



REVIEW

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}, 3Cl like 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).

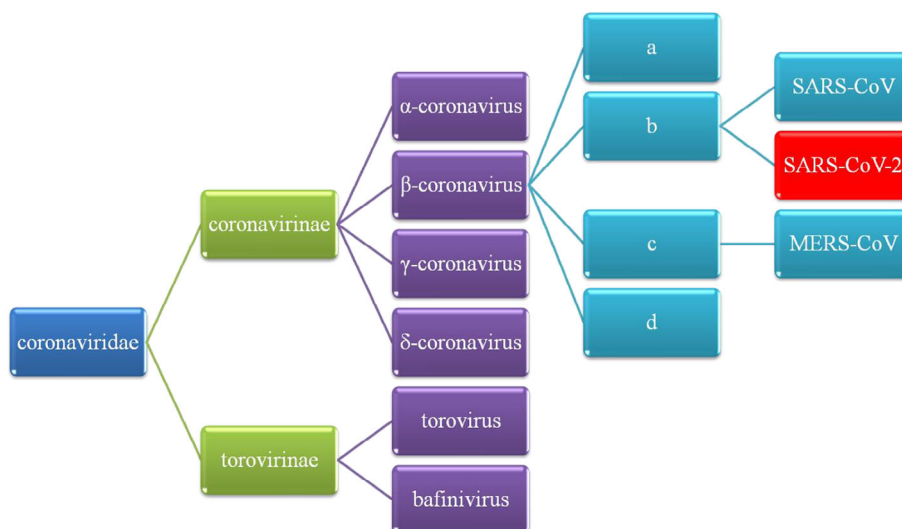
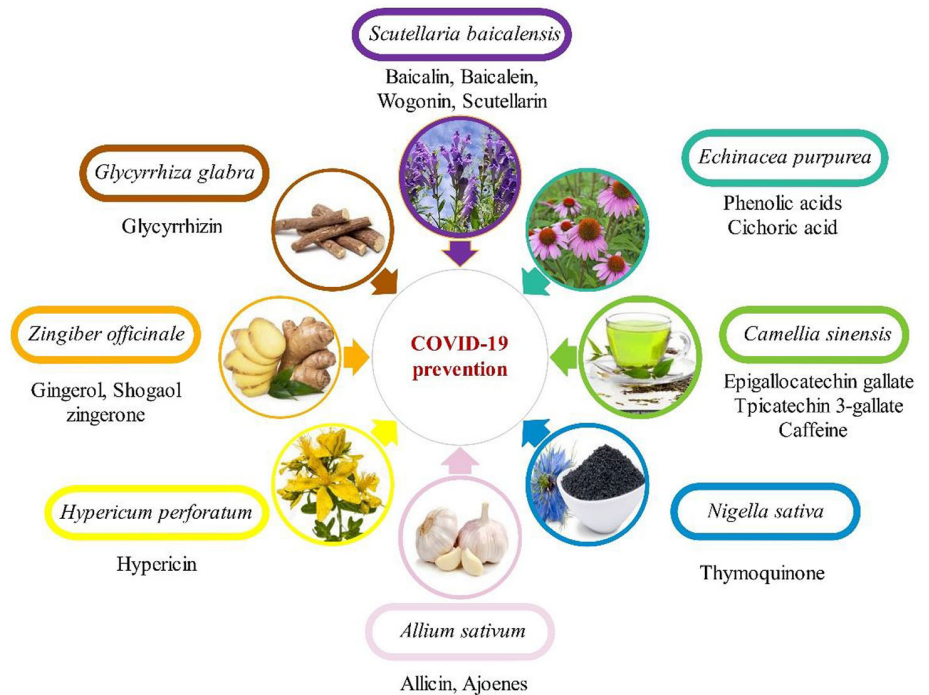


FIGURE 1 Classification of different types of coronavirus [Colour figure can be viewed at wileyonlinelibrary.com]

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 $\mu\text{g/ml}$. 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-acetylesterase 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 (3CL^{pro}) 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 (IC₅₀: 2.6 μM) and pristimerin (IC₅₀: 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 (IC₅₀: 3 μM) and 3-Isotheaflavin-3 gallate (IC₅₀: 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
<i>Rheum palmatum</i> extract	—	—	IC ₅₀ : 13.76 μg/ml	(Luo et al., 2009)
<i>Salvia miltiorrhiza</i>	Rosmariquinone	Abietane analog	IC ₅₀ : 21.1 μM	(Park et al., 2012b)
<i>Salvia miltiorrhiza</i>	Methyl tanshinonate	Abietane diterpen	IC ₅₀ : 21.1 μM	(Park, Kim, et al., 2012b)
<i>Salvia miltiorrhiza</i>	Dihydrotanshinone I	Abietane diterpen	IC ₅₀ : 14.4 μM	(Park, Kim, et al., 2012b)
<i>Angelica keiskei</i>	Xanthoangelol E	Alkylated chalcones	IC ₅₀ : 11.4 μM	(Park et al., 2016)
<i>Angelica keiskei</i>	Xanthoangelol B	Alkylated chalcones	IC ₅₀ : 22.2 μM	(Park et al., 2016)
<i>Camellia sinensis</i> black tea	Theaflavin-3,3' digallate	Polyphenols (tannins)	IC ₅₀ : 9.5 μM	(Chen et al., 2005a)
<i>Camellia sinensis</i>	3-Isotheaflavin-3 gallate	Polyphenols (tannins)	IC ₅₀ : 7 μM	(Chen, Lin, et al., 2005a)
<i>Camellia sinensis</i>	Tannic acid	Polyphenols (tannins)	IC ₅₀ : 3 μM	(Chen, Lin, et al., 2005a)
<i>Isatis indigotica</i>	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)
<i>Torreya nucifera</i>	Amentoflavone	Bioflavonoids	IC ₅₀ : 8.3 μM	(Ryu, Jeong, et al., 2010a)
<i>Torreya nucifera</i>	Apigenin	Flavonoids	IC ₅₀ : 280.8 μM	(Ryu, Jeong, et al., 2010a)
<i>Juniperus formosana</i>	Betulinic acid	Terpenoids	IC ₅₀ : 10 μM Competitive inhibitor (K _i : 8.2 μM)	(Wen et al., 2007)
<i>Chamaecyparis obtusa</i>	Savinin	Lignoids	IC ₅₀ : 25 μM Competitive inhibitor (K _i : 9.1 μM)	(Wen et al., 2007)
<i>Tritergyium regelii</i>	Celastrol	Terpenoids	IC ₅₀ : 10.3 μM Competitive inhibitor	(Ryu et al., 2010b)
<i>Tritergyium regelii</i>	Pristimerin	Terpenoids	IC ₅₀ : 5.5 μM Competitive inhibitor	(Ryu, Park, et al., 2010b)
<i>Tritergyium regelii</i>	Tingenone	Terpenoids	IC ₅₀ : 9.9 μM Competitive inhibitor	(Ryu, Park, et al., 2010b)
<i>Tritergyium regelii</i>	Iguesterin	Terpenoids	IC ₅₀ : 2.6 μM Competitive inhibitor	(Ryu, Park, et al., 2010b)
<i>Curcuma longa</i>	Curcumin	Diaryl heptanoid	IC ₅₀ : 40 μM	(Wen et al., 2007)

4.2.2 | Papain-like protease (PL^{pro}) 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}. IC₅₀ values of Cryptotanshinone, Tanshinone IIA, and Dihydro-tanshinone 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} (IC₅₀: 4.1 μM) and curcumin from *Curcuma longa* (IC₅₀: 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 IC₅₀ 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
<i>Salvia miltiorrhiza</i>	Tanshinone I	Abietane diterpen	IC ₅₀ : 8.8 μM	(Park, Kim, et al., 2012b)
<i>Salvia miltiorrhiza</i>	Tanshinone IIA	Abietane diterpen	IC ₅₀ : 1.6 μM	(Park, Kim, et al., 2012b)
<i>Salvia miltiorrhiza</i>	Cryptotanshinone	Abietane diterpen	IC ₅₀ : 0.8 μM	(Park, Kim, et al., 2012b)
<i>Salvia miltiorrhiza</i>	Dihydro-tanshinone I	Abietane diterpen	IC ₅₀ : 4.9 μM	(Park, Kim, et al., 2012b)
<i>Paulownia tomentosa</i>	Tomentin A	Prenylated flavonoids	IC ₅₀ : 6.2 μM competitive inhibitor (K _i : 4.8)	(Cho et al., 2013)
<i>Paulownia tomentosa</i>	Tomentin B	Prenylated flavonoids	IC ₅₀ : 6.1 μM competitive inhibitor (K _i : 3.5)	(Cho et al., 2013)
<i>Paulownia tomentosa</i>	Tomentin C	Prenylated flavonoids	IC ₅₀ : 11.6 μM competitive inhibitor (K _i : 5.0)	(Cho et al., 2013)
<i>Paulownia tomentosa</i>	Tomentin D	Prenylated flavonoids	IC ₅₀ : 12.5 μM competitive inhibitor (K _i : 13.0)	(Cho et al., 2013)
<i>Paulownia tomentosa</i>	Tomentin E	Prenylated flavonoids	IC ₅₀ : 5.0 μM competitive inhibitor (K _i : 3.7)	(Cho et al., 2013)
<i>Paulownia tomentosa</i>	3'-O-methyl-diplacol	Prenylated flavonoids	IC ₅₀ : 9.5 μM competitive inhibitor (K _i : 6.6)	(Cho et al., 2013)
<i>Paulownia tomentosa</i>	4'-O-methyl-diplacol	Prenylated flavonoids	IC ₅₀ : 9.2 μM competitive inhibitor (K _i : 6.3)	(Cho et al., 2013)
<i>Paulownia tomentosa</i>	3'-O-methyl-diplacone	Prenylated flavonoids	IC ₅₀ : 13.2 μM competitive inhibitor (K _i : 7.1)	(Cho et al., 2013)
<i>Paulownia tomentosa</i>	4'-O-methyl-diplacone	Prenylated flavonoids	IC ₅₀ : 12.7 μM competitive inhibitor (K _i : 6.9)	(Cho et al., 2013)
<i>Paulownia tomentosa</i>	Mimulone	Prenylated flavonoids	IC ₅₀ : 14.4 μM competitive inhibitor (K _i : 7.8)	(Cho et al., 2013)
<i>Paulownia tomentosa</i>	Diplacone	Prenylated flavonoids	IC ₅₀ : 10.4 μM competitive inhibitor (K _i : 5.1)	(Cho et al., 2013)
<i>Paulownia tomentosa</i>	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)
<i>Alnus japonica</i>	Hirsutenone	Diaryl heptanoid	IC ₅₀ : 4.1 μM	(Park et al., 2012a)
<i>Curcuma longa</i>	Curcumin	Diaryl heptanoid	IC ₅₀ : 5.7 μM	(Park, Jeong, et al., 2012a)
<i>Angelica keiskei</i>	Xanthoangelol E	Alkylated chalcones	IC ₅₀ : 1.2 μM	(Park et al., 2016)
<i>Angelica keiskei</i>	Xanthoangelol F	Alkylated chalcones	IC ₅₀ : 5.6 μM	(Park et al., 2016)
<i>Angelica keiskei</i>	Xanthoangelol	Alkylated chalcones	IC ₅₀ : 11.7 μM	(Park et al., 2016)
<i>Angelica keiskei</i>	Xanthoangelol B	Alkylated chalcones	IC ₅₀ : 11.7 μM	(Park et al., 2016)
<i>Angelica keiskei</i>	Isobavachalcone	Alkylated chalcones	IC ₅₀ : 13.0 μM	(Park et al., 2016)
<i>Psoralea corylifolia</i>	Bavachinin	Prenylated flavonoids	IC ₅₀ : 38.4 μM	(Kim et al., 2014)
<i>Psoralea corylifolia</i>	Corylifol A	Prenylated isoflavonoids	IC ₅₀ : 32.3 μM	(Kim et al., 2014)
<i>Psoralea corylifolia</i>	Isobavachalcone	Alkylated chalcones	IC ₅₀ : 18.3 μM	(Kim et al., 2014)
<i>Psoralea corylifolia</i>	4'-O-methylbavachalcone	Alkylated chalcones	IC ₅₀ : 10.1 μM	(Kim et al., 2014)
<i>Psoralea corylifolia</i>	Neobavaisoflavone	Prenylated isoflavonoids	IC ₅₀ : 18.3 μM	(Kim et al., 2014)
<i>Psoralea corylifolia</i>	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 $IC_{50} = 0.16 \mu\text{M}$. 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 previous *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*. 3 β -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 $\mu\text{g/ml}$) 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 (IC₅₀: 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} (IC₅₀: 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} (IC₅₀: 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.

