Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Phytomedicine 85 (2021) 153311

Contents lists available at ScienceDirect

Phytomedicine

journal homepage: www.elsevier.com/locate/phymed

Review

Screening for natural and derived bio-active compounds in preclinical and clinical studies: One of the frontlines of fighting the coronaviruses pandemic

Shaden A.M. Khalifa [a], Nermeen Yosri [b,c], Mohamed F. El-Mallah [b], Reem Ghonaim [b], Zhiming Guo [c], Syed Ghulam Musharraf [d], Ming Du [e], Alfi Khatib [f,g], Jianbo Xiao [h], Aamer Saeed [i], Haged H.R. El-Seedi [j], Chao Zhao [k], Thomas Efferth [l], Hesham R. El-Seedi [a,b,d,m,*]

[a] Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, S-106 91, Stockholm, Sweden
[b] Department of Chemistry, Faculty of Science, Menoufia University, 32512 Shebin El-Kom, Egypt
[c] School of Food and Biological Engineering, Jiangsu University, Zhenjiang 212013, China
[d] H.E.J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan
[e] School of Food Science and Technology, National Engineering Research Center of Seafood, Dalian Polytechnic University, Dalian 116024, China
[f] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, International Islamic University Malaysia, Kuantan, 25200, Pahang, Malaysia
[g] Faculty of Pharmacy, Airlangga University, Surabaya 60155, Indonesia
[h] Institute of Chinese Medical Sciences, State Key Laboratory of Quality Control in Chinese Medicine, University of Macau, Macau
[i] Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan
[j] Karolinska Institutet, 171 77 Solna, Sweden
[k] College of Food Science, Fujian Agriculture and Forestry University, Fuzhou 350002, China
[l] Department of Pharmaceutical Biology, Institute of Pharmceutical and Biomedical Sciences, Johannes Gutenberg University, Staudinger Weg 5, 55128 Mainz, Germany
[m] International Research Center for Food Nutrition and Safety, Jiangsu University, Zhenjiang 212013, China

ARTICLE INFO

Keywords:
COVID-19
Natural products
Antiviral
Clinical trials
Patent
Protection

ABSTRACT

Background: Starting December 2019, mankind faced an unprecedented enemy, the COVID-19 virus. The world convened in international efforts, experiences and technologies in order to fight the emerging pandemic. Isolation, hygiene measure, diagnosis, and treatment are the most efficient ways of prevention and intervention nowadays. The health organizations and global care systems screened the available resources and offered recommendations of approved and proposed medications. However, the search for a specific selective therapy or vaccine against COVID-19 remains a challenge.

Methods: A literature search was performed for the screening of natural and derived bio-active compounds which showed potent antiviral activity against coronaviruses using published articles, patents, clinical trials website (https://clinicaltrials.gov/) and web databases (PubMed, SCI Finder, Science Direct, and Google Scholar).

Results: Through the screening for natural products with antiviral activities against different types of the human coronavirus, extracts of *Lycoris radiata* (L'Hér.), *Gentiana scabra* Bunge, *Dioscorea batatas* Decne., *Cassia tora* L., *Taxillus chinensis* (DC.), *Cibotium barometz* L. and *Echinacea purpurea* L. showed a promising effect against SARS-CoV. Out of the listed compound Lycorine, emetine dihydrochloride hydrate, pristimerin, harmine, conessine, berbamine, 4`-hydroxychalcone, papaverine, mycophenolic acid, mycophenolate mofetil, monensin sodium, cycloheximide, oligomycin and valinomycin show potent activity against human coronaviruses. Additionally, it

Abbreviations: $3CL^{pro}$, 3C-like protease; ACE2, Angiotensin-converting enzyme 2; ARDS, Acute respiratory distress syndrome; CC_{50}, Half maximal cytotoxic concentration; CD13, Human aminopeptidase N receptor; COVID-19, Corona virus disease 2019; DPP4, Dipeptidyl peptidase 4; Nsp3, Non-structural proteins proteases 3; EC_{50}, Half maximal effective concentration; ER, Endoplasmic reticulum; EtOH, Ethanol; EtOAc, Ethyl acetate; FDA, Food and Drug Administration; HCoV-229E, Human coronavirus 229E; HCoV-HKU1, Human coronavirus Hong Kong University 1; HCoV-NL63, Human coronavirus NL63; HCoV-OC43, Human coronavirus OC43; HIV, Human immunodeficiency Virus; IC_{50}, Half maximal inhibitory concentration; IL-6, Interleukin 6; IL-6R, Interleukin-6 receptor; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; MHV-A59, Coronavirus Murine hepatitis virus; N, Unaltered natural product; ND, Natural product derivative; Nsp5, Non-structural proteins proteases 5; ORF1a/b, Nonstructural open-reading frames; RdRp, RNA dependent RNA polymerase; RNA, Ribonucleic acid; SARS-CoV, Severe acute respiratory syndrome coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TEM, Transmission electron microscope.

* Corresponding author at: Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, S-106 91, Stockholm, Sweden.
E-mail address: hesham.elseedi@su.se (H.R. El-Seedi).

https://doi.org/10.1016/j.phymed.2020.153311
Received 6 June 2020; Received in revised form 15 July 2020; Accepted 21 August 2020
Available online 29 August 2020

is worth noting that some compounds have already moved into clinical trials for their activity against COVID-19 including fingolimod, methylprednisolone, chloroquine, tetrandrine and tocilizumab.
Conclusion: Natural compounds and their derivatives could be used for developing potent therapeutics with significant activity against SARS-COV-2, providing a promising frontline in the fighting against COVID-19.

Introduction

Coronaviruses were isolated in 1965 from the respiratory tract of adult humans with common cold symptoms (Kahn and McIntosh, 2005). At the beginning, the endemic corona viruses such as: HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 caused mild upper respiratory disease in humans (Chan and Chan, 2013). In the past two decades coronaviruses have appeared on a large pandemic scale displayed by the appearance of the severe acute respiratory syndrome virus (SARS-CoV) followed by the other types of Coronaviruses like (MERS-CoV) (Chan-Yeung and Xu, 2003). The severe respiratory syndrome virus reached many countries and affected many people after crossover from animal (bats as a natural reservoir host) to human, causing high fatality rates (Yuan et al., 2017). The novel SARS-CoV-2 belongs to the coronavirus family that appears to have originated from bats with unknown intermediate host (s) (Deng et al., 2020).

Nowadays, the incidence and spread of the new coronavirus disease 2019 (COVID-19) in Wuhan City, Hubei province in China became a threat to the world and a recent public health crisis (Singhal, 2020). On the 11th of February 2020 the International Committee on Taxonomy of Viruses called it the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Chhikara et al., 2020). The primary causative factor of infection transmission is the direct contact with patients such as: handshakes, contaminated surfaces and indirect inhalation of infected respiratory droplets, hence the incubation period which should be enforced around 14 days (Chhikara et al., 2020; Sohrabi et al., 2020).

The usual clinical signs are manifested as: dry cough, fever, headache, pneumonia, and breathing difficulties (dyspnea). Subsequently, the respiratory infection causes alveolar damage and respiratory failure, additionally, a decrease in the number of white blood cells, especially lymphocytes, were observed which, all in all, can lead to death in some cases (Zhou et al., 2020). The virus spread from China to other countries such as South Korea, Italy, Iran, USA, which, combined with the increasing incidence of infections worldwide made the World Health Organization (WHO) classify COVID-19 as a pandemic disease (Khalifa et al., 2020; Zingone et al., 2020). The recent update from the WHO on the 14th of July 2020, confirmed a total around 12 million infected cases and more than 500,000 deaths reported in different regions and countries (World Health Organization, 2020a).

Since a long time, alternative herbal medicines have been used as a rich source for developing antiviral drugs (Lin et al., 2014). For instance, the Chinese herbal medicine was applied as the frontline remedies towards mild and moderate cases of COVID-19 infections. Based on the historical records of Chinese herbal medicine in preventing and treating several health ailments, *Glycyrrhiza*, bitter almond, gypsum, *Trichosanthes*, reed root, amomum, and ephedra were highly recommended to relieve cough, remove toxicity, increase immunity, and combat the fever of the admitted patients (Wan et al., 2020a). Similarly, many purified natural products have been administrated as anti-coronavirus. For instance, phenolic compounds isolated from *Isatis indigotica* and amentoflavone isolated from *Torreya nucifera* work as a 3CLprotease inhibitor and were used against SARS-CoV earlier. While saikosaponins B2 isolated from *Bupleurum* spp. was utilized against HCoV-229E and known to inhibit the viral attachment to host cells (Cheng et al., 2006; Islam et al., 2020). Furthermore, neem tree extract was used to help improve the immune system (Ray et al., 1996). The traditional medicinal herbs were described by the Chinese medical health care system in more than 23 provinces in China as alternatives for the prevention and treatment of the COVID-19 virus (Luo et al., 2020). The main aim of this review is to highlight the role of natural products especially, plants, microorganisms, marines, and/or their derivatives as a promising drug lead against different species of coronaviruses.

Coronaviruses

Coronaviruses types and classifications

Human coronaviruses (CoVs) are enveloped viruses, classified into various types namely HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV, MERS-CoV and SARS-CoV-2 (COVID-19) (Fig. 1) (Corman et al., 2018; Pillaiyar et al., 2020). The first two CoVs were reported in 1960′s, followed by the discovery of four other types in the 1970′s (Lau et al., 2006). The first four have been accompanied by symptoms such as the common cold, cough, fever, nasal congestion, sore throat, sneezing, and neurological diseases (Walsh et al., 2013; Woo et al., 2005). Their distribution was related mainly to temperate climates during the winter and spring months but geographically they have been observed all over the world (Talbot et al., 2009). HCoV-229E entered cells *via* binding to the aminopeptidase N receptor (CD13) found on the surface (Yeager et al., 1992). The incubation period ranged between 2 and 5 days (Lessler et al., 2009). The HCoV-229E virus replicated in the epithelial cell line of the trachea (Shirato et al., 2017). The First isolation for the HCoV-NL63 type was observed in a 7-month-old baby in early 2004 (Fielding, 2011). Different clinical evidences were reported and showed that HCoV-NL63 induced similar symptoms to those associated with HCoV-229E and HCoV-OC43 (Talbot et al., 2009). Since HCoV-NL63 and HCoV-229E can share 65% of their amino acid identity, they have an identical mechanism of cellular entry (van der Hoek et al., 2004).

Severe Acute Respiratory Syndrome Coronavirus (SARS CoV) disproportionately infected adults, with notable severe symptoms *i.e.* fever, chills, myalgia, malaise, and headache, followed by a non-productive cough and dyspnea 3–5 days later (Fowler et al., 2003; Tsui et al., 2003). SARS-CoV was also named atypical pneumonia and was recorded as the first pandemic virus in human history (Peiris et al., 2003). Its incubation period is 2–10 days (World Health Organization, 2003). Young children and infants infected with SARS-CoV suffered from less severe symptoms than youth and adults (Bitnun et al., 2003). Infection with SARS-CoV type started by the inoculation of respiratory tract mucosa through Angiotensin-converting enzyme 2 (Li et al., 2003). Middle East Respiratory Syndrome Coronavirus (MERS-CoV) rarely infected children, but it can cause severe infections for youth. Infected cases with MERS-CoV suffered from many symptoms *i.e.* fever, cough, chills, sore throat, myalgia, arthralgia, dyspnea, pneumonia, diarrhea and vomiting (Assiri et al., 2013). It was isolated for the first time in a Saudi Arabian patient in 2012, then in another case from South Korea in 2015. About 2500 fatality cases were reported in February 2020 (Gao et al., 2016; Hilgenfeld and Peiris, 2013; Ye et al., 2020). Its incubation period ranged from 2 to 13 days (Coleman and Frieman, 2013). MERS-CoV infection started with inoculation of the respiratory tract mucosa mediated by functional receptors such as dipeptidyl peptidase 4 (DPP4) (Ng et al., 2016). Then the world faced a new challenge in December 2019, starting with the recording of the first SARS-CoV-2 case in Wuhan, Hubei province, China (Huang et al., 2020). The statistics reported on the of 14th July 2020, confirmed that the number of fatality cases reached 570,288 total cases worldwide (World Health Organization, 2020a). SARS-CoV-2 causes severe respiratory infection accompanied by different symptoms *i.e.* fever, cough, dyspnea, myalgia, and

headache (Huang et al., 2020). SARS-CoV-2 is mostly less pathogenic, but spreads more compared to SARS-CoV and MERS-CoV (Zhou et al., 2020).

SARS-CoV-2 origin, taxonomy and structure

In Wuhan, the capital of central China's Hubei province, the Coronavirus (COVID-19) outbreak appeared at the end of 2019, where China's Infectious Disease Information System recorded the first case on December 8, 2019 (Bai et al., 2020; Wu and McGoogan, 2020). The city's Huanan Seafood Market was the origin of the zoonotic virus SARS-CoV-2 which was transferred rapidly (Chan et al., 2020). The recent phylogenetic analysis detected that SARS-CoV-2 may be evolved from a strain found in bats, thus considered the natural reservoir host of SARS-CoV-2 (Chen et al., 2020a; Zhou et al., 2020). Till now, the researchers are not sure about the intermediate host (s) of SARS-CoV-2 or whether the infection can be transmitted directly from bat to human (Ye et al., 2020). It was then recognized as worldwide pandemic disease that can be transmitted rapidly between humans through droplets or direct contact (Li et al., 2020b).

2019-nCoV (COVID-19) also named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel member of the coronaviruses (Wang et al., 2020b). Nevertheless, it has a specific gene sequence that differentiates it from previously sequenced coronaviruses (Zhou et al., 2020). Interestingly, it has an 88% shared identity with SARS-CoV and about 50% to MERS-CoV, indicating that it belongs to the same species (Chen et al., 2020a; Lu et al., 2020). The phylogenetic analysis done to classify SARS-CoV-2 revealed that it falls into the Sarbecovirus subgenus of the genus Betacoronavirus (Lu et al., 2020; Zhu et al., 2020).

In general, HCoVs are long and positive single stranded RNA viruses characteristic of two groups of proteins; the first group is namely the structural proteins: Spike (S), Nucleocapsid (N), Matrix (M), and Envelope (E) (Fig. 2), while the second group is non-structural proteins: proteases (nsp3 and nsp5) and RdRp (nsp12) (Elfiky et al., 2017). In the case of SARS-CoV-2, the densely glycosylated spike protein found on the outer surface is arranged in this way in order to facilitate the recognition, attachment, and entry into the host cell (Ibrahim et al., 2020). Similarly, the genetic material of SARS-CoV-2 is a positive sense RNA strand (Chhikara et al., 2020). SARS-CoV-2 was described with a transmission electron microscope (TEM) where the double-wall surface of SARS-CoV-2 was seen, but it gives only a poor description of the different organelles in the cytoplasm (Chhikara et al., 2020; Walls et al., 2020). Thus, it was assumed that SARS-CoV-2 has distinct ultrastructural features similar to the coronavirus family such double-membrane vesicles, large granular areas of cytoplasm and nucleocapsid inclusions, in addition to viral proteins and genetic material RNA (Chhikara et al., 2020).

Replication, pathogenesis and transmission

SARS-CoV and SARS-CoV-2 (COVID-19) are similar in the mechanism of replication (He et al., 2020). Their replication begin with the binding of its spike protein (S) into the host's cell surface molecules (Sahin et al., 2020). Usually, (S) protein is divided functionally into the S1 domain, responsible for binding to human receptors, and the S2 domain is responsible for cell membrane fusion (He et al., 2004). SARS-CoV-2 enters the host cells through recognition of human receptor angiotensin-converting enzyme 2 (ACE2) (Zhou et al., 2020). RNA material of SARS-CoV-2 undergoes replication and transcription after the fusion with the plasma membrane. Replicase proteins of SARS-CoV-2 are generated from translation of positive sense RNA genomes through open reading frame 1a/b (ORF1a/b). These proteins use positive sense RNA as a template to generate full-length negative sense RNA. Then proteins are collected with new RNA genome assembly in the endoplasmic reticulum

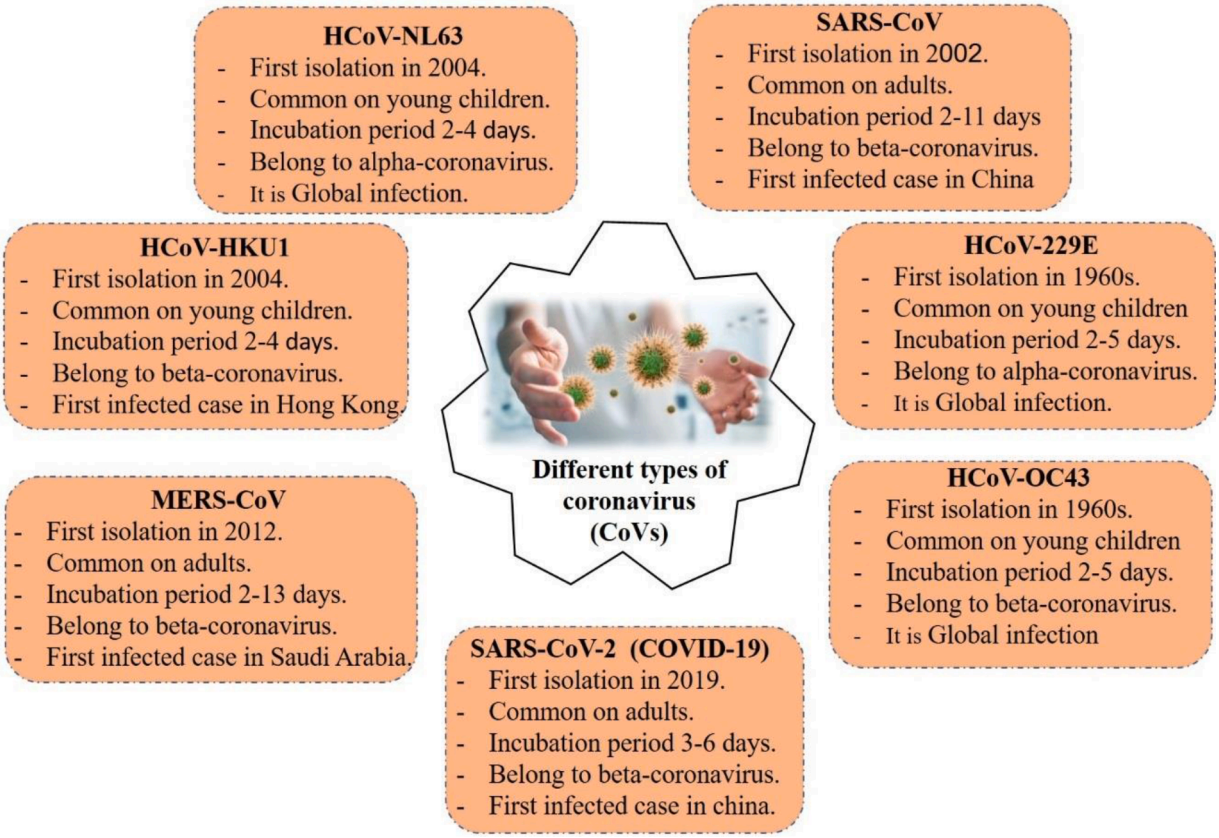

Fig. 1. Different types of coronavirus (CoVs) and their pathogenesis.

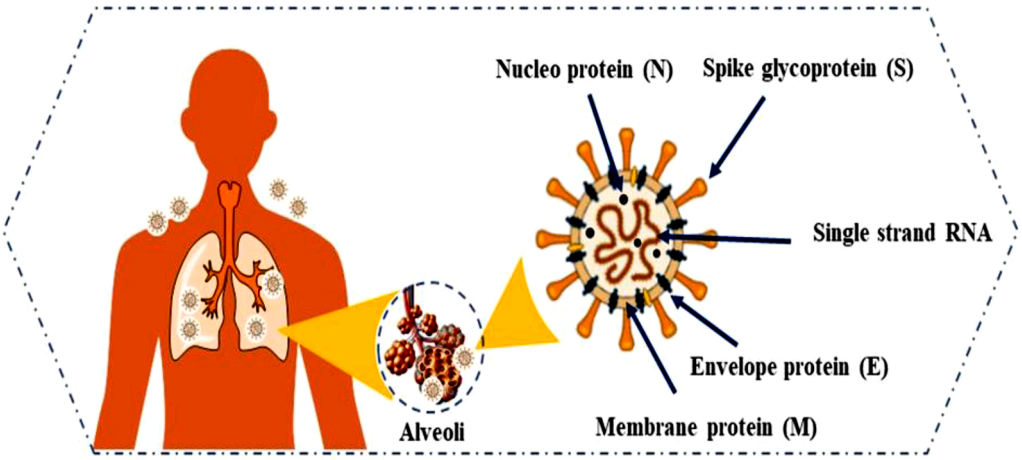

Fig. 2. Illustrating the structure of SARS-CoV-2 (COVID-19).

(ER) and Golgi-apparatus (Fig. 3) (He et al., 2020). Biophysical and structural analysis confirmed that the S protein of SARS-CoV-2 has an affinity to bind with ACE2 about 10–20 times higher than the S protein of SARS-CoV (Wrapp et al., 2020). The high affinity of the S protein for human ACE2 can facilitate the spread of SARS-CoV-2 between humans (Zhou et al., 2020).

The studies conducted on the COVID-19 infection mechanism showed an increase in leukocyte levels, plasma pro-inflammatory cytokines *i.e.* IL-6, and blood C-reactive protein values from the normal range (Lei et al., 2020). Lower numbers of T and B lymphocytes in peripheral blood are observed and coagulation parameters *i.e.* D-Dimer raise abnormally (Lin et al., 2020). The main pathogenesis of the COVID-19 infection is described as extreme pneumonia, RNA aemia, and acute cardiac injury (Huang et al., 2020). The high rate of renal failure was observed in patients with COVID-19, suggesting the development of renal dysfunction (Li et al., 2020a; Li et al., 2020b).

The human-to-human spread is now the primary way of transmission of the infection; from both symptomatic and asymptomatic individuals. The transmission from symptomatic patients occurs to nearby individuals but does not occur through air. Transmission from asymptomatic individuals occurs through direct contact, handshaking (Kam et al., 2020), touching contaminated surfaces (Bai et al., 2020) or droplets spread by coughing or sneezing then touching the mouth, nose or eyes (Pan et al., 2020b). Therefore, the human-to-human

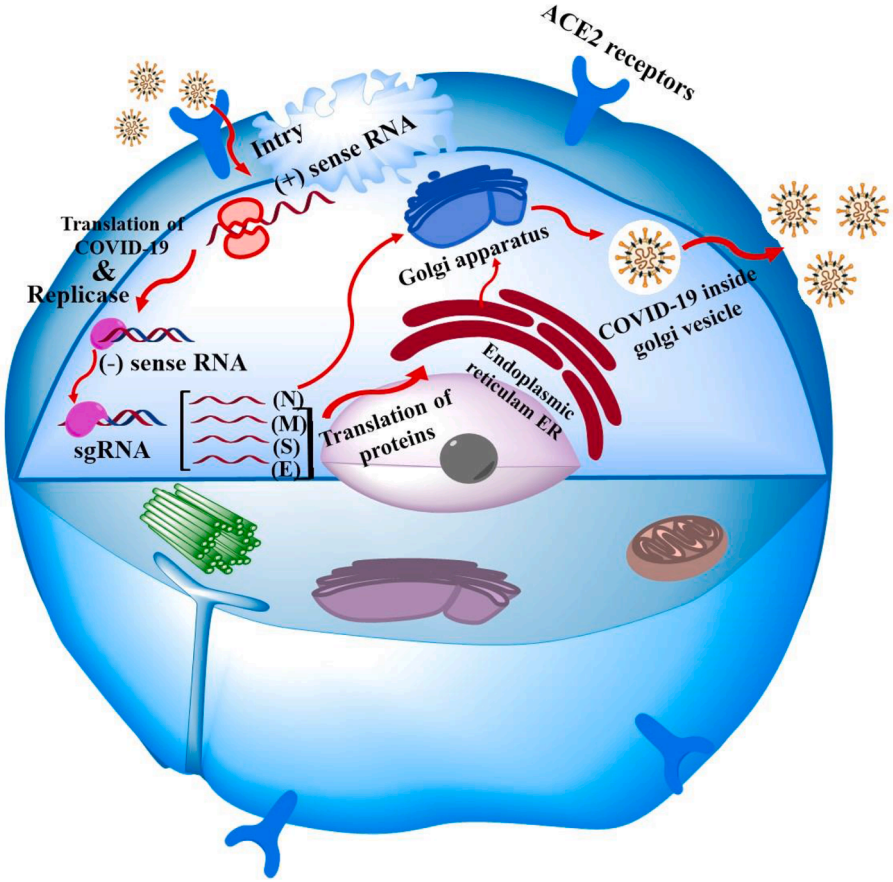

Fig. 3. Mechanism of SARS-CoV-2 replication.

transmission depends on proximity and increased population density. Also, Leung et al. (2020) proved that inadequate use of masks could lead to increased chances of infection transmission (Leung et al., 2020). A study conducted by Chen et al. (2020a) on confirmed pregnant women cases, demonstrated no evidence of trans-placental transmission. These women underwent cesarean sections, so the transmission by vaginal birth is still under debate (Chen et al., 2020a).

In the previous years, SARS-CoV (2003) infected about 8098 individuals in 26 regions around the world with a mortality rate of 9% (World Health Organization, 2003). On the other hand, SARS-CoV-2 has infected roughly 7,690,708 individuals in more than 200 countries until the 14th of June 2020 (World Health Organization, 2020b). Meaning that the transmission of SARS-CoV-2 is higher than SARS-CoV. Li et al., 2020a proved that the high spread of COVID-19 is due to the genetic recombinant S protein (Li et al., 2020a). Initial reports identified two species of snakes that may be a reservoir of SARS-CoV-2 (Ji et al., 2020; Rothan and Byrareddy, 2020). Mammals or birds are the only evidenced reservoirs of SARS-CoV-2 (Bassetti et al., 2020). Genomic sequence analysis of SARS-CoV-2 showed an 88% identity share with two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses (Chan et al., 2020; Lu et al., 2020; Wan et al., 2020b). Despite the fact that the genetic material of SARS-CoV-2 is compatible with other types of coronavirus, its gene sequences remarkably differ from previous sequences of other CoV types (Zhou et al., 2020). The genetic studies of SARS-CoV-2 showed that its sequence shared 79% identity with the other CoVs types (Lu et al., 2020).

Rational use of natural products based antiviral agents

Drugs management in preclinical studies (in vivo, in vitro)

Despite huge efforts, the world has been unable to discover potential therapies or vaccines against COVID-19, thus most of the scientific efforts are now allocated towards trying to locate a proper medication from the old conventional drugs applied earlier for previous coronavirus varieties, among them are HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 which caused mild upper respiratory disease in humans, as well as severe acute respiratory syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS)-CoV (Pillaiyar et al., 2020). Natural products, mainly plants, remain as a rich source of novel therapeutic agents for the treatment of different human illnesses (Yang et al., 2020b) . In this context, many natural product derivative therapeutic agents have been reported to inhibit entry and replication of many coronaviruses; SARS, MERS, etc. (*in vitro* and *in vivo*) (Tables 1 and 2; Fig. 4–6)

Glycyrrhizin **(34)** is an active terpenoid saponin compound isolated from liquorice roots (*Glycyrrhiza glabra* L.). Liquorice roots have been used in traditional medicine as prophylactic agent for gastric and duodenal ulcers, anti-inflammatory, contraceptive, laxative, anti-asthmatic, galactagogue, and antiviral, and expectorant (Damle, 2014; Sato et al., 1996). Cinatl et al. demonstrated that glycyrrhizin inhibited SARS virus replication by inhibition of adsorption. The penetration of the virus at early steps of the replicative cycle was stopped at both concentrations of (EC_{50} of 300 mg/l) and CC_{50} value of >20 000 mg/l in comparison to ribavirin (positive control) when greater than >1000 that could not be tolerated by the target tissue or organs (Cinatl et al., 2003).

In 2005, Li and his co-authors tested around 200 Chinese medicinal plants against Severe Acute Respiratory Syndrome associated coronavirus (SARS-CoV) using MTS assay. The results demonstrated that 4 of the 200 plants extracts, namely *L. radiata* (L'Hér.), *A. annua*l ., *P. lingua* Mirb. and *L. aggregate* Sims, showed superior activity at EC_{50} of 2.4, 34.5, 43.2 and 88.2 μg/ml respectively compared with interferon alpha as a positive control (EC_{50} = 660.3 IU/ml). Four potent extracts recorded CC_{50} values ranged between 886.6 ± 35.0 to 2378.0 ± 87.3 μg/ml. CC_{50} was determined based on reducing cell viability by using different concentration of extracts. As *L. radiata* (L'Hér.) was the most active one, it was subjected to fractionation and purification to find the most active compound, identified as lycorine **(45)**. Lycorine is an alkaloid compound that gave EC_{50} of 15.7 nM and CC_{50} value of 14,980.0 nM against SARS-CoV (Li et al., 2005). Lycorine have been investigated later against the other types of coronaviruses, HCoV-OC43, HCoV-NL63, MERS-CoV and MHV-A59 to give EC_{50} values ranging from 0.15 μM to 1.63 μM (Shen et al., 2019).

Emetine is a natural plant alkaloid of ipecac (*Carapichea ipecacuanha* L.), emetine dihydrochloride **(31)**, a derivative of emetine inhibiting the viral protein synthesis of coronaviruses, with an EC_{50} value of 0.12 to 1.43 μM. Emetine hydrochloride revealed the strongest anti-CoV activities against MERS-CoV and SARS-CoV with the lowest EC_{50} of 0.014 and 0.05 μM, whilst the activity against HCoV-NL63, HCoV-OC43, MERS-CoV and MHV-A59 showed EC_{50} values of 1.43 μM, 0.30, 0.34 and 0.12 μM respectively *via* blocking of viral propagation at an early stage of infection, thereby minimizing the chance of the virus to adapt and acquire drug resistance. It also has CC_{50} values of 3.63, 2.69, 3.08 and 3.51 μM respectively (Dyall et al., 2017; Shen et al., 2019).

Toona sinensis Roem, is a Chinese traditional plant belonging to the Meliaceae family. In the folk medicine, the leaves of the plant were used to treat gastric ulcers, enteritis, dysentery, cerebrovascular, and cardiovascular diseases (Kakumu et al., 2014). TSL-1, a fraction of the aqueous extract of the plant leaves showed anti-viral activity against SARS-coronavirus with EC_{50} of 30 μg/ml and CC_{50} value > 500 μg/ml *via* inhibition of the viral replication. Determination of CC_{50} takes place by decreasing the cell viability by 50% (Chen et al., 2008). Another study was conducted by Wen et al., where 200 plants were tested and only five of them, namely *Gentiana scabra, Dioscorea batatas, Cassia tora*, and *Taxillus chinensis*, exerted survival inhibition of SARS-CoV (Wen et al., 2011). The plants possess a wide range of folk applications including liver disorder, inflammation and pneumonia treatment (Liang et al., 2007; Oh et al., 2004; Pawar and D'mello, 2011; Zhang et al., 2013). The potent inhibition of SARS-CoV viral enzymatic activity (SARS-CoV 3CLprotease) occurred between 25 and 200 μg/ml and the most potent plants were *C. barometz* and *D. batatas* with IC_{50} value of 39 and 44 μg/ml respectively. The six plant extracts recorded the same CC_{50} value of > 500 μg/ml in comparison with valinomycin (positive control) that has value of 75.01 μg/ml. The determination of CC_{50} showed that reduction of cell viability by 50% and there was no effect on the growth of host cells, indicating the effectiveness and safety of these extracts (Wen et al., 2011).

Celastrus orbiculatus Thunb. family (Celastraceae), a Chinese herbal plant, traditionally used in the treatment of fever, chills, edema and bacterial infection (Wu et al., 2004), showed significant effect *via* inhibition of the $3CL^{pro}$ enzyme. Three different extracts (EtOH, EtOAc and water fraction) have been tested against SARS-CoV infection, and exhibited IC_{50} values of 19.4, 17.8 and 38.7 μg/ml respectively (Kumar et al., 2013). Similarly, hydroethanolic extraction of *Echinacea purpurea* plant roots showed potent activity against HCoV-229E, SARS-CoV and MERS-CoV with IC_{50} values of 3.2, 50 and 50 μg/ml respectively (Signer et al., 2020).

Furthermore, the essential oils of many plants play an important role against viral diseases *i.e. Laurus nobilis, Juniperus oxycedrus* ssp. *oxycedrus, Thuja orientalis, Cupressus sempervirens* ssp. *pyramidalis, Pistacia palaestina, Salvia officinalis*, and *Satureja thymbra*. The essential oils were investigated against SARS-CoV and HSV-1 viruses. The potent activity of *L. nobilis* oil was reported against SARS-CoV with IC_{50} value of 120 μg/ml. The plant oil is characterized by the excitation of β-ocimene, 1,8-cineole, α-pinene, and β-pinene as the principle constituents. These plants act *via* the inhibition of viral replication (Loizzo et al., 2008).

Marines natural products, *i.e.* halitunal **(69)**, mycalamide **(70)** and esculetin-4-carboxylic acid ethyl ester **(68)** showed antiviral activity against coronaviruses. Halitunal is a diterpene aldehyde isolated from the marine alga *Halimeda tuna*, known to exert an impact against murine coronavirus strain A59 at a dose of 20 μg by reduction of cell fusion (Koehn et al., 1991). Mycalamide is an alkaloid compound isolated from the *Mycale* sp. sponge that inhibited the MHV-A59 coronavirus

Table 1
List of isolated anti-viral natural products compounds and their derivatives.

Compound name, chemical class	Origin	Mechanism of action	Virus type	IC_{50} or EC_{50} (CC_{50}) value μg/ml	Reference
Plants					
2,3,4,6,7-pentamethoxy-12,13-dihydro-11*H* dibenzo[*f,h*]pyrrolo- [1,2-*β*] isoquinolin-10-ium (ND), alkaloid **(1)**	*Ficus septica* L.	Inhibits viral replication	TGEV	14.906±2468 (>100,000) nM	Yang et al., 2010a
3,14*α*-dihydroxy-4,6,7-trimethoxyphenanthroindolizidine (ND), alkaloid **(2)**	*T. ovata* L.	Inhibits viral replication	TGEV	8 ± 2 (59.943±2786) nM	Yang et al., 2010a
3,14*α* -dihydroxy-6,7-dimethoxyp-henanthroindolizidine (ND), alkaloid **(3)**	*T. ovata* L.	Inhibits viral replication	TGEV	18±1 (31,632±1192) nM	Yang et al., 2010a
3′-*O*-methyldiplacol (N), flavonoid **(4)**	*Paulownia tomentosa* (Thunb).	Inhibits PL^{pro} enzyme	SARS-CoV	9.5 ± 0.10 μM	Cho et al., 2013
3′-*O*-methyldiplacone (N), flavonoid **(5)**	*P. tomentosa* (Thunb).	Inhibits PL^{pro} enzyme	SARS-CoV	13.2 ± 0.14 μM	Cho et al., 2013
3′-(3-methylbut-2-enyl)-3′,4,7-trihydroxyflavane (N), flavonoid **(6)**	*Broussonetia papyrifera*	Inhibits coronavirus proteases enzyme	MERS-CoV SARS-CoV	48.8 ± 6.6 μM 30.2 ± 6.8 μM	Park et al., 2017
3*β*,12-diacetoxyabieta-6,8,11,13-tetraene (N), diterpenoid **(7)**	*Juniperus formosana* L.	Inhibits viral replication	SARS-CoV	1.57 (303.3) μM	Wen et al., 2007
4`-Hydroxychalcone (ND), flavonoid **(8)**	*Cinnamomum* spp.	Inhibits viral replication	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59	1.52 (>20) μM 7.25 (>20) μM 10.23 (>20) μM 9.75 (>20) μM	Jarvill-Taylor et al., 2001; Orlikova et al., 2011; Shen et al., 2019
4`-*O*-methyldiplacol (N), flavonoid **(9)**	*P. tomentosa* (Thunb).	Inhibits PL^{pro} enzyme	SARS-CoV	9.2 ± 0.13 μM	Cho et al., 2013
4`-*O*-methyldiplacone (N), flavonoid **(10)**	*P. tomentosa* (Thunb).	Inhibits PL^{pro} enzyme	SARS-CoV	12.7 ± 0.19 μM	Cho et al., 2013
4-hydroxyisolonchocarpin (N), flavonoid **(11)**	*B. papyrifera*	Inhibits coronavirus proteases enzyme	MERS-CoV SARS-CoV	171.6 ± 10.2 μM 202.7 ± 3.9 μM	Park et al., 2017
6,7-dehydroroyleanone (N), diterpenoid **(12)**	*Chamaecyparis obtusa* var. *formosana*	Inhibits viral replication	SARS-CoV	5.55 (89.7) μM	Wen et al., 2007
6-geranyl-4′,5,7-trihydroxy-3′,5′-dimethoxyflavanone (N), flavonoid **(13)**	*P. tomentosa* (Thunb).	Inhibits PL^{pro} enzyme	SARS-CoV	13.9 ± 0.18 μM	Cho et al., 2013
7*β* -hydroxydeoxycryptojaponol (N), diterpenoid **(14)**	*C. japonica* L.	Inhibits viral replication	SARS-CoV	1.15 (127) μM	Wen et al., 2007
8*β*-hydroxyabieta-9(11),13-dien-12-one (N), diterpenoid **(15)**	*C. obtuse* var. *formosana*	Inhibits viral replication	SARS-CoV	1.47 (> 750) μM	Wen et al., 2007
Acetyl-*O*-methyltylophorinidine (ND), alkaloid **(16)**	*T.indica* L.	Inhibits viral replication	TGEV	403 ± 22 (> 100,000) nM	Govindachari et al., 1973; Yang et al., 2010a
Aloeemodin (N), anthraquinone **(17)**	*Isatis indigotica*	Inhibits enzymatic activity of virus	SARS-CoV	366 (11,592) μM	Lin et al., 2005
Baicalin (N), flavonoid **(18)**	*Scutellaria baicalensis*	Inhibits the enzymatic activity	SARS-CoV	12.5–25 (> 100) μg/ml	Chen et al., 2004; Deng et al., 2012
Berbamine (N), bis-benzylisoquinoline alkaloids **(19)**	*Berberis amurensis*	Inhibits viral replication	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59	1.48 (> 20) μM 9.46 (> 20) μM 13.14 (> 20) μM 10.91 (> 20) μM	Meng et al., 2013; Shen et al., 2019
Beta-sitosterol (N), steroid **(20)**	*I. indigotica*	Inhibits enzymatic activity of virus	SARS-CoV	1210 (1475) μM	Lin et al., 2005
Betulonic acid (N), triterpene **(21)**	*J. formosana* L.	Inhibits viral replication	SARS-CoV	0.63 (112) μM	Wen et al., 2007
Broussochalcone A (N), polyphenol **(22)**	*B. papyrifera*	Inhibits coronavirus proteases enzyme	MERS-CoV SARS-CoV	42.1 ± 5.0 μM 88.1 ± 13.0 μM	Park et al., 2017
Broussochalcone B (N), polyphenol **(23)**	*Broussonetia papyrifera*	Inhibits coronavirus proteases enzyme	MERS-CoV SARS-CoV	112.9 ± 10.1 μM 57.8 ± 0.5 μM	Park et al., 2017
Broussoflavan A (N), flavonoid **(24)**	*B. papyrifera*	Inhibits coronavirus proteases enzyme	MERS-CoV SARS-CoV	49.1 ± 7.5 μM 92.4 ± 2.1 μM	Park et al., 2017
Cedrane-3 *β*,12-diol (N), sesquiterpenoid **(25)**	*J. formosana* L.	Inhibits viral replication	SARS-CoV	> 10 (> 750) μM	Wen et al., 2007
Cepharanthine, (N), (bis-benzylisoquinoline alkaloids) **(26)**	*S. tetrandra*	Inhibits viral S and N protein expression/ Suppressed the replication	HCoV-229E	729.7 nM	Kim et al., 2019
Chloroquine (S*), alkaloid **(27)**	*Cinchona* spp.	Inhibits viral replication	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59 SARS-CoV	0.33 (> 20) μM 4.89 (> 20) μM 16.44 (> 20) μM 15.92 (> 20) μM 8.8 ± 1.2 μM	Keyaerts et al., 2009; Oliveira et al., 2009; Shen et al., 2019
Conessine (N), steroid alkaloid **(28)**	*Holarrhena antidysenterica*	Inhibits viral replication	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59	2.34 (> 20) μM 10.75 (> 20) μM 4.98 (> 20) μM 11.46 (> 20) μM	Dua et al., 2013; Shen et al., 2019
Cryptojaponol (N), diterpenoid **(29)**	*Cryptomeria japonica* L.	Inhibits viral replication	SARS-CoV	> 10 (78.5) μM	Wen et al., 2007
Dehydroabieta-7-one, (N), diterpenoid **(30)**	*C. obtuse* var *formosana*	Inhibits viral replication	SARS-CoV	4 (305.1) μM	Wen et al., 2007

(*continued on next page*)

Table 1 (*continued*)

Compound name, chemical class	Origin	Mechanism of action	Virus type	IC_{50} or EC_{50} (CC_{50}) value μg/ml	Reference
Emetine dihydrochloride hydrate (S*), alkaloid **(31)**	*Carapichea ipecacuanha* L.	Inhibits RNA, DNA, and protein synthesis	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59 SARS-CoV	0.30 (2.69) μM 1.43 (3.63) μM 0.34 (3.08)/ 0.014 μM 0.12 (3.51) μM 0.05 μM	Dyall et al., 2017; Pillaiyar et al., 2020; Shen et al., 2019
Fangchinoline, (N), (Bis-benzylisoquinoline alkaloids) **(32)**	*S. tetrandra*	Inhibits viral S and N protein expression	HCoV-229E	919.2 nM	Kim et al., 2019
Ferruginol, (N), diterpenoid **(33)**	*C. obtuse* var. *formosana*	Inhibits viral replication	SARS-CoV	1.39 (80.4) μM	Wen et al., 2007
Glycyrrhizin (N), terpenoid saponin **(34)**	*Glycyrrhiza glabra* L.	Inhibits replication, adsorption and penetration of the virus at early steps of the replicative cycle	SARS-CV	300 mg/l	Cinatl et al., 2003
Harmine (N), alkaloid **(35)**	*Peganum harmala*	Inhibits viral replication	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59	1.90 (> 20) μM 13.46 (> 20) μM 4.93 (> 20) μM 13.77 (> 20) μM	Moloudizargari et al., 2013; Shen et al., 2019
Hesperetin, (N), flavonoid **(36)**	*Citrus aurantium*	Inhibits viral replication	SARS-CoV	8.3 (2718 μM)	Lin et al., 2005
Hinokinin (N), lignoid **(37)**	*C. obtuse* var.	Inhibits viral replication	SARS-CoV	> 10 (> 750) μM	Wen et al., 2007
Indigo (N), alkaloid **(38)**	*I. indigotica*	Inhibits enzymatic activity of virus	SARS-CoV	752 (7375) μM	Lin et al., 2005
Indirubin (N), alkaloid **(39)**	*I. indigotica*	Inhibits enzymatic activity of virus	SARS-CoV	–	Lin et al., 2005
Kazinol A (N), flavonoid **(40)**	*B. papyrifera*	Inhibits coronavirus proteases enzyme	MERS-CoV SARS-CoV	88.5 ± 3.9 μM 84.8 ± 10.4 μM	Park et al., 2017
Kazinol B (N), flavonoid **(41)**	*B. papyrifera*	Inhibits coronavirus proteases enzyme	MERS-CoV SARS-CoV	94.9 ± 13.1μM 233.3 ± 6.7 μM	Park et al., 2017
Kazinol F (N), flavonoid **(42)**	*B. papyrifera*	Inhibits coronavirus proteases enzyme	MERS-CoV SARS-CoV	39.5 ± 5.1 μM 43.3 ± 10.4 μM	Park et al., 2017
Kazinol J (N), flavonoid **(43)**	*B. papyrifera*	Inhibits coronavirus proteases enzyme	MERS-CoV SARS-CoV	55.0 ± 1.3 μM 64.2 ± 1.7 μM	Park et al., 2017
Luteolin (N), flavonoid **(44)**	*Rhodiola kirilowii* L.	Inhibits entry of virus to cell	SARS-CoV	10.6 μM (0.155) mM	Yi et al., 2004
Lycorine (N), alkaloid **(45)**	*Lycoris radiata* (L'Hér.)	Inhibits cell division, antineoplastic, antiviral	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59 SARS-CoV	0.15 (4.37) μM 0.47 (3.81) μM 1.63 (3.14) μM 0.31 (3.51) μM 0.0157 (14.98) μM	Li et al., 2005; Pillaiyar et al., 2020; Shen et al., 2019
Mimulone (N), flavonoid **(46)**	*P. tomentosa* (Thunb).	Inhibits PL^{pro} enzyme	SARS-CoV	14.4 ± 0.27 μM	Cho et al., 2013
N-acetylglucosamine (N), alkaloid **(47)**	*Urtica dioica* agglutinin	Inhibits viral replication	SARS-CoV	2.6 ± 3.7 (12.5 ± 4.4) (μg/ml	Kumaki et al., 2011; Liu et al., 2008
Papaverine (N), alkaloid **(48)**	*Papaver somniferum* L.	Inhibits viral replication	HCoV—OC43 HCoV-NL63 MERS-CoV MHV-A59	1.61 (12.11) μM 7.32 (11.71) μM 9.45 (11.98) μM 11.46 (12.44) μM	Labanca et al., 2018; Shen et al., 2019
Papyriflavonol A (N), flavonoid **(49)**	*B. papyrifera*	Inhibits coronavirus proteases enzyme	MERS-CoV SARS-CoV	112.5 ± 7.3 μM 103.6 ± 17.4μM	Park et al., 2017
Pinusolidic acid, (N), diterpenoid **(50)**	*C. obtuse* var.	Inhibits viral replication	SARS-CoV	4.71 (> 750) μM	Wen et al., 2007
Pristimerin (N), triterpenoid **(51)**	*Pristimerae indica, Tripterygium regelii*	Inhibits viral replication	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59 SARS-CoV	1.99 (> 20) μM 1.63 (> 20) μM 13.87 (> 20) μM 9.17 (> 20) μM 5.5 μM	Li et al., 2019; Ryu et al., 2010; Shen et al., 2019
Saikosaponin A (N), triterpenoid saponins **(52)**	*Bupleurum* spp., *Heteromorpha* spp., *Scrophularia scorodonia*	Inhibits viral attachment and penetration into cells	HCoV-229E	8.6 ± 0.3 (228.1 ± 3.8) μmol/l	Cheng et al., 2006
Saikosaponin B2 (N), triterpenoid saponins **(53)**	*Bupleurum* spp., *Heteromorpha* spp., *S. scorodonia*	Inhibits viral attachment and penetration into cells	HCoV-229E	1.7 ± 0.1 (383.3 ± 0.2) μmol/l	Cheng et al., 2006
Saikosaponin C (N), triterpenoid saponins **(54)**	*Bupleurum* spp., *Heteromorpha* spp., *S. scorodonia*	Inhibits viral attachment and penetration into cells	HCoV-229E	19.9 ± 0.1 (121.5 ± 0.1) μmol/l	Cheng et al., 2006
Saikosaponin D (N), triterpenoid saponins **(55)**	*Bupleurum* spp., *Heteromorpha* spp., *S. scorodonia*	Inhibits viral attachment and penetration into cells	HCoV-229E	13.2 ± 0.3 (176.2 ± 0.2) μmol/l	Cheng et al., 2006
Savinin (N), lignoid **(56)**	*C. obtuse* var.	Inhibits viral replication Inhibits enzymatic activity of virus	SARS-CoV	25, 1.13, (> 750) μM	Wen et al., 2007
Sinigrin (N), glycoside **(57)**	*I. indigotica*	Inhibits enzymatic activity of virus	SARS-CoV	217 (> 10,000) μM	Lin et al., 2005

(*continued on next page*)

Table 1 (*continued*)

Compound name, chemical class	Origin	Mechanism of action	Virus type	IC_{50} or EC_{50} (CC_{50}) value μg/ml	Reference
Tetrandrine, (N), (bis-benzylisoquinoline alkaloids) **(58)**	*Stephania tetrandra*	Inhibits viral S and N protein expression	HCoV-229E	295.6 nM	Kim et al., 2019
Tetra-*O*-galloyl-D-glucose (N), tannin **(59)**	*Galla chinensis* L.	Inhibits entry of virus to cell	SARS-CoV	4.5 μM (1.08 mM)	Yi et al., 2004
Tomentin A (N), coumarin **(60)**	*Paulownia tomentosa* (Thunb).	Inhibits PL^{pro} enzyme	SARS-CoV	6.2 ± 0.04 μM	Cho et al., 2013
Tomentin B (N), coumarin **(61)**	*P. tomentosa* (Thunb).	Inhibits PL^{pro} enzyme	SARS-CoV	6.1 ± 0.02 μM	Cho et al., 2013
Tomentin C (N), coumarin **(62)**	*P. tomentosa* (Thunb).	Inhibits PL^{pro} enzyme	SARS-CoV	11.6 ± 0.13 μM	Cho et al., 2013
Tomentin D (N), coumarin **(63)**	*P. tomentosa* (Thunb).	Inhibits PL^{pro} enzyme	SARS-CoV	12.5 ± 0.22 μM	Cho et al., 2013
Tomentin E (N), coumarin **(64)**	*P. tomentosa* (Thunb).	Inhibits PL^{pro} enzyme	SARS-CoV	5.0 ± 0.06 μM	Cho et al., 2013
Tylophorine (N), alkaloid **(65)**	*T. indica* L.	Inhibits viral replication	TGEV	95±17 (> 100.000) nM	Yang et al., 2010a
Tylophorinine (N), alkaloid **(66)**	*T. indica* L.	Inhibits viral replication	TGEV	82 ± 8 (> 100.000) nM	Yang et al., 2010a
α-cadinol, (N), sesquiterpenoid **(67)**	*C. obtuse* var.	Inhibits viral replication	SARS-CoV	4.44 (76.8) μM	Wen et al., 2007
Marine					
Esculetin-4-carboxylic acid ethyl ester (N), coumarin **(68)**	*Axinella cf. corrugate*, Sponge	Inhibit enzymatic activity of virus	SARS-CoV	> 800 μmol l^{-1}, 112 μmol l^{-1}	Lira et al., 2007
Halitunal (N), diterpene aldehyde **(69)**	*Hulimeda tuna*, Algae	Reduction in cell fusion and cytopathic effects	Murine coronavirus	20 μg	Koehn et al., 1991
Mycalamide A (N), alkaloid **(70)**	*Mycale* sp., Sponge	Protein synthesis inhibitors of virus	MHV-A59	Tested dose 0.2 μg/kg daily	Donia and Hamann, 2003
Microorganisms					
Antimycin A (N), alkaloid **(71)**	*Streptomyces* spp., Bacteria	Antibiotic	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59	1.65 (3.62) μM 6.05 (4.21) μM 6.89 (4.32) μM 5.42 (3.98) μM	Shen et al., 2019; Van Tamelen et al., 1961
Cycloheximide (N), alkaloid **(72)**	*Streptomyces* spp., Bacteria	Protein synthesis inhibitor	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59	0.43 (3.12) μM 2.64 (3.24) μM 2.56 (2.96) μM 5.21 (3.19) μM	Shen et al., 2019; Sisler and Siegel, 1967
Monensin sodium (ND), salt **(73)**	*Streptomyces cinnamonensis*, Bacteria	Inhibit viral replication	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59	3.81 (>20) μM 1.54 (>20) μM 3.27(>20) μM 0.18 (>20) μM	Łowicki and Huczyński, 2013; Pillaiyar et al., 2020; Shen et al., 2019
Mycophenolate mofetil (ND) **(74)**	*Penicillium* spp., Fungus	Immune suppressant, antineoplastic, antiviral	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59	1.58 (3.43) μM 0.23 (3.01) μM 1.54 (3.17) μM 0.27 (3.33) μM	Bittencourt et al., 2000; Pillaiyar et al., 2020; Shen et al., 2019; Sollinger, 2004
Mycophenolic acid (N) **(75)**	*Penicillium* spp., Fungus	Immune suppressant, antineoplastic, antiviral	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59 SARS-CoV	1.95 (3.55) μM 0.18 (3.44) μM 1.95 (3.21) μM 0.17 (4.18) μM > 0.15	Cinatl et al., 2003; Hart et al., 2014; Pillaiyar et al., 2020; Shen et al., 2019; Sollinger, 2004
Valinomycin (N), Peptide **(76)**	*Streptomyces* sp., Bacteria	Antibiotic	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59	4.43 (6.15) μM 1.89 (4.12) μM 6.07 (5.88) μM 6.78 (5.11) μM	Cheng, 2006; Shen et al., 2019
Oligomycin (N), Macrolide **(77)**	*Streptomyces* sp., Bacteria	Inhibits viral replication	HCoV-OC43 HCoV-NL63 MERS-CoV MHV-A59	0.19 (6.56) μM 2.63 (4.26) μM 0.21 (5.16) μM 6.43 (6.78) μM	Shen et al., 2019; Yang et al., 2010b

TGEV: Coronavirus infected Pigs.

replication by blocking the protein synthesis (Donia and Hamann, 2003). Additionally, esculetin-4-carboxylic acid ethyl ester, is a coumarin compound derived from the *Axinella cf. corrugate* sponge that down-regulates the SARS 3CL-protease (Lira et al., 2007).

Streptomyces spp. compounds including monensin sodium **(73)**, cycloheximide **(72)**, oligomycins **(77)**, valinomycin **(76)**, and antimycin A **(71)** were isolated and investigated in opposition to SARS-CoV-2. Monensin sodium is an antibacterial salt isolated from *Streptomyces cinnamonensi* actinobacteria culture containing glucose, soybean oil, and grit (Łowicki and Huczyński, 2013). Monensin sodium exhibited antiviral activity against diverse coronaviruses (EC_{50} = 0.18–3.81 μM) (Shen et al., 2019). Formerly, monensin and monensin sodium inhibited avian infectious bronchitis virus replication by blocking glycoprotein transport to plasma membranes at the level of the Golgi complex (Alonso-Caplen et al., 1984; Niemann et al., 1982) . Cycloheximide, oligomycins, valinomycin and antimycin A were used against a wide spectrum of Coronaviruses by inhibiting protein synthesis and viral replication with EC_{50} of (0.43–5.21), (0.19 -6.43), (1.89–6.78) and (1.65–6.89), respectively. As well these compounds recorded CC_{50} value range between (2.96- 3.24), (4.26–6.78), (4.12–6.15) and (3.62–4.32) respectively (Shen et al., 2019).

Mycophenolic acid (MPA) **(75)** was first isolated from *Penicillium* spp. fungi by Bartolomeo Gosio in 1893 and was reported to have an immunosuppressive activity against psoriasis (Sollinger, 2004). Recently, mycophenolic acid was investigated against different types of coronavirus using a high-throughput screening approach, where the MPA showed potent anti- MHV-A59 activity *in vitro* at an EC_{50} value of 0.17 μM compared to of HCoV-OC43, HCoV-NL63 and MERS-CoV (EC_{50}

Table 2
List of plants extracts used as anti-coronaviruses.

Plants	Type of extract	Organism/ Mechanism	IC_{50} or EC_{50} (CC_{50}) value ug/ ml	References
Artemisia annua L., Whole plant	EtOH	SARS-CoV Reduces RNA replication	34.5 (1053)	Li et al., 2005
Cassia tora (CTH)	EtOH	SARS-CoV Inhibits viral replication Inhibits enzymatic activity	8.43 (> 500) > 50	Wen et al., 2011
Celastrus orbiculatus Thunb.	EtOH	SARS-CoV NR	19.4	Kumar et al., 2013
	EtOAc	SARS-CoV NR	17.8	
	Aqueous	SARS-CoV NR	38.7	
Cibotium barometz (CBE)	EtOH	SARS-CoV Inhibits viral replication, Inhibits enzymatic activity	8.42 (> 500) > 50	Wen et al., 2011
C. barometz (CBM)	EtOH	SARS-CoV Inhibits viral replication Inhibits enzymatic activity	> 10 (> 500) 39	Wen et al., 2011
Dioscorea batatas (DBM)	EtOH	SARS-CoV Inhibits viral replication Inhibits enzymatic activity	8.06 (> 500) 44	Wen et al., 2011
Echinacea purpurea, Roots	Aqueous ethanol	SARS-CoV Inhibits viral replication	50	Signer et al., 2020
		MERS-CoV Inhibits viral replication	50	
		HCoV-229E Inhibits viral replication	3.2	
Gentiana scabra (GSH), Rhizomes	EtOH	SARS-CoV Inhibits viral replication Inhibits enzymatic activity	8.70 (> 500) > 50	Wen et al., 2011
J. oxycredrus, Berries	Essential oil	SARS-CoV Inhibits viral replication	270	Loizzo et al., 2008
l. nobilis, Berries	Essential oil	SARS-CoV Inhibits viral replication	120	Loizzo et al., 2008
Lindera aggregate Sims, Roots	EtOH	SARS-CoV Reduces RNA replication	88.2 (1374)	Li et al., 2005
Lycoris radiata (L'Hér.), Stem	EtOH	SARS-CoV Reduces RNA replication	2.4 (886.6)	Li et al., 2005
P. palaestina, Fruits	Essential oil	SARS-CoV Inhibits viral replication	> 1000	Loizzo et al., 2008
Pyrrosia lingua Mirb., Leaves	$CHCl_3$	SARS-CoV Reduce RNA replication	43.2 (2378)	Li et al., 2005
T. orientalis, Fruits	Essential oil	SARS-CoV Inhibits viral replication	130	Loizzo et al., 2008
Taxillus chinensis (TCH)	EtOH	SARS-CoV Inhibits viral replication Inhibits enzymatic activity	5.39 (> 500) > 50	Wen et al., 2011
Toona sinensis Roem Leaves	Aqueous	SARS-CoV Inhibits viral replication	30 (> 500)	Chen et al., 2008

values ranging from 0.18 to 1.95 μM). The value of CC_{50} of MHV-A59 equals 4.18 μM that is greater than the values of HCoV-OC43, HCoV-NL63 and MERS-CoV ranging from 3.21 to 3.55 μM (Shen et al., 2019). Another promising MPA derivative called mycophenolate mofetil **(74)** was reported to be an immunosuppressant, antineoplastic, and antiviral agent against HCoV-OC43, HCoV-NL63, MERS-CoV and SARS-CoV at EC_{50} of 1.58, 0.23, 1.54 and 0.27 μM. The CC_{50} of this compound ranged from 3.01 to 3.43 μM. The two compounds have similar chemical structures, but MPA showed a higher activity against MHV-A59 (EC_{50} = 0.17 μM) (Shen et al., 2019).

Curative efficacy of clinical studies and approved drugs

For a long time, natural products and their molecular frameworks constitute valuable starting points or sources for drug discovery (El-Seedi et al., 2019; Rodrigues et al., 2016). In line with Newman and Cragg, the number of antiviral drugs approved by the FDA in the period between 1981 to 2019 are 186 drugs, among them 87 are vaccines like FluMist®, Invivac®, Bilive®, Anflu®, Afluria® and Optaflu®, and are used against the influenza virus, 26 are synthetic but the pharmacophores are natural products, 17 are biological sources like peptides and proteins and 6 are natural products derivatives such as Tamiflu®, Zanamivir® and Virreal®, 21 are synthetic drugs (NP pharmacophore)/ mimics of natural products and other 19 compounds are synthetics (Newman and Cragg, 2020).

Nowadays, there are around 80 running and pending clinical trials in China in a serious attempt to find a potential treatment for COVID-19 (Maxmen, 2020). In 2020, several compounds isolated from natural products (Fig. 7; Table 3) were tested against coronavirus (COVID-19), *i. e. Xiyanping* (Mix of **78** and **79**). *Xiyanping*, is a semi-synthetic product derived from the active components of the *Andrographis paniculata* plant, and licensed in China as an anti-inflammatory agent (Chong et al., 2013; Xiao et al., 2013). *Xiyanping* injection was investigated on 426 patients diagnosed with moderate to severe SARS-CoV-2 infection, every patient was injected with 10–20 ml of *Xiyanping* at 500 mg per 20 ml daily plus lopinavir/ritonavir tablets and α-interferon nebulization. The stated drug (lopinavir/ritonavir) has the ability to inhibit protease and CYP3A metabolism thus showing antiviral properties (Driggin et al., 2020) (ClinicalTrials.gov; NCT04275388)

Fingolimod (FTY720) **(80)**, another compound derived from myriocin (ISP-1), is a metabolite of the *Isaria sinclairii* fungus. Fingolimod has been approved by the regulatory authorities of the US, EU, Australia, and Russia, to treat the relapsing remitting multiple sclerosis. Fingolimod consequently represents the primary oral drug for treatment of this central nervous autoimmune disease (Ingwersen et al., 2012). In China, the Fingolimod drug was tested with 30 patients infected with COVID-19. Every patient was given 0.5 mg of Fingolimod orally daily, for three consecutive days. Fingolimod was used in the current study as an effective agent against COVID-19 acting *via* an immunology modulation of phingosine-1-phosphate receptors (ClinicalTrials.gov; NCT04280588) (Driggin et al., 2020).

Tetrandrine **(58)** represents the predominant constituent of the *Stephania tetrandra* plant, a Chinese traditional medicinal plant. Tetrandrine is bisbenzylisoquinoline alkaloid and recommended in the Chinese Pharmacopoeia as an analgesic and diuretic agent and also for treatment of hypertension and various other ailments like asthma, tuberculosis, dysentery, hyperglycemia, malaria, cancer and fever. It was also used against the Ebola virus infection (Bhagya and Chandrashekar, 2016). In the clinical studies, tetrandrine has been proven effective against COVID-19 *via* reducing the clinical progress, improving the prognosis, reducing the incidence of pulmonary fibrosis during rehabilitation, and improving patients' quality of life (ClinicalTrials.gov; NCT04308317). Tetrandrine has shown potential in decreasing the entry of SARS-CoV-2 S pseudovirions (Ou et al., 2020). Tocilizumab **(82)**, is a humanized monoclonal antibody that interacts with the interleukin-6 receptor (IL-6R) and is nowadays approved by China's National Health

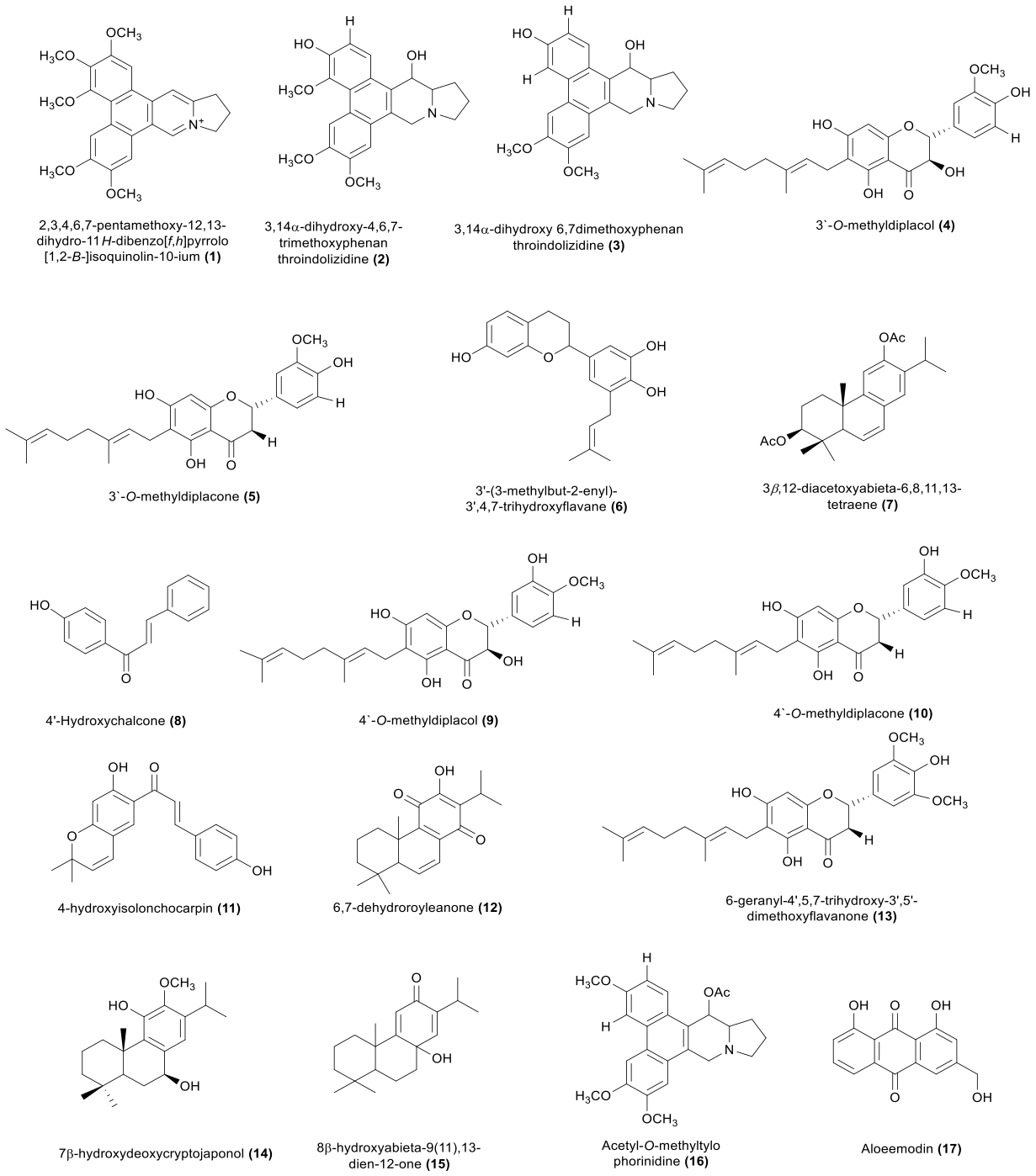

Fig. 4. Structures of isolated anti-viral compounds of plant origin and their derivatives.

Commission for the treatment of inflammation in patients with COVID-19 (Cron and Chatham, 2020). Previously, Tocilizumab (Actemra®) was permitted by means of the FDA as a drug used for inflammatory bowel disease treatment (Newman and Cragg, 2020). Recently, some physicians in Italy (Pascale Hospital, Naples) claimed that Actemra® (Tocilizumab) succeeded in treating severely ill patients *via* blocking the inflammatory molecule interleukin-6, decreasing systemic inflammation, improving survival rate, adjusting hemodynamic and relieving the respiratory distress (Day, 2020).

Streptokinase and Heparin were investigated as a treatment for patients infected by Severe Acute Respiratory Syndrome (SARS) and Severe Acute Respiratory Distress Syndrome (ARDS), the first one is an enzyme isolated from the *Streptococci* bacteria and the other is a glycosaminoglycan derived from dog liver (Anderson et al., 1948; McLean, 1959). The two compounds had been administrated in 40 patients infected with ARDS. The first 20 patients were treated with heparin (10.000 IU) and the other 20 were treated with Streptokinase (250.000 IU). Each drug was prepared in a 3 ml volume of distilled water and nebulized for a period of 15 min every 4 h. The outcome of the study revealed an improvement of the hypoxemia as determined by PaO_2/FiO_2 ratio >100, an improvement of the pulmonary compliance of the patient defined as dynamic compliance >50 ml/cm H_2O, and a decrease of the occurrence of complications such as bleeding or coagulopathy within 72 h of initiation of therapy. Streptokinase and Heparin may prevent /or

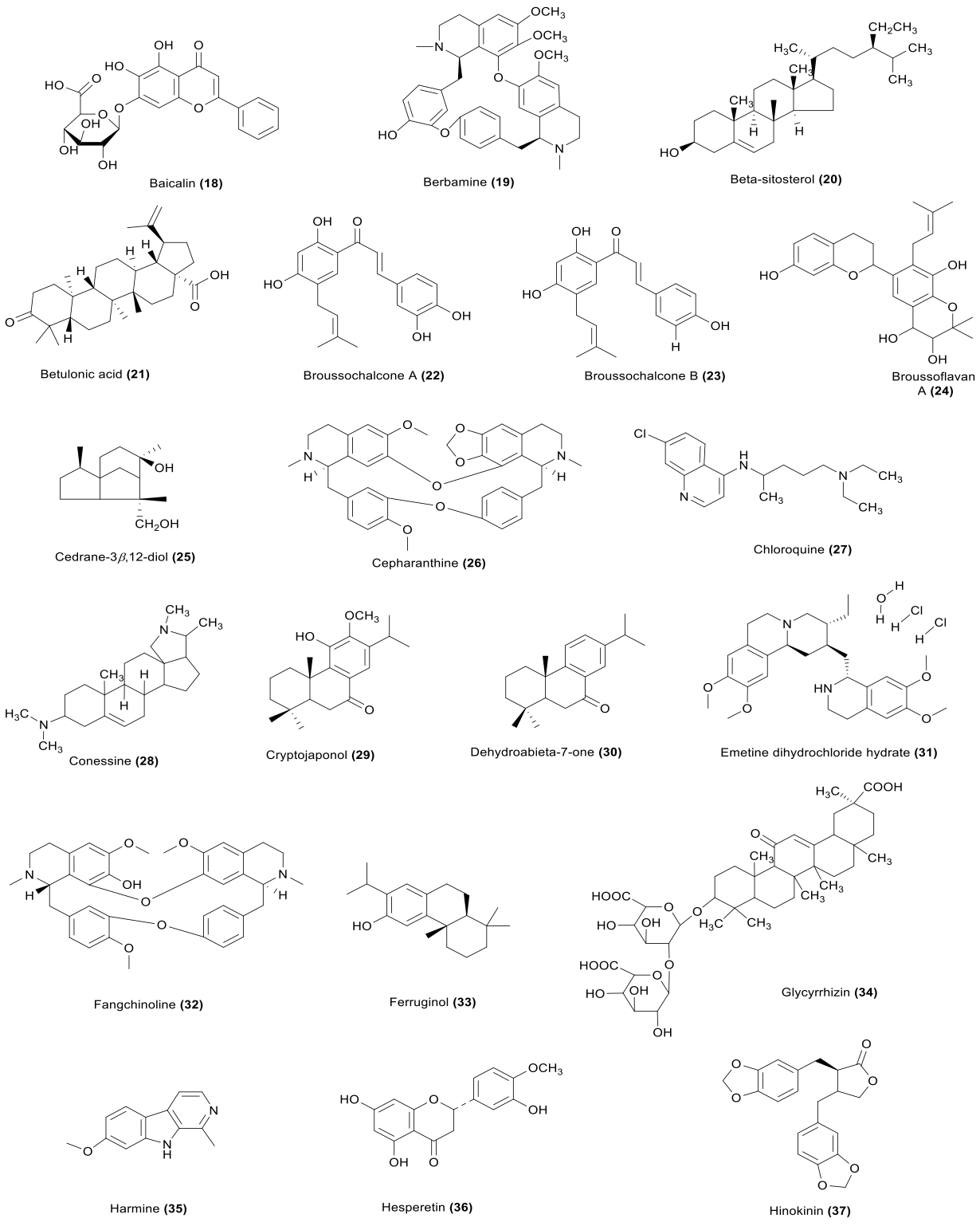

Fig. 4. (*continued*).

dissolve intra-alveolar fibrin clots respectively helping alveolar re-expansion (ClinicalTrials.gov; NCT03465085).

Methylprednisolone **(81)** is a natural products derivative (prednisolone derivative glucocorticoid) implemented by the FDA as an anticancer drug (Feinberg et al., 1957; Hall, 1992; Newman and Cragg, 2020; Ravina, 2011). In early 2020, two clinical studies had been conducted on methylprednisolone against SARS-CoV-2 with 86 and 80 participants respectively. In both studies, all participants recovered except for one case that died in the first study (ClinicalTrials.gov; NCT04273321; NCT04244591).

Chloroquine **(27)** is a synthetic drug but its pharmacophore is a natural product origin (Quinin isolated from *Cinchona* spp. plant) (Oliveira et al., 2009), and approved antiphrastic (anti-malaria) drug as per the FDA (Newman and Cragg, 2020). In the 1960′s, it was investigated as an antiviral *in vitro* for the first time (Touret and de Lamballerie, 2020). Chloroquine was able to inhibit MERS-CoV replication at a very early

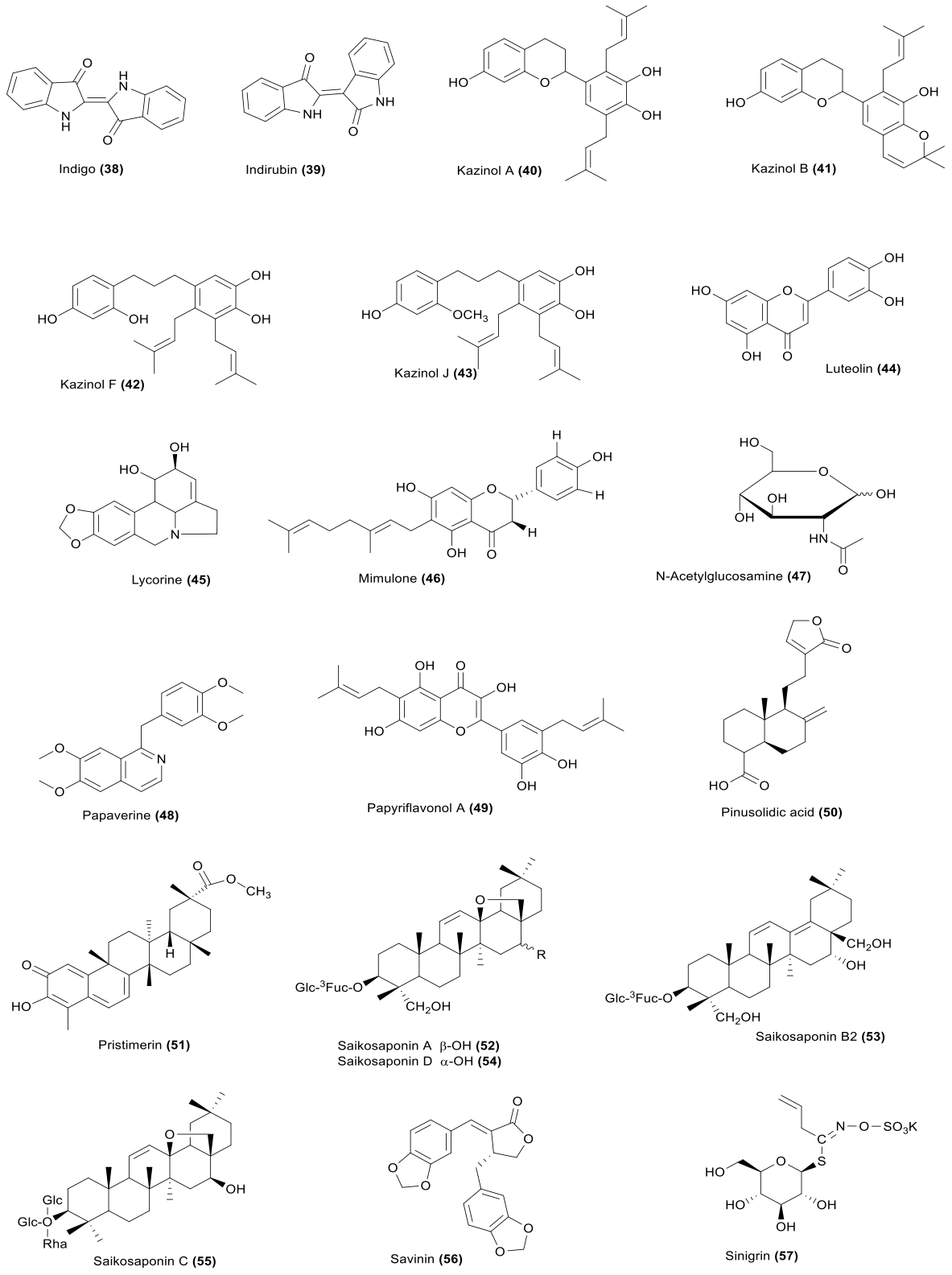

Fig. 4. (*continued*).

stage of infection with EC_{50} of 3.0 μM, and it was reported as a potent anti-viral agent against flavivirus, influenza virus, HIV, Ebola virus, and Nipha-Hendravirus (Pillaiyar et al., 2020). Nevertheless, many clinical studies were conducted on chloroquine as an anti- COVID-19 virus agent (ClinicalTrials.gov; NCT04303507), and its efficacy and safety remain unclear. It is proven highly effective in blocking viral replication in other infections including the SARS-associated coronavirus (CoV) (Cortegiani et al., 2020). However, in a recent observational study, hydroxychloroquine treated patient was more seriously ill than those who hadn't received hydroxychloroquine (Geleris et al., 2020).

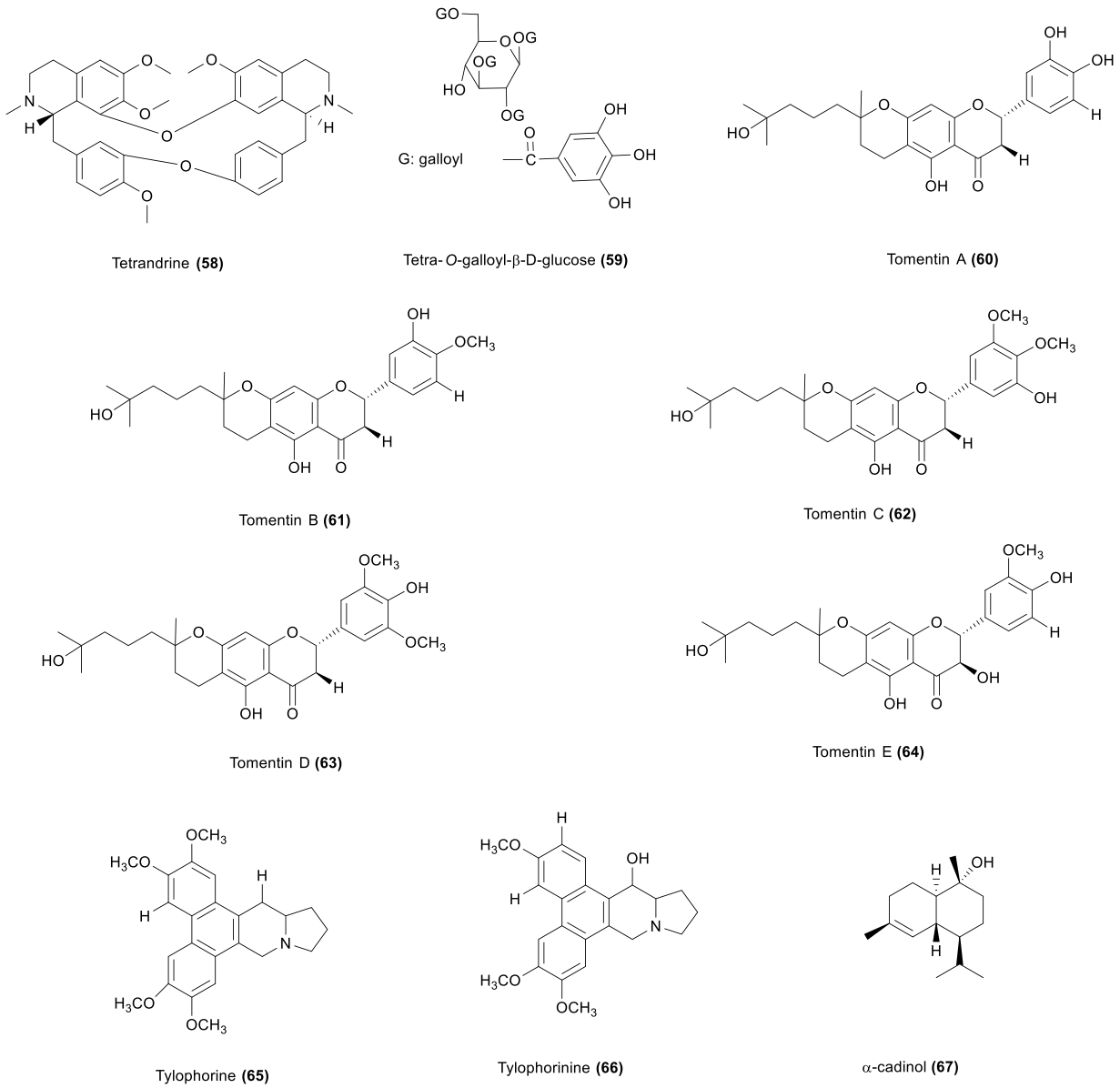

Fig. 4. (*continued*).

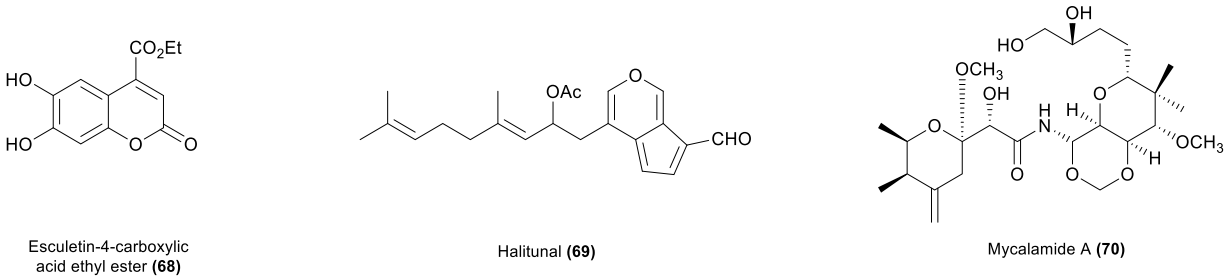

Fig. 5. Structures of isolated anti-viral compounds of marine origin or their derivatives.

Patents of natural products prescriptions against COVID-19 pandemic

As discussed earlier, small-molecule, approved drugs, and natural products are promising entities to combat COVID-19 depending on various mechanisms of action. Traditional Chinese medicine (TCM) has a synergistic effect that plays a vital role in resisting the virus and resisting inflammation of the lung and thus some TCM formulas have been proposed and approved as patents against coronaviruses. Our review devotes to patents from natural product sources (Table 4).

One prescription for treating pneumonia caused by the new coronavirus infection was inspired by the TCM composition and discloses. The prescription raw materials combine, parts by weight, of the following TCM materials: 9 parts of *Ephedra*, 6 parts of honey-fried licorice root, 9 parts of almond, 15–30 parts of *Gypsum*, 9 parts of *Cassia*

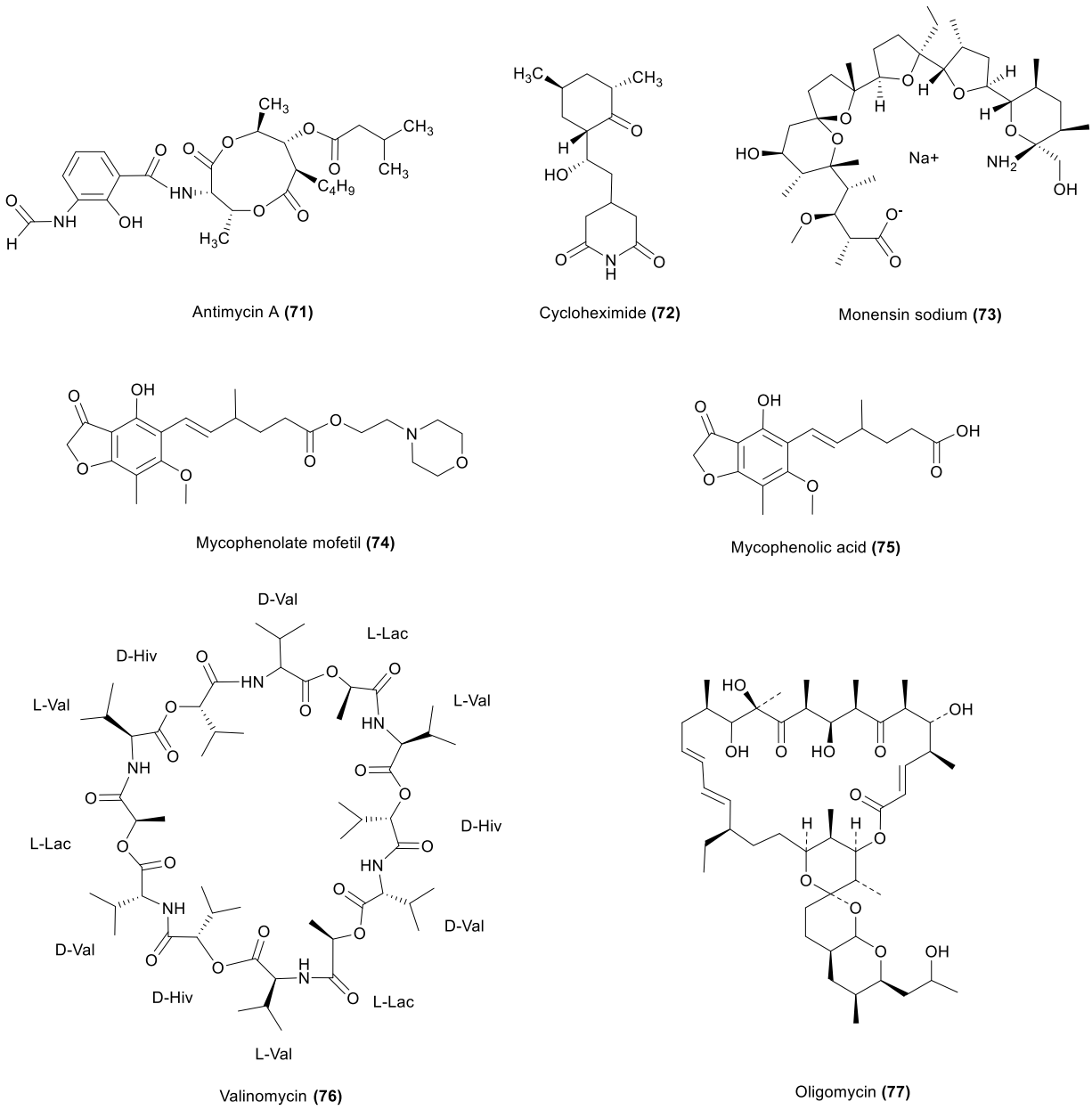

Fig. 6. Structures of isolated anti-viral compounds of microbial origin or their derivatives.

Twig, 9 parts of Rhizoma Alismatis, 9 parts of *Frifola*, 9 parts of bighead *Atractylodes* rhizome, 15 parts of *Poria cocos*, 16 parts of *Radix Bupleuri*, 6 parts of *Scutellaria baicalensis*, 9 parts of ginger processed Pinellia tuber, 9 parts of ginger, 9 parts of aster, 9 parts of Flos Farae, 9 parts of *Blackberry lily*, 6 parts of *Asarum*, 12 parts of Chinese yam, 6 parts of immature bitter orange, 6 parts of dried orange peel and 9 parts of wrinkled *Gianthyssop* herb. The effective rate of treatment was reported to 95%. The percent of effective rates was calculated based on the number of confirmed diagnosis and the number of treated patients from different places. This patent was documented in patent office CN with publication number (CN110870402A) (Ge, 2020).

Another TCM prescription is composed of the following raw materials in parts by weight: 40 parts of Folium isatidis, 40 parts of the wild *Chrysanthemum* flower, 20 parts of *Coptis chinensis*, 30 parts of sweetsop seed, 20 parts of wrinkled *Gianthyssop* herb, 20 parts of Rhizoma Atractylodis, 20 parts of Radix Bupleuri, 2 parts of Calculus Bovis Factitius, 20 parts of *Houttuynia cordata*, 5 parts of dandelion root, 30 parts of honeysuckle, 30 parts of Fructus Forsythiae, 20 parts of *Scutellaria baicalensis*, 20 parts of blackberry lily, 15 parts of *Salvia miltiorrhiza*, 15 parts of Bulbus Fritillariae Cirrhosae, 10 parts of *Saussurea involucrate*, 60 parts of *Astragalus mongholicus*, 20 parts of *Cordyceps sinensis*, 20 parts of *Codonopsis*. Observation of clinical experiments shows that the patent boosted the pneumonia symptoms caused by the new SARS-CoV-2 coronavirus. This patent was documented in patent office CN with publication number (CN111150792A) (Zhang and Yang, 2020).

Tripterygium wilfordii is the main formula for one of the TCM patents. The composition of this patent has the following raw materials as parts by weight: 3–15 parts of *Tripterygium wilfordii*, 10–50 parts of *Gypsum*, 8–24 parts of raw Chinese yam, 5–15 parts of Radix Scrophulariae, 4–12 parts of Fructus Forsythiae, 4–10 parts of *Periostracum cicada*, 4–12 parts of *Codonopsis pilosula*, 3–8 parts of mint, 3–10 parts of burdock and 4–20 parts of raw ochre. This patent was claimed suitable for the severe stage of COVID-19 pneumonia diseases, regulating immunity and decreasing the fever. The administration rate of the prescription (3–5 times) can decrease body temperature to the normal range. *Tripterygium wilfordii* relates to Chinese herbal medicine, and used in traditional medicine for

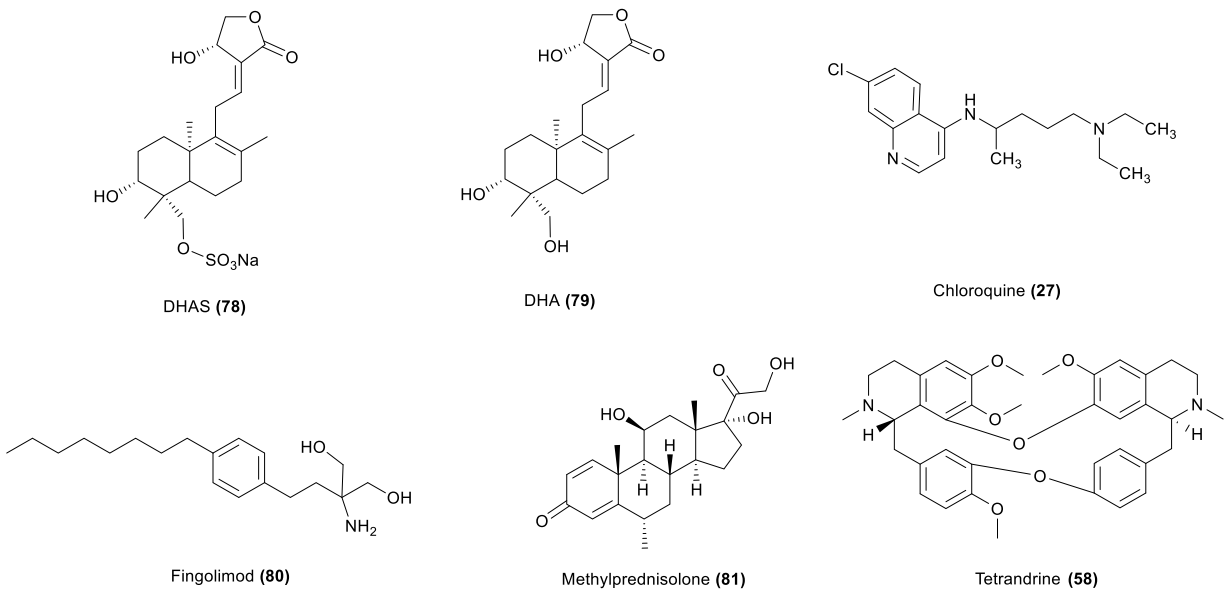

Fig. 7. Structures of isolated compounds and their derivatives from natural products sources in clinical trial studies against COVID-19.

Table. 3
List of ongoing clinical trials of natural products-based drugs targeting (COVID-19).

Compounds	Natural products origin	Clinical trials/phase/ Type of the study/ No of participants	Dose/ administration route/ Mechanism of action	ReferencesClinicalTrials.govIdentifier
(9-Dehydro-17-hydro-andrographolide (DHA) **(78)** and sodium 9-dehydro-17-hydro-andrographolide-19-yl sulfate (DHAS) (ND), *Xiyanping* products **(79)**	*Andrographis paniculata*, plant	2019 Novel Coronavirus Pneumonia/ Observational/ 426 P	10–20 ml daily of *Xiyanping* plus lopinavir tablet or ritonavir tablet plus α-interferon nebulization, For 14 days/ injection	(https://clinicaltrials.gov, NCT04275388)
Chloroquine (S*), alkaloid **(27)**	*Cinchona* spp., Plant	COVID19, Coronavirus, Acute Respiratory Illnesses/ Interventional/ 40,000 P	10 mg/kg followed by155 mg daily (250 mg chloroquine phosphate salt or 200 mg of or hydroxychloroquine sulphate)/ for 3 m	(https://clinicaltrials.gov, NCT04303507)
		SARS-CoV, Severe Acute Respiratory Syndrome (SARS) Pneumonia/ Phase 2/ Interventional / 440 P	150 mg/ twice daily/ 10 days	(https://clinicaltrials.gov, NCT04323527)
Fingolimod (ND), Alkaloid **(80)**	*Isaria sinclairii*, Fungus	Coronavirus Disease (COVID-19)/ Phase 2/ Interventional/ 30 P	0.5 mg/ once daily, for three consecutive days/ oral / effective agent against COVID-19 *via* an immunology modulation of phingosine-1-phosphate receptors	(https://clinicaltrials.gov, NCT04280588)
Methylprednisolone (ND), Steroid **(81)**	*Corynebacterium simplex*, Bacteria	COVID-19, Novel Coronavirus Pneumonia/ Interventional/ 86 P	1 mg/kg/ day/ for 7 days/ intravenous	(https://clinicaltrials.gov, NCT04273321)
		COVID-19 Infections/ Phase 2/ Interventional/ 80 P	40 mg/ 12 h for 5 days	(https://clinicaltrials.gov, NCT04244591)
Tetrandrine (N), alkaloid **(58)**	*Stephania tetrandra*, Plant	Corona Virus Disease 2019, COVID-19/ Phase 4/ Interventional/ 60 P	60 mg QD for 1week	(https://clinicaltrials.gov, NCT04308317)
Tocilizumab (B), Protein **(82)**	Interleukin-6 (IL-6) receptor antibody, Biological source	Covid-19/ Observational/ 120 P	8 mg/kg / once in 100 ml 0.9% saline solution and administered intravenously within no less than 60 min/ Blocking the inflammatory molecule interleukin-6, decreased systemic inflammation, improved survival rate, better hemodynamic and improved of respiratory distress	(https://clinicaltrials.gov, NCT04306705)

promoting blood circulation, killing parasites, regulating immunity, and has a good medicinal effect when utilized in treating 2019 new coronavirus pneumonia. This patent was documented in patent office CN with publication number (CN111184805A) (Lei and Yang, 2020).

One more patent that also relates to TCM, is possessing a formula for treating or preventing both novel coronavirus pneumonia and viral influenza. This formula combines raw materials, parts by weight, as a following: 15–45 parts of prepared aconite, 10–30 parts of dried ginger, 30–60 parts of honey-fried licorice root, 15–30 parts of American ginseng, 10–30 parts of *Ephedra*, 15–30 parts of *Cassia* twig, 5–10 parts of *Asarum*, 10–70 parts of honeysuckle flower, 10–30 parts of Fructus Forsythiae, 10–30 parts of *Isatis* root, 10–30 parts of reed rhizome, 15–30 parts of Folium Isatidis, 20–240 parts of *Gypsum*, 10–30 parts of lalang grass rhizome, 10–15 parts of Rhizoma Paridis, 5–15 parts of wrinkled *Gianthyssop* herb, 5–10 parts of *Eupatorium*, 5–10 parts of safflower, 5–15 parts of Cortex Moutan, 5–15 parts of *Rheum officinale*, 15–45 parts of ginger, 10–30 parts of Chinese date and 5–9 parts of musk. This patent has a corollary effect on ventilating lungs and improving human immunity. It was used for coronavirus, influenza, and pneumonia prevention or treatment. The findings showed that 24

Table. 4
List of patents on the treatment of COVID-19 by using Traditional Chinese Medicine.

Inventor	Ingredients (parts by weight)/ Patent form	Title/ Publication number/ Patent office	Type of virus/ Effective rate or (cure rate)/ Mode of action	References
Chinese name: 葛又文 English name: Ge Youwen	9 parts of ephedra, 6 parts of honey-fried licorice root, 9 parts of almond, 15–30 parts of *Gypsum*, 9 parts of *Cassia* Twig, 9 parts of Rhizoma Alismatis, 9 parts of *Grifola*, 9 parts of bighead *Atractylodes* rhizome, 15 parts of *Poria cocos*, 16 parts of Radix Bupleuri, 6 parts of *Scutellaria baicalensis*, 9 parts of ginger processed Pinellia tuber, 9 parts of ginger, 9 parts of aster, 9 parts of Flos Farae, 9 parts of blackberry lily, 6 parts of *Asarum*, 12 parts of Chinese yam, 6 parts of immature bitter orange, 6 parts of dried orange peel and 9 parts of wrinkled *Gianthyssop* herb/ **Decoction**	Prescription for treating pneumonia caused by novel coronavirus infection and application thereof / (CN110870402A)/ CN	SARS-CoV-2/ 95.12%/ Treating pneumonia	Ge, 2020
Chinese name: 张宁 and 杨海军 English name: Zhang Ning and Yang Haijun	40 parts of Folium Isatidis, 40 parts of the wild *Chrysanthemum* flower, 20 parts of *Coptis chinensis*, 30 parts of sweetsop seed, 20 parts of wrinkled *Gianthyssop* herb, 20 parts of Rhizoma Atractylodis, 20 parts of Radix Bupleuri, 2 parts of Calculus Bovis Factitius, 20 parts of *Houttuynia cordata*, 5 parts of dandelion root, 30 parts of honeysuckle, 30 parts of Fructus Forsythiae, 20 parts of *Scutellaria baicalensis*, 20 parts of blackberry lily, 15 parts of *Salvia miltiorrhiza*, 15 parts of Bulbus Fritillariae Cirrhosae, 10 parts of *Saussurea involucrate*, 60 parts of *Astragalus mongholicus*, 20 parts of *Cordyceps sinensis*, 20 parts of *Codonopsis*/ **Tablet, capsule, granule, pill or oral liquid.**	Traditional Chinese medicine composition with function of resisting novel coronavirus SARS-CoV-2 and preparation method and application thereof/ (CN111150792A)/ CN	SARS-CoV-2/ Not reported/ Improve the pneumonia symptom	Zhang and Yang, 2020
Chinese name: 雷鸣 and 养立 English name: Lei Ming and Yang Li	33–15 parts of *Tripterygium wilfordii*, 10–50 parts of *Gypsum*, 8–24 parts of raw Chinese yam, 5–15 parts of Radix Scrophulariae, 4–12 parts of Fructus Forsythiae, 4–10 parts of Periostracum Cicada, 4–12 parts of *Codonopsis pilosula*, 3–8 parts of mint, 3–10 parts of burdock and 4–20 parts of raw ochre/ **Not reported**	Traditional Chinese medicine composition and application thereof/ (CN111184805A)/ CN	SARS-CoV-2/ Not reported/ Regulating immunity and utilized to treating SARS-CoV-2	Lei and Yang, 2020
Chinese name: 吴通武, 梁力, 张堂江 and 梁洪海 English name: Wu Tongwu, Liang Li, Zhang Tangjiang and Liang Honghai	15–45 parts of prepared aconite, 10–30 parts of dried ginger, 30–60 parts of honey-fried licorice root, 15–30 parts of American ginseng, 10–30 parts of *Ephedra*, 15–30 parts of *Cassia* twig, 5–10 parts of *Asarum*, 10–70 parts of honeysuckle flower, 10–30 parts of Fructus Forsythiae, 10–30 parts of *Isatis* root, 10–30 parts of reed rhizome, 15–30 parts of Folium Isatidis, 20–240 parts of *Gypsum*, 10–30 parts of lalang grass rhizome, 10–15 parts of Rhizoma Paridis, 5–15 parts of wrinkled *Gianthyssop* herb, 5–10 parts of *Eupatorium*, 5–10 parts of safflower, 5–15 parts of Cortex Moutan, 5–15 parts of *Rheum officinale*, 15–45 parts of ginger, 10–30 parts of Chinese date and 5–9 parts of musk/ **Liquid**	Traditional Chinese medicine formula for treating or preventing novel coronavirus pneumonia and viral influenza/ (CN111110819A)/ CN	SARS-CoV-2/(80%)/ Improving human immunity and prevention or treatment of SARS-CoV-2	Wu et al., 2020
Chinese name: 潘耀宗, 王恒斌, 张丹丹, 张邦国, 李全, 罗年翠, 曹泽庆 and 翟云良 English name: Pan Yaozong, Wang Hengbin, Zhang Dandan, Zhang Bangguo, Li Quan, Luo Niancui, Cao Zeqing and Zhai Yunliang	40 parts of wrinkled *Gianthyssop* herb, 40 parts of wild *Chrysanthemum* flower, 24 parts of Chinese mosla herb and 40 parts of sweet wormwood herb/ **Tablets, capsules, pills, oral liquid, or mixtures.**	Chinese medicine composition for preventing and treating viral diseases and application thereof/ (CN111150755A)/ CN	SARS-CoV-2/Not reported/ Inhibiting cytokine expression *i.e.* TNF- α and IL-6 produced by SARS-CoV-2	Pan et al., 2020a
Chinese name: 王学昌, 张董喆 and 程少丹 English name: Wang xuechang, Zhang Dongzhe and Cheng Shaodan	50–80 parts of clove, 20–30 parts of Cacumen Biotae and 15–20 parts of *Angelica dahurica*; 10–15 parts of honeysuckle; 10–15 parts of *Agastache rugosus*, 10–15 parts of *Eupatorium fortunei*, 10–15 parts of *Cassia* twig, 10–15 parts of camphor, 10–15 parts of *Saposhnikovia divaricate* root, 10–15 parts of	Sachet for efficiently preventing novel coronavirus pneumonia and influenza/ (CN111214689A)/ CN	SARS-CoV-2/ Not reported/ Preventing novel coronavirus pneumonia and preventing and treating respiratory diseases	Wang et al., 2020a

(*continued on next page*)

Table. 4 (*continued*)

Inventor	Ingredients (parts by weight)/ Patent form	Title/ Publication number/ Patent office	Type of virus/ Effective rate or (cure rate)/ Mode of action	References
	isatis root, 10–15 parts of folium *Artemisiae argyi* and 10–15 parts of borneol/ **Capsule**			
Chinese name: 张涛涛, 何莉华 and 彭严 English name: Zhang Taotao, He Lihua and Peng Yan	3–18 parts of *Ephedra*, 2–10 parts of liquorice, 3–18 parts of almond, 5–45 parts of *Gypsum* (decocted first), 3–18 parts of *Cassia* twig, 3–18 parts of Rhizoma Alismatis, 3–18 parts of *Grifola*, 3–18 parts of bighead *Atractylodes* rhizome, 5–25 parts of *Poria cocos*, 6–26 parts of Radix Bupleuri, 2–10 parts of *Scutellaria baicalensis*, 3–18 parts of ginger *Pinellia ternata*, 3–18 parts of ginger, 3–18 parts of aster, 3–18 parts of Flos Farfarae, 3–18 parts of blackberry lily, 2–10 parts of *Asarum*, 6–18 parts of Chinese yam, 2–10 parts of immature bitter orange, 2–10 parts of dried orange peel, 2–10 parts of Rhizoma Atractylodis, and the like, 3–18 parts of *Agastache rugosus*/ **Tablets, powder, soft capsules, syrup, pills and granules.**	Traditional Chinese medicine composition and preparation method and pharmaceutical application thereof/ (CN111214637A)/ CN	SARS-CoV-2/ Not reported/ Treating or preventing the new coronavirus 2019-nCoV	Zhang et al., 2020
Chinese name: 奚肇庆, 束雅春, 刘志辉, 马朝群, 汪悦, 史锁芳, 乔飞, 吴磊 and 吴旭彤 English name: Xi Zhaoqing, Shu Yachun, Liu Zhihui, Ma Chaoqun, Wang Yue, Shi Suofang, Qiao Fei, Wu Lei and Wu Xutong	6–30 parts of *Astragalus membranaceus*, 6–30 parts of *Codonopsis pilosula*, 5–18 parts of bran-fried bighead *Atractylodes* rhizome, 6–15 parts of *Poria cocos*, 3–30 parts of *Perilla* leaf, 3–15 parts of *Saposhnikovia divaricata* root, 3–20 parts of dried orange peel, 2–15 parts of Chinese date and 2–9 parts of liquorice/ **Extract, granules, capsules or pills**	Epidemic prevention traditional Chinese medicine composition and preparation method and application thereof/ (CN111214566A)/ CN	SARS-CoV-2/ Not reported/ Prevent the infection of the new coronavirus SARS-CoV-2	Xi et al., 2020
Chinese name: 杨汉梅, 陈彩虹,陈天跃 and 杨仪鎏 English name: Yang Hanmei, Chen Caihong, Chen Tianyue and Yang Yiliao	8–12 parts of *semiliquidambar cathayensis*, 8–12 parts of *cinnamomum camphora* root, 8–12 parts of citronella, 8–12 parts of *Sculellaria barbata*, 8–12 parts of giant knotweed rhizome, 8–12 parts of honeysuckle stem, 8–12 parts of weeping forsythia, 8–12 parts of dandelion, 8–12 parts of radix bupleuri, 8–12 parts of *Cnanchum glaucescens*, 8–12 parts of bitter apricot kernel, 8–12 parts of aster, 8–12 parts of reed rhizome and 8–12 parts of euphorbia lathyrism/ **Pills**	Fumigation bath preparation for preventing and treating pestilence, and its application method and application/ (CN111184823A)/ CN	SARS-CoV-2/ 90% (80%)/ Improve human immunity and has prevention and treatment effects on new coronavirus pneumonia	Yang et al., 2020a
Chinese name: 陈文才 English name: Chen Wencai	20–100 g of *Laggera pterodonta*, 10–50 g of honeysuckle, 10–30 g of dried ginger, 10–40 g of divaricate saposhnikovia root, 10–50 g of *Officinal magnolia* bark and 10–60 g of pilose asiabell root/ **liquid**	Laggera pterodonta composition for treating new COVID-19 and application thereof/ (CN111166862A)/ CN	SARS-CoV-2/ Not reported/ Preventing and treating infectious plague and common respiratory diseases, resisting virus and enhancing immunity	Chen, 2020

patients out of 30 were cured and that this formula was helpful in treating the new coronavirus pneumonia effectively. The cure rate was estimated to 80%. This patent was documented in patent office CN with publication number (CN111110819A) (Wu et al., 2020).

Another formula was studied *in vitro* against common coronavirus and new coronavirus. The formula composed of the following raw materials, as parts by weight: 40 parts of wrinkled *Gianthyssop* herb, 40 parts of wild *Chrysanthemum* flower, 24 parts of Chinese mosla herb and 40 parts of sweet wormwood herb. This formula has a potent effect on inhibiting cytokine expression *i.e.* TNF- α and IL-6 produced by SARS-Cov-2. The formula was used earlier as a therapeutic agent against pneumonia, nephritis, hepatitis. It has very good prospects for clinical application and thus it was approved from CN patent office under publication number (CN111150755A) (Pan et al., 2020a).

The protective role of plants and their constituents against COVID-19

The consumption of healthy diets is one way to boost the immune system and in return help in fighting off viruses (Galanakis, 2020). There is a wide range of plants that contribute to boosting the immune system given their high content of a wide variety of nutrients and biological active compounds (Sultan et al., 2014). A strong immune system is essential for fighting against COVID-19. COVID-19 seems to be hazardous for people with comorbidities and those have a weaker immune system than healthy ones (Chen et al., 2020b; Jiang et al., 2020). Garlic stimulates the immune system as it is rich with a wide plethora of nutrients, vitamins, and sulfur-containing compounds (Iciek et al., 2009). Certain vegetables such as broccoli, spinach and sweet potatoes are abundant with vitamin A which include retinol, retinoic acid and β-carotene. These fat-soluble compounds participate in enhancement of the immune function. Additionally, isotretinoin (vitamin A derivative), inhibits ACE2 and the entry of SARS-COV-2 into the body thereby lower the susceptibility to infections (Galanakis, 2020). Citrus fruits are one of the best sources for vitamin C. Vitamin C increases the production of white blood cells providing a key role in fighting infections (Calder et al., 2020). Vitamins are recommended for the protection against coronavirus as they increase patients' resistance against infection (Basiri, 2020).

Conclusions

The outbreak of COVID-19 has swept across the world rapidly spreading in a very alarming pace invading more than 200 countries, territories, areas leaving a trail of victims behind. Although SARS-CoV-2 is accompanied by symptoms similar to that of SARS-CoV-2 *i.e.* fever, cough, and fatigue, SARS-CoV-2 is far more contagious. It can be

transmitted by droplets or close contact. Given the affinity by which SARS-CoV-2 protein S can bind to ACE2 receptors, human to human transmission seems to spread much faster than the common flu or even the previous coronaviruses. Thus, containing the outbreak is a burning issue requires extensive measures and developing specific safe drugs. Natural products have so far proven to be promising for the development of effective and less toxic antiviral agents. Owing to the genetic resemblance between coronaviruses, the drugs and antiviral agents which are usually effective against the other types of coronaviruses could be used to treat COVID-19. Some of the reported antivirals showed a promising antiviral activity against at least four types of human coronaviruses with significant EC_{50} and CC_{50} values. Other therapeutic agents have also been reported and are already moving into clinical trials including *Xiyanping*, fingolimod, methylprednisolone, streptokinase, and heparin.

Funding

This work was supported by the Swedish Research Council Vetenskapsrådet (grants 2015-05468 and 2016-05885)

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

H. R. El-Seedi is very grateful to the Swedish Research links grant 2016–05885 (VR for the years 2017 - 2019) and the Department of Molecular Biosciences, Wenner-Grens Institute, Stockholm University, Sweden for the financial support.

References

Alonso-Caplen, F.V, Matsuoka, Y., Wilcox, G.E., Compans, R.W., 1984. Replication and morphogenesis of avian coronavirus in Vero cells and their inhibition by monensin. Virus Res. 1, 153–167.

Anderson, H.C., Kunkel, H.G., McCarty, M., 1948. Quantitative antistreptokinase studies in patients infected with group A hemolytic streptococci: a comparison with serum antistreptolysin and gamma globulin levels with special reference to the occurrence of rheumatic fever. J. Clin. Invest. 27, 425–434.

Assiri, A., Al-Tawfiq, J.A., Al-Rabeeah, A.A., Al-Rabiah, F.A., Al-Hajjar, S., Al-Barrak, A., Flemban, H., Al-Nassir, W.N., Balkhy, H.H., Al-Hakeem, R.F., Makhdoom, H.Q., Zumla, A.I., Memish, Z.A., 2013. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect. Dis. 13, 752–761.

Bai, Y., Yao, L., Wei, T., Tian, F., Jin, D.-Y., Chen, L., Wang, M., 2020. Presumed asymptomatic carrier transmission of COVID-19. JAMAJAMA 323, 1406–1407.

Basiri, M.R., 2020. Theory about Treatments and Morbidity Prevention of Corona Virus Disease (Covid-19). J. Pharm. Pharmacol. 8, 89–90.

Bassetti, M., Vena, A., Giacobbe, D.R., 2020. The Novel Chinese Coronavirus (2019-nCoV) Infections: challenges for fighting the storm. Eur. J. Clin. Invest. 50, e13209.

Bhagya, N., Chandrashekar, K.R., 2016. Tetrandrine–A molecule of wide bioactivity. PhytochemistryPhytochemistry 125, 5–13.

Bitnun, A., Allen, U., Heurter, H., King, S.M., Opavsky, M.A., Ford-Jones, E.L., Matlow, A., Kitai, I., Tellier, R., Richardson, S., Manson, D., Babyn, P., Read, S., 2003. Children hospitalized with severe acute respiratory syndrome-related illness in Toronto. PediatricsPediatrics 112, e261.

Bittencourt, V.R.E.P., Mascarenhas, A.G., de Menezes, G.C.R., Monteiro, S.G., 2000. *In vitro* action of Metarhizium anisopliae (Metschnikoff, 1879) Sorokin, 1883 and Beauveria bassiana (Balsamo) Vuillemin, 1912 on eggs of the tick Anocentor nitens (Neummann, 1897)(Acari: ixodidae). Rev. Bras. Med. Veterinária 22, 248–251.

Calder, P.C., Carr, A.C., Gombart, A.F., Eggersdorfer, M., 2020. Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections. Nutrients 12, 1181.

Chan-Yeung, M., Xu, R.H., 2003. SARS: epidemiology. Respirology 8, S9–S14.

Chan, J.F.-W., Yuan, S., Kok, K.-H., To, K.K.-W., Chu, H., Yang, J., Xing, F., Liu, J., Yip, C. C.-Y., Poon, R.W.-S., Chan, W.-M., Daniel, J., Cai, J.-P., Cheng, V.C.-C., Chen, H., Hui, C.K.-M., Yuen, K.-Y., 2020. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 395, 514–523.

Chan, P.K.S., Chan, M.C.W., 2013. Tracing the SARS-coronavirus. J. Thorac. Dis. 5, S118–S121.

Chen, C.-J., Michaelis, M., Hsu, H.-K., Tsai, C.-C., Yang, K.D., Wu, Y.-C., Cinatl, J., Doerr, H.W., 2008. Toona sinensis Roem tender leaf extract inhibits SARS coronavirus replication. J. Ethnopharmacol. 120, 108–111. https://doi.org/10.1016/j.jep.2008.07.048.

Chen, F., Chan, K.H., Jiang, Y., Kao, R.Y.T., Lu, H.T., Fan, K.W., Cheng, V.C.C., Tsui, W. H.W., Hung, I.F.N., Lee, T.S.W., Guan, Y., Peiris, J.S, Yuen, K, 2004. *In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J. Clin. Virol. 31, 69–75.

Chen, H., Guo, J., Wang, C., Luo, F., Yu, X., Zhang, W., Li, J., Zhao, D., Xu, D., Gong, Q., Liao, J., Yang, H., Hou, W., Zhang, Y., 2020a. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 395, 809–815.

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., Zhang, L., 2020b. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395, 507–513. https://doi.org/10.1016/S0140-6736(20)30211-7.

Chen, W., 2020. Laggera pterodonta composition for treating covid-19 and application thereof. CN111166862A.

Cheng, P.-W., Ng, L.-T., Chiang, L.-C., Lin, C.-C., 2006. Antiviral effects of saikosaponins on human coronavirus 229E *in vitro*. Clin. Exp. Pharmacol. Physiol. 33, 612–616. https://doi.org/10.1111/j.1440-1681.2006.04415.x.

Cheng, Y., 2006. Deciphering the biosynthetic codes for the potent anti-SARS-CoV cyclodepsipeptide valinomycin in Streptomyces tsusimaensis ATCC 15141. ChemBioChem 7, 471–477.

Chhikara, B.S., Rathi, B., Singh, J., Poonam, F.N.U., 2020. Corona virus SARS-CoV-2 disease COVID-19: infection, prevention and clinical advances of the prospective chemical drug therapeutics. Chem. Biol. Lett. 7, 63–72.

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. Bioorg. Med. Chem. 21, 3051–3057.

Chong, L., Chen, W., Luo, Y., Jiang, Z., 2013. Simultaneous determination of 9-dehydro‐17-hydro-andrographolide and sodium 9-dehydro-17-hydro-andrographolide-19-yl sulfate in rat plasma by UHPLC-ESI-MS/MS after administration of xiyanping injection: application to a pharmacokinetic study. Biomed. Chromatogr. 27, 825–830.

Cinatl, J., Morgenstern, B., Bauer, G., Chandra, P., Rabenau, H., Doerr, H.W., 2003. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 361, 2045–2046.

Coleman, C.M., Frieman, M.B., 2013. Emergence of the Middle East respiratory syndrome coronavirus. PLoS Pathog 9, e1003595.

Corman, V.M., Muth, D., Niemeyer, D., Drosten, C., 2018. Hosts and Sources of Endemic Human Coronaviruses. Adv. Virus Res. 100, 163–188.

Cortegiani, A., Ingoglia, G., Ippolito, M., Giarratano, A., Einav, S., 2020. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J. Crit. Care 57, 279–283.

Cron, R.Q., Chatham, W.W., 2020. The Rheumatologist's Role in Covid-19. J. Rheumatol. 47, 639–642.

Damle, M., 2014. Glycyrrhiza glabra (Liquorice)-a potent medicinal herb. Int. J. Herb. Med 2, 132–136.

Day, M., 2020. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ 368, m1086.

Deng, J., Jin, Yipeng, Liu, Y., Sun, J., Hao, L., Bai, J., Huang, T., Lin, D., Jin, Yaping, Tian, K., 2020. Serological survey of SARS-CoV-2 for experimental, domestic, companion and wild animals excludes intermediate hosts of 35 different species of animals. Transbound. Emerg. Dis. 67, 1745–1749.

Deng, Y.F., Aluko, R.E., Jin, Q., Zhang, Y., Yuan, L.J., 2012. Inhibitory activities of baicalin against renin and angiotensin-converting enzyme. Pharm. Biol. 50, 401–406.

Donia, M., Hamann, M.T., 2003. Marine natural products and their potential applications as anti-infective agents. Lancet Infect. Dis. 3, 338–348.

Driggin, E., Madhavan, M.V, Bikdeli, B., Chuich, T., Laracy, J., Bondi-Zoccai, G., Brown, T.S., Der Nigoghossian, C, Zidar, D.A, Haythe, J, Brodie, D, Beckman, J.A, Kirtane, A.J, Stone, G.W, Krumholz, H.M, Parikh, S.A, 2020. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. J. Am. