes cusia*, *Isatis tinctoria*, *Couroupita guianensis*, and *Calanthe discolor*, has different pharmacological activities such as antimalarial, antiallergic, antimicrobial, and antiviral (Khan & Maalik, 2015). It has been demonstrated that some isatin derivatives are potent inhibitors of rhinovirus 3CL^{pro} (Webber et al., 1996). The protease structure of rhinovirus and SARS-CoV is similar and isatin derivatives inhibited SARS-CoV 3CL^{pro} in low amounts (Chen et al., 2005b; Liu et al., 2014); therefore, isatin derivatives can be promising candidates for a novel treatment for COVID-19. The structures of effective alkaloids in COVID-19 treatment are shown in Figure 5.

5.4 | Miscellaneous compounds

One of the promising antibiotic compounds against SARS-CoV is valinomycin with cyclododecadepsipeptide structure that isolated from *Streptomyces tsusimaensis* with low cytotoxicity and high efficacy against HCoV (Cheng, 2006; Wu et al., 2004).

In another study in 2008, the leaf extract of *Toona sinensis* (also known as *Cedrela sinensis*, belongs to the family Meliaceae) was found to have an evident effect against SARS-CoV with selectivity index 12–17 in vitro. Therefore, this vegetable can be introduced as a new antiviral drug against SARS-CoV (Chen et al., 2008). The structures of effective miscellaneous compounds in COVID-19 treatment are shown in Figure 6.

6 | LIMITATIONS OF THE STUDY

This review article has limitations. It was limited to the English studies in period time (1990–2020). In this review article, we just explained

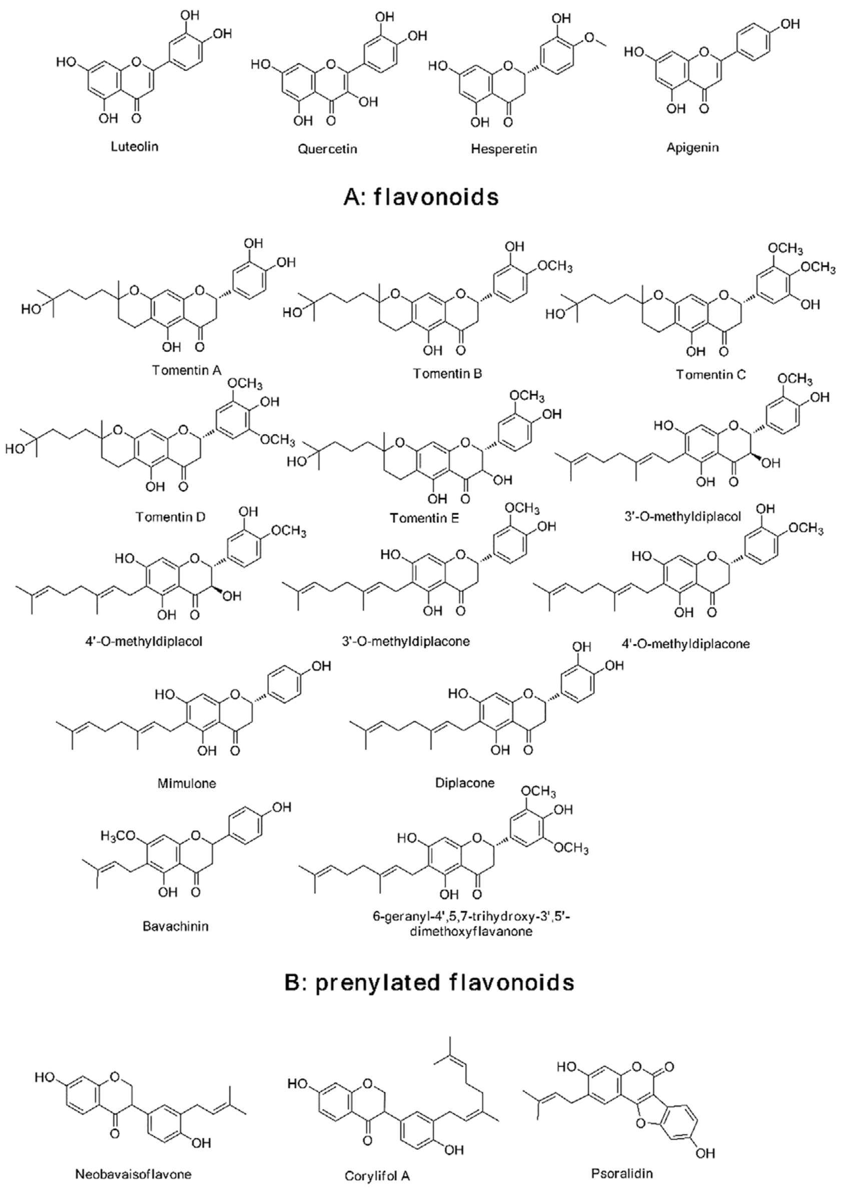

FIGURE 4 Chemical structures of polyphenols for SARS-CoV-2 treatment

experimental data and ignored in silico data. Furthermore, more of these natural products expressed in this article just examined in vitro. So, more in vivo and clinical studies should be done to confirm the effectivity against coronavirus infection. Furthermore, the standardization of herbal extract and analytical validation should be considered in phytotherapy studies.

7 | CONCLUSION AND FUTURE PERSPECTIVE

Novel coronavirus infection (COVID-19) is an important life-threatening disease. For many years, natural products were used for the treatment of viral infection and enhancement of the host immune response. In previous coronavirus infections including SARS and MERS, natural products have significant therapeutic effects; so natural products may be useful and promising in novel infection. Herbal medicines such as *Allium sativum*, *Camellia sinensis*, *Zingiber officinale*, *Nigella sativa*, *Echinacea* spp. *Hypericum perforatum*, and *Glycyrrhiza glabra*, *Scutellaria baicalensis* can improve the immune response and useful for COVID-19 prevention. In this review, based on the previous herbal effective treatments for SARS and MERS the potential herbal treatments for COVID-19 are suggested. Natural products can inhibit coronaviruses in different stages (Figure 7). Some natural products such as emodin-inhibited S protein and ACE2 in a dose-dependent manner and protected from virus attachment. Some natural products inhibit virus replication enzymes. It seems that different types of terpenoids such as abietane

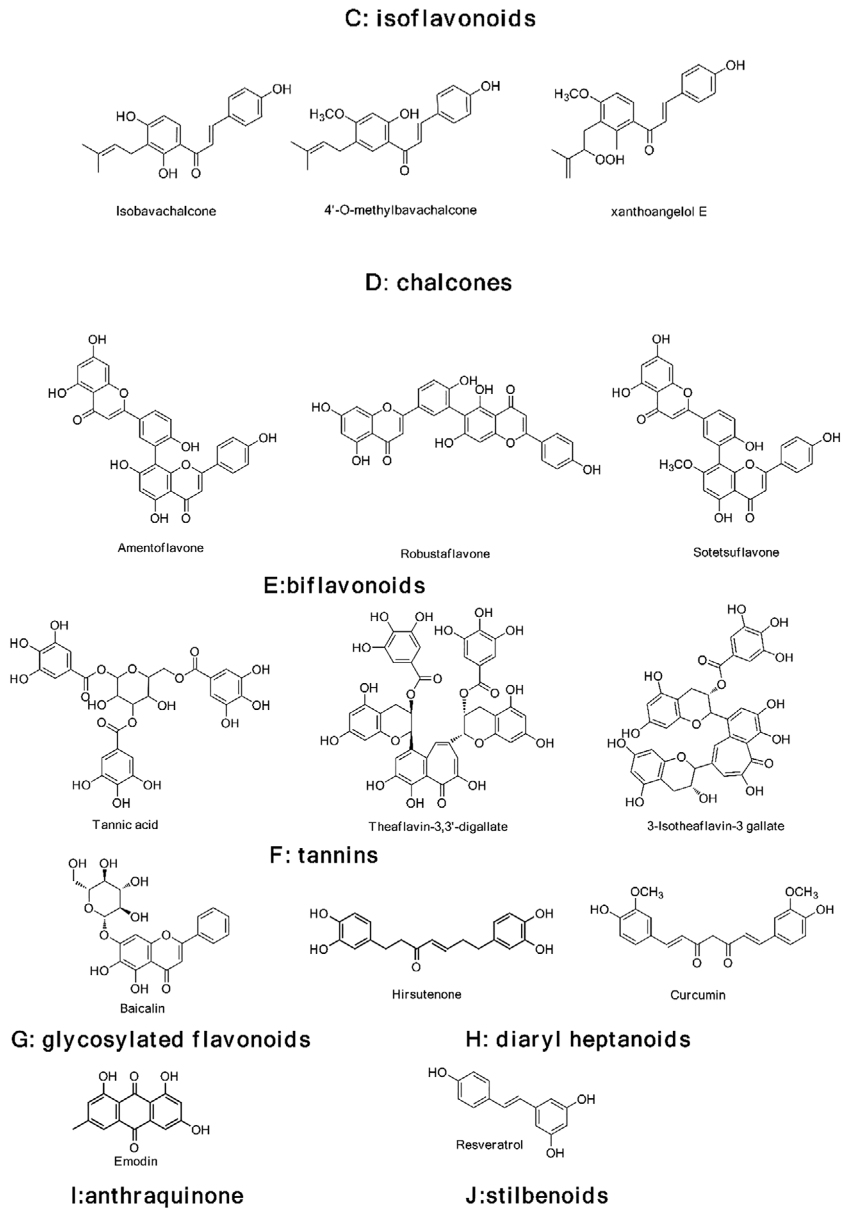

FIGURE 4 (Continued)

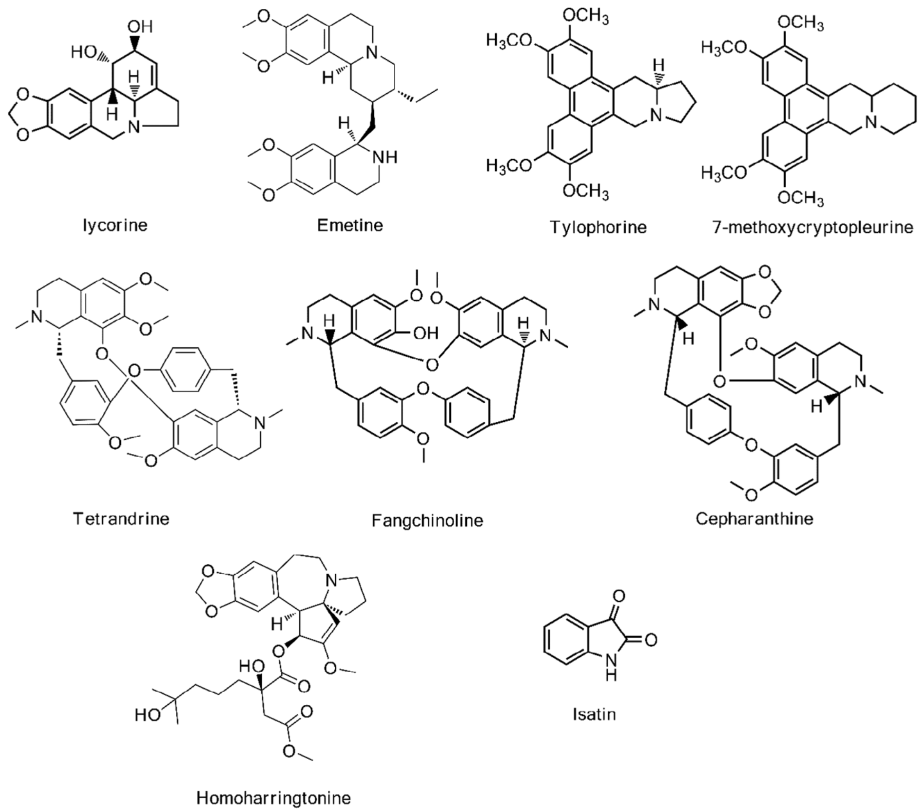

FIGURE 5 Chemical structures of alkaloids for SARS-CoV-2 treatment

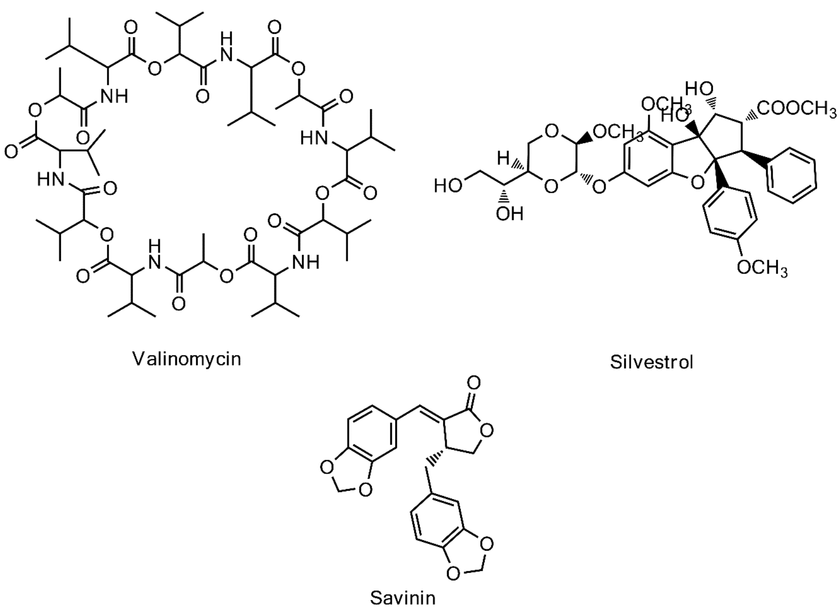

FIGURE 6 Chemical structures of miscellaneous compounds for SARS-CoV-2 treatment

diterpenes especially tanshinones (Cryptotanshinone, Tanshinone IIA), quinone-methide triterpenes (Iguesterin), simple triterpenes (3β-Friedelanol), and saponins (glycyrrhizin) have promising effects in viral replication inhibition and could be introduced for future studies. Some of the alkaloids have a strong anti-coronavirus effect such as homoharringtonine, lycorin, and emetine. Furthermore, Isatin derivatives inhibited SARS-CoV 3CL^{pro} in low amounts. Considering the effectiveness of different classes of natural compounds, it can be concluded that glycosylated compounds, especially glycosylated terpenoids as well as terpenoid alkaloids can be promising compounds in the treatment of COVID-19. Following the novel coronavirus infection, identification of natural products with

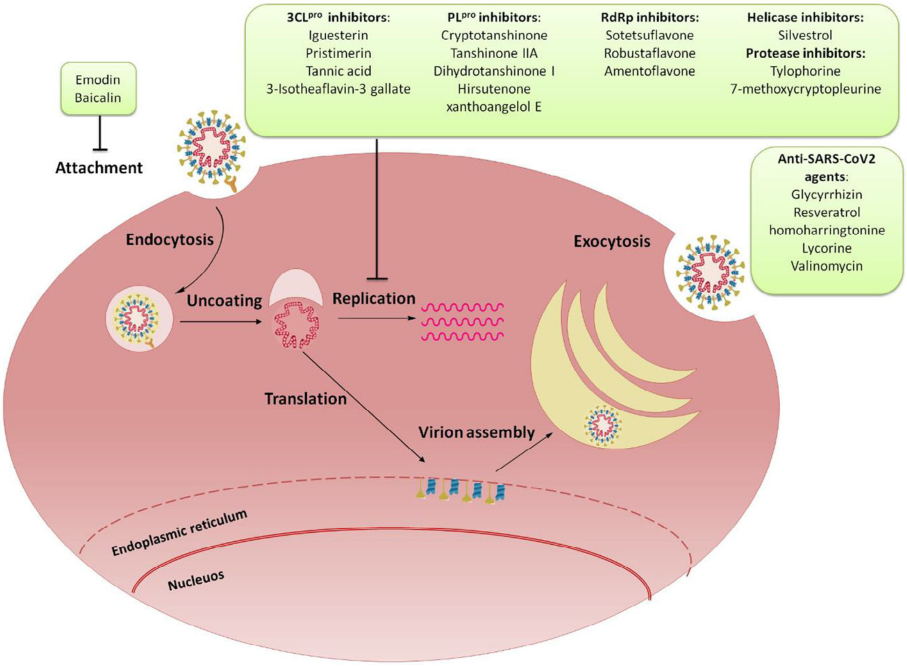

FIGURE 7 Inhibitory effects of natural products in coronavirus pathogenesis [Colour figure can be viewed at wileyonlinelibrary.com]

antiviral activity against SARS-CoV, MERS-CoV, and other CoVs is an important research priority. Natural products can be introduced as preventive and therapeutic agents in the fight against viruses. To expand and promote research projects on effective natural products for prevention and treatment of COVID-19, the following approaches could be considered of value: further studies for the use of other natural products as effective anti-coronavirus agents; standardize quality control studies for herbal extracts that use as an immune-boosting medication; identify different targets for combat against coronavirus; study about the pharmacokinetics and pharmacodynamics properties (absorption, distribution, metabolism, and excretion) and the toxicities (chronic and acute toxicity studies) of pure natural products; design new medication according to the SAR analysis and scientific in vivo and clinical researches for the development of new promising drugs against coronavirus infection.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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