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 EC₅₀ 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 (EC₅₀: 0.15 μM), MERS-CoV (EC₅₀: 1.63 μM), and HCoV-NL63 (EC₅₀: 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 (EC₅₀: 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 (IC₅₀: 58 nM) and 7-methoxycryptopleurine (IC₅₀: 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 (IC₅₀: 14.51 μM), fangchinoline (IC₅₀: 12.40 μM), and cepharanthine (IC₅₀: 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 IC₅₀ (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

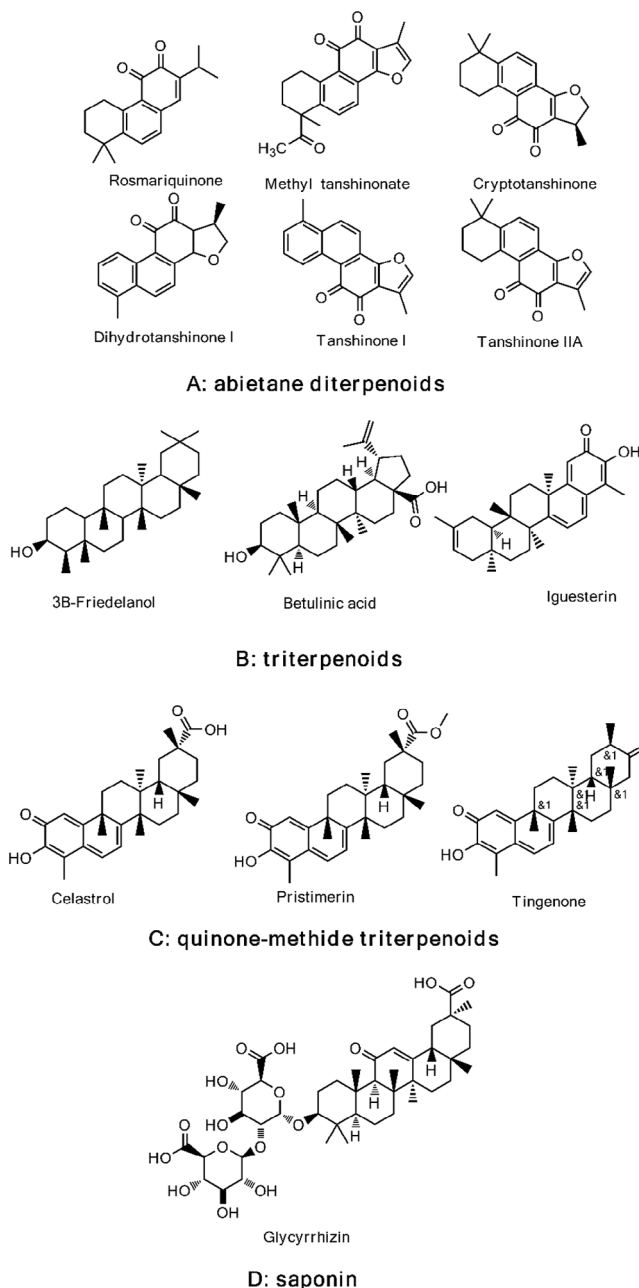


FIGURE 3 Chemical structures of terpenoids for SARS-CoV-2 treatment

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

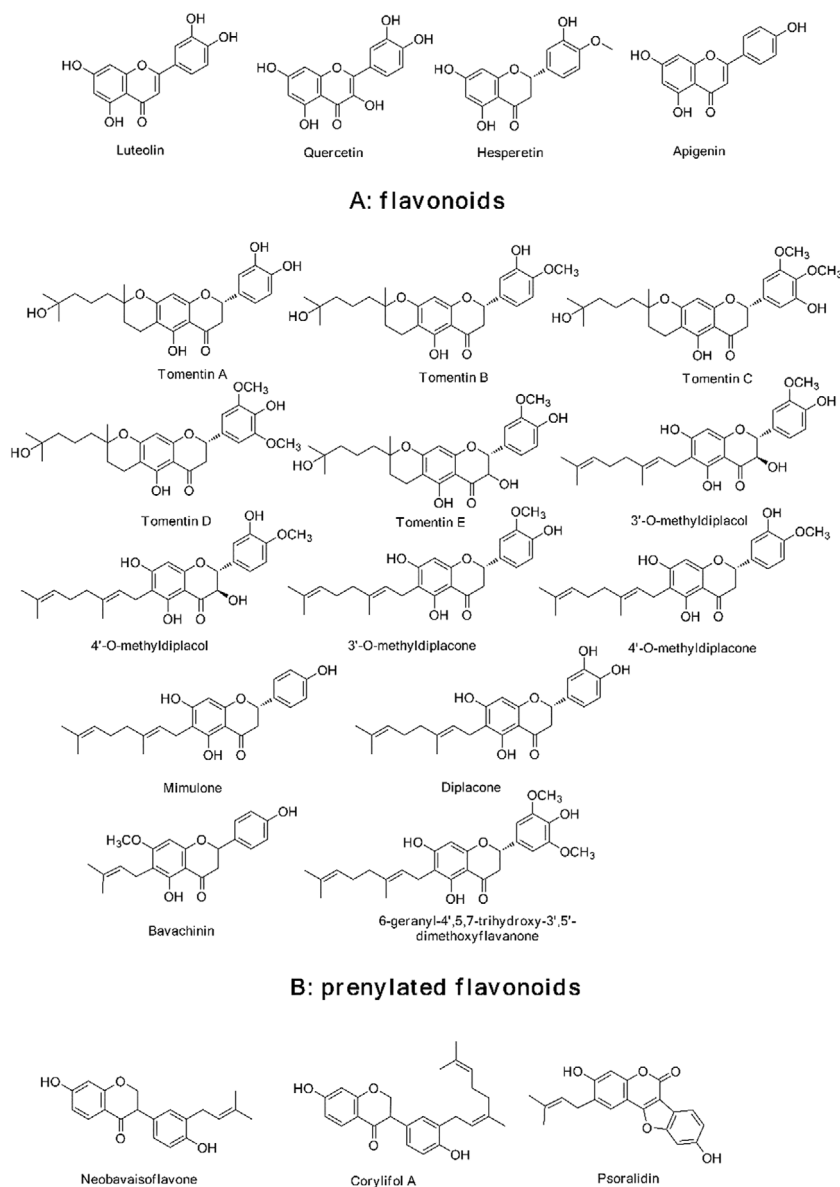


FIGURE 4 Chemical structures of polyphenols for SARS-CoV-2 treatment

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

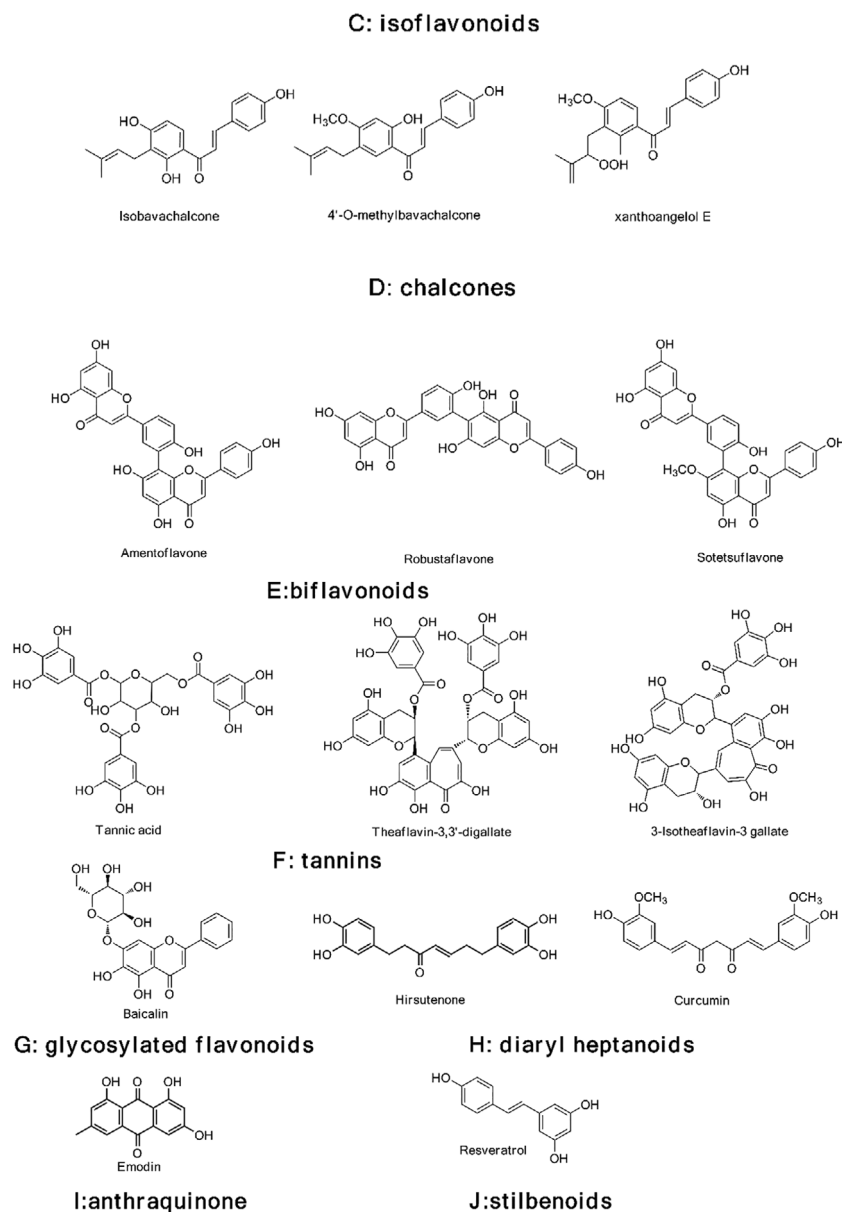


FIGURE 4 (Continued)

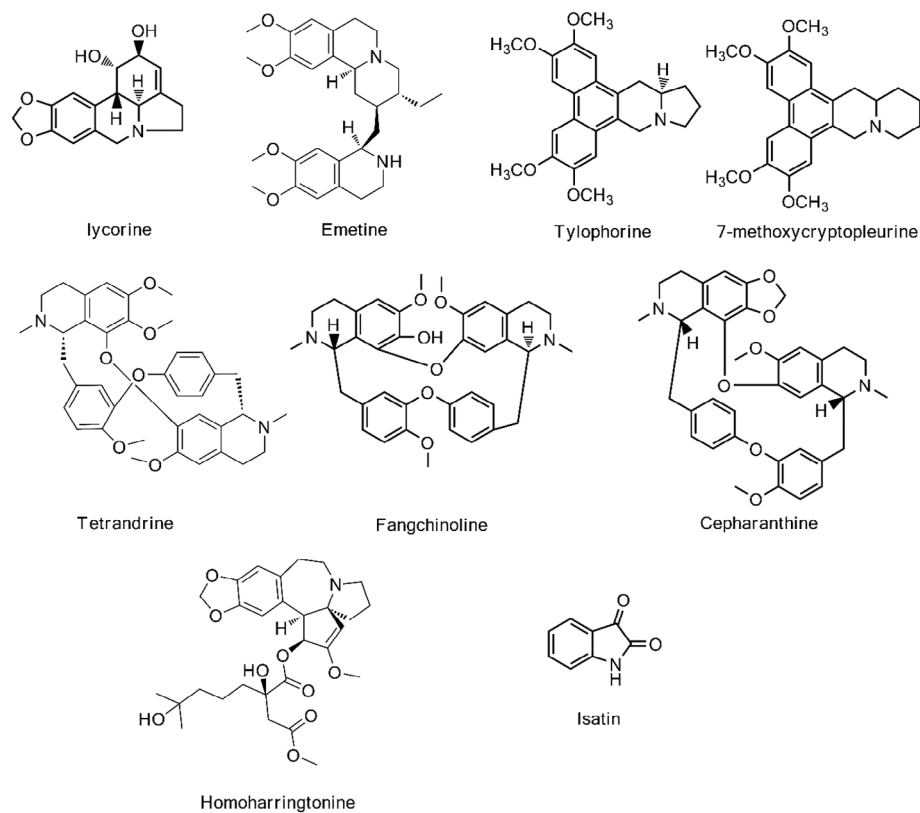


FIGURE 5 Chemical structures of alkaloids for SARS-CoV-2 treatment

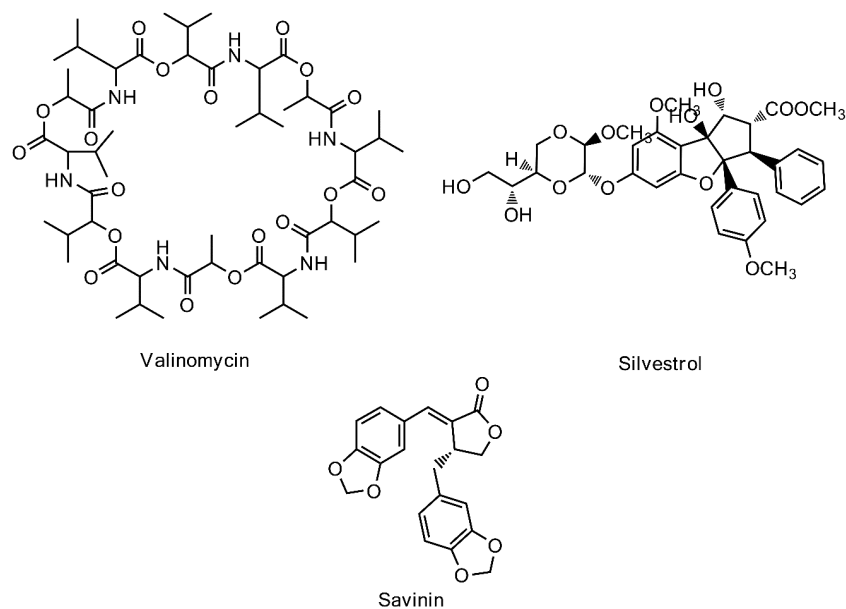
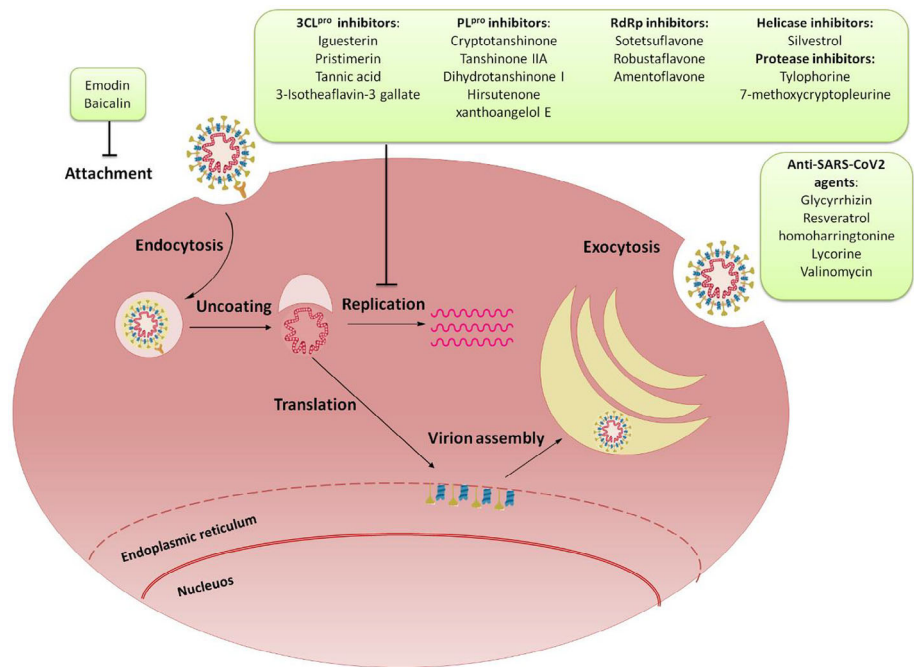


FIGURE 6 Chemical structures of miscellaneous compounds for SARS-CoV-2 treatment

diterpenes especially tanshinones (Cryptotanshinone, Tanshinone IIA), quinone-methide triterpenes (Iguesterin), simple triterpenes (β -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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REFERENCES

- Brojakowska, A., Narula, J., Shimony, R., & Bander, J. (2020). Clinical implications of SARS-Cov2 interaction with renin angiotensin system. *Journal of the American College of Cardiology*, 75, 3085–3095.
- Cao, J., Forrest, J. C., & Zhang, X. (2015). A screen of the NIH clinical collection small molecule library identifies potential anti-coronavirus drugs. *Antiviral Research*, 114, 1–10.
- Cascella, M., Rajnik, M., Cuomo, A., Dulebohn, S. C., & Di Napoli, R. (2020). Features, evaluation and treatment coronavirus (COVID-19), *StatPearls [internet]*, Treasure Island: StatPearls Publishing.
- Chan, J. F.-W., Kok, K.-H., Zhu, Z., Chu, H., To, K.K.-W., Yuan, S., & Yuen, K.-Y. (2020). Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging Microbes & Infections*, 9, 221–236.
- Chan, J. F., Lau, S. K., To, K. K., Cheng, V. C., Woo, P. C., & Yuen, K.-Y. (2015). Middle East respiratory syndrome coronavirus: Another zoonotic betacoronavirus causing SARS-like disease. *Clinical Microbiology Reviews*, 28, 465–522.
- Chang, F.-R., Yen, C.-T., Ei-Shazly, M., Lin, W.-H., Yen, M.-H., Lin, K.-H., & Wu, Y.-C. (2012). Anti-human coronavirus (anti-HCoV) triterpenoids from the leaves of *Euphorbia neriifolia*. *Natural Product Communications*, 7(11), 1415–1417.
- Cheever, F. S., Daniels, J. B., Pappenheimer, A. M., & Bailey, O. T. (1949). A murine virus (JHM) causing disseminated encephalomyelitis with extensive destruction of myelin: I. Isolation and biological properties of the virus. *Journal of Experimental Medicine*, 90, 181.
- Chen, C.-J., Michaelis, M., Hsu, H.-K., Tsai, C.-C., Yang, K. D., Wu, Y.-C., ... Doerr, H. W. (2008). *Toona sinensis* Roem tender leaf extract inhibits SARS coronavirus replication. *Journal of Ethnopharmacology*, 120, 108–111.
- Chen, C.-N., Lin, C. P., Huang, K.-K., Chen, W.-C., Hsieh, H.-P., Liang, P.-H., & Hsu, J. T.-A. (2005a). Inhibition of SARS-CoV 3C-like protease activity by theaflavin-3, 3'-digallate (TF3). *Evidence-Based Complementary and Alternative Medicine*, 2, 209–215.
- Chen, F., Chan, K., Jiang, Y., Kao, R., Lu, H., Fan, K., ... Lee, T. (2004). In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *Journal of Clinical Virology*, 31, 69–75.
- Chen, L.-R., Wang, Y.-C., Lin, Y. W., Chou, S.-Y., Chen, S.-F., Liu, L. T., ... Juang, S.-H. (2005b). Synthesis and evaluation of isatin derivatives as effective SARS coronavirus 3CL protease inhibitors. *Bioorganic & Medicinal Chemistry Letters*, 15, 3058–3062.
- Chen, L., Li, J., Luo, C., Liu, H., Xu, W., Chen, G., ... Shen, X. (2006). Binding interaction of quercetin-3- β -galactoside and its synthetic derivatives with SARS-CoV 3CLpro: Structure–activity relationship studies reveal salient pharmacophore features. *Bioorganic & Medicinal Chemistry*, 14, 8295–8306.
- Cheng, Y. Q. (2006). Deciphering the biosynthetic codes for the potent anti-SARS-CoV cyclodepsipeptide valinomycin in *Streptomyces tsusimaensis* ATCC 15141. *ChemBiochem*, 7, 471–477.

- Cho, J. K., Curtis-Long, M. J., Lee, K. H., Kim, D. W., Ryu, H. W., Yuk, H. J., & Park, K. H. (2013). Geranylated flavonoids displaying SARS-CoV papain-like protease inhibition from the fruits of *Paulownia tomentosa*. *Bioorganic & Medicinal Chemistry*, 21, 3051–3057.
- Cinatl, J., Morgenstern, B., Bauer, G., Chandra, P., Rabenau, H., & Doerr, H. (2003). Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *Lancet*, 361, 2045–2046.
- Clementz, M. A., Chen, Z., Banach, B. S., Wang, Y., Sun, L., Ratia, K., ... Ghosh, A. K. (2010). Deubiquitinating and interferon antagonism activities of coronavirus papain-like proteases. *Journal of Virology*, 84, 4619–4629.
- Coulerie, P., Nour, M., Maciuk, A., Eydoux, C., Guillemot, J.-C., Lebouvier, N., ... Canard, B. (2013). Structure-activity relationship study of biflavonoids on the Dengue virus polymerase DENV-NS5 RdRp. *Planta Medica*, 79, 1313–1318.
- De Groot, R. J. (2006). Structure, function and evolution of the hemagglutinin-esterase proteins of corona- and toroviruses. *Glycoconjugate Journal*, 23, 59–72.
- Drosten, C., Günther, S., Preiser, W., Van Der Werf, S., Brodt, H.-R., Becker, S., ... Fouchier, R. A. (2003). Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *The New England Journal of Medicine*, 348, 1967–1976.
- Ho, T.-Y., Wu, S.-L., Chen, J.-C., Li, C.-C., & Hsiang, C.-Y. (2007). Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. *Antiviral Research*, 74, 92–101.
- Hoffmann, M., Kleine-Weber, H., Krüger, N., Mueller, M. A., Drosten, C., & Pöhlmann, S. (2020). The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. *BioRxiv*. [Epub ahead of print]. Available from: <https://www.biorxiv.org/content/10.1101/2020.01.31.929042v1>.
- Hsu, C.-H., Hwang, K.-C., Chao, C.-L., Chang, S. G., Ho, M.-S., Lin, J.-G., ... Chou, P. (2008). An evaluation of the additive effect of natural herbal medicine on SARS or SARS-like infectious diseases in 2003: A randomized, double-blind, and controlled pilot study. *Evidence-Based Complementary and Alternative Medicine*, 5, 355–362.
- Ji, Y., Gao, F., Sun, B., Hao, J., & Liu, Z. (2015). Angiotensin-converting enzyme 2 inhibits apoptosis of pulmonary endothelial cells during acute lung injury through suppressing smad2 phosphorylation. *Cellular Physiology and Biochemistry*, 35, 2203–2212.
- Khan, A., Benthin, C., Zeno, B., Albertson, T. E., Boyd, J., Christie, J. D., ... Tidswell, M. (2017). A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Critical Care*, 21, 234.
- Khan, F. A., & Maalik, A. (2015). Advances in pharmacology of isatin and its derivatives: A review. *Tropical Journal of Pharmaceutical Research*, 14, 1937–1942.
- Kim, D. E., Min, J. S., Jang, M. S., Lee, J. Y., Shin, Y. S., Park, C. M., ... Jin, Y.-H. (2019). Natural bis-benzylisoquinoline alkaloids-tetrandrine, fangchinoline, and cepharanthine, inhibit human coronavirus OC43 infection of MRC-5 human lung cells. *Biomolecules*, 9, 696.
- Kim, D. W., Seo, K. H., Curtis-Long, M. J., Oh, K. Y., Oh, J.-W., Cho, J. K., ... Park, K. H. (2014). Phenolic phytochemical displaying SARS-CoV papain-like protease inhibition from the seeds of *Psoralea corylifolia*. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 29, 59–63.
- Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., ... Deng, W. (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nature Medicine*, 11, 875–879.
- Leibowitz, J. L. (2008). Coronaviruses: molecular and cellular biology [book review]. *Emerg Infect Dis*, 14(4), 693–694.
- Li, S.-y., Chen, C., Zhang, H.-q., Guo, H.-y., Wang, H., Wang, L., ... Xiao, P.-g. (2005). Identification of natural compounds with antiviral activities against SARS-associated coronavirus. *Antiviral Research*, 67, 18–23.
- Li, W., Moore, M. J., Vasilieva, N., Sui, J., Wong, S. K., Berne, M. A., ... Greenough, T. C. (2003). Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*, 426, 450–454.
- Lin, C.-W., Tsai, F.-J., Tsai, C.-H., Lai, C.-C., Wan, L., Ho, T.-Y., ... Chao, P.-D. L. (2005). Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. *Antiviral Research*, 68, 36–42.
- Lin, S.-C., Ho, C.-T., Chuo, W.-H., Li, S., Wang, T. T., & Lin, C.-C. (2017). Effective inhibition of MERS-CoV infection by resveratrol. *BMC Infectious Diseases*, 17, 144.
- Liu, J., Chen, Q., Liu, S., Yang, X., Zhang, Y., & Huang, F. (2018). Sini decoction alleviates *E. coli* induced acute lung injury in mice via equilibrating ACE-AngII-AT1R and ACE2-Ang-(1-7)-Mas axis. *Life Sciences*, 208, 139–148.
- Liu, W., Zhu, H.-M., Niu, G.-J., Shi, E.-Z., Chen, J., Sun, B., ... Yang, C. (2014). Synthesis, modification and docking studies of 5-sulfonyl isatin derivatives as SARS-CoV 3C-like protease inhibitors. *Bioorganic & Medicinal Chemistry*, 22, 292–302.
- Luo, H., Tang, Q.-l., Shang, Y.-x., Liang, S.-b., Yang, M., Robinson, N., & Liu, J.-p. (2020). Can Chinese medicine be used for prevention of corona virus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs. *Chinese Journal of Integrative Medicine*, 1–8. [Epub ahead of print] <https://doi.org/10.1007/s11655-020-3192-6>.
- Luo, W., Su, X., Gong, S., Qin, Y., Liu, W., Li, J., ... Xu, Q. (2009). Anti-SARS coronavirus 3C-like protease effects of *Rheum palmatum* L. extracts. *Bioscience Trends*, 3(4), 124–126.
- Mesecar, A. D., & Ratia, K. (2008). Viral destruction of cell surface receptors. *Proceedings of the National Academy of Sciences of the United States of America*, 105, 8807–8808.
- Müller, C., Schulte, F. W., Lange-Grünweller, K., Obermann, W., Madhugiri, R., Pleschka, S., ... Grünweller, A. (2018). Broad-spectrum antiviral activity of the eIF4A inhibitor silvestrol against corona- and picornaviruses. *Antiviral Research*, 150, 123–129.
- Nassiri-Asl, M., & Hosseinzadeh, H. (2009). Review of the pharmacological effects of *Vitis vinifera* (grape) and its bioactive compounds. *Phytotherapy Research*, 23, 1197–1204.
- Nassiri-Asl, M., & Hosseinzadeh, H. (2007). Review of antiviral effects of *Glycyrrhiza glabra* L. and its active component, Glycyrrhizin. *The Journal of Medicinal Plants*, 2, 1–12.
- Pan, L., Woodard, J. L., Lucas, D. M., Fuchs, J. R., & Kinghorn, A. D. (2014). Rocaglamide, silvestrol and structurally related bioactive compounds from *Aglaia* species. *Natural Product Reports*, 31, 924–939.
- Park, J.-Y., Jeong, H. J., Kim, J. H., Kim, Y. M., Park, S.-J., Kim, D., ... Ryu, Y. B. (2012a). Diarylheptanoids from *Alnus japonica* inhibit papain-like protease of severe acute respiratory syndrome coronavirus. *Biological & Pharmaceutical Bulletin*, 35, 2036–2042.
- Park, J.-Y., Kim, J. H., Kim, Y. M., Jeong, H. J., Kim, D. W., Park, K. H., ... Ryu, Y. B. (2012b). Tanshinones as selective and slow-binding inhibitors for SARS-CoV cysteine proteases. *Bioorganic & Medicinal Chemistry*, 20, 5928–5935.
- Park, J.-Y., Ko, J.-A., Kim, D. W., Kim, Y. M., Kwon, H.-J., Jeong, H. J., ... Ryu, Y. B. (2016). Chalcones isolated from *Angelica keiskei* inhibit cysteine proteases of SARS-CoV. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 31, 23–30.
- Ryu, Y. B., Jeong, H. J., Kim, J. H., Kim, Y. M., Park, J.-Y., Kim, D., ... Park, K. H. (2010a). Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CLpro inhibition. *Bioorganic & Medicinal Chemistry*, 18, 7940–7947.
- Ryu, Y. B., Park, S.-J., Kim, Y. M., Lee, J.-Y., Seo, W. D., Chang, J. S., ... Lee, W. S. (2010b). SARS-CoV 3CLpro inhibitory effects of quinone-methide triterpenes from *Tripterygium regelii*. *Bioorganic & Medicinal Chemistry Letters*, 20, 1873–1876.
- Shen, L., Niu, J., Wang, C., Huang, B., Wang, W., Zhu, N., ... Cen, S. (2019). High-throughput screening and identification of potent broad-

- spectrum inhibitors of coronaviruses. *Journal of Virology*, 93, e00023–e00019.
- Soleimani, V., Sahebkar, A., & Hosseinzadeh, H. (2018). Turmeric (*Curcuma longa*) and its major constituent (curcumin) as nontoxic and safe substances. *Phytotherapy Research*, 32, 985–995.
- Sultan, M. T., Buttxs, M. S., Qayyum, M. M. N., & Suleria, H. A. R. (2014). Immunity: Plants as effective mediators. *Critical Reviews in Food Science and Nutrition*, 54, 1298–1308.
- Sun, M., Yang, J., Sun, Y., & Su, G. (2020). Inhibitors of RAS might be a good choice for the therapy of COVID-19 pneumonia. *Zhonghua Jie he he Hu Xi Za Zhi*, 43, E014–E014.
- Tseng, Y.-T., Wang, S.-M., Huang, K.-J., Amber, I., Lee, R., Chiang, C.-C., & Wang, C.-T. (2010). Self-assembly of severe acute respiratory syndrome coronavirus membrane protein. *The Journal of Biological Chemistry*, 285, 12862–12872.
- Webber, S. E., Tikhe, J., Worland, S. T., Fuhrman, S. A., Hendrickson, T. F., Matthews, D. A., ... Ferre, R. A. (1996). Design, synthesis, and evaluation of nonpeptidic inhibitors of human rhinovirus 3C protease. *Journal of Medicinal Chemistry*, 39, 5072–5082.
- Weber, C., & Opatz, T. (2019). Bisbenzylisoquinoline alkaloids. *Alkaloids Chem Biol*, 81, 1–114.
- Wei, X., Zhu, X., Hu, N., Zhang, X., Sun, T., Xu, J., & Bian, X. (2015). Baicalin attenuates angiotensin II-induced endothelial dysfunction. *Biochemical and Biophysical Research Communications*, 465, 101–107.
- Weiss, S. R., & Leibowitz, J. L. (2011). *Coronavirus pathogenesis, advances in virus research* (pp. 85–164). New York: Academic Press Elsevier.
- Wen, C.-C., Kuo, Y.-H., Jan, J.-T., Liang, P.-H., Wang, S.-Y., Liu, H.-G., ... Lee, S.-S. (2007). Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. *Journal of Medicinal Chemistry*, 50, 4087–4095.
- Wu, C.-Y., Jan, J.-T., Ma, S.-H., Kuo, C.-J., Juan, H.-F., Cheng, Y.-S. E., ... Brik, A. (2004). Small molecules targeting severe acute respiratory syndrome human coronavirus. *Proceedings of the National Academy of Sciences*, 101, 10012–10017.
- Wu, Z., & McGoogan, J. M. (2020). Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *Journal of the American Medical Association*, 323, 1239.
- Xia, S., Liu, Q., Wang, Q., Sun, Z., Su, S., Du, L., ... Jiang, S. (2014). Middle East respiratory syndrome coronavirus (MERS-CoV) entry inhibitors targeting spike protein. *Virus Research*, 194, 200–210.
- Yang, C.-W., Lee, Y.-Z., Hsu, H.-Y., Shih, C., Chao, Y.-S., Chang, H.-Y., & Lee, S.-J. (2017). Targeting coronavirus replication and cellular JAK2 mediated dominant NF- κ B activation for comprehensive and ultimate inhibition of coronavirus activity. *Scientific Reports*, 7, 1–13.
- Yang, C.-W., Lee, Y.-Z., Kang, I.-J., Barnard, D. L., Jan, J.-T., Lin, D., ... Lee, S.-J. (2010). Identification of phenanthroindolizines and phenanthroquinolizidines as novel potent anti-coronavirus agents for porcine enteropathogenic coronavirus transmissible gastroenteritis virus and human severe acute respiratory syndrome coronavirus. *Antiviral Research*, 88, 160–168.
- Yi, L., Li, Z., Yuan, K., Qu, X., Chen, J., Wang, G., ... Jiang, P. (2004). Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. *Journal of Virology*, 78, 11334–11339.
- Yu, X., Lin, Q., Qin, X., Ruan, Z., Zhou, J., Lin, Z., ... Liu, Z. (2016). ACE2 antagonizes VEGFa to reduce vascular permeability during acute lung injury. *Cellular Physiology and Biochemistry*, 38, 1055–1062.

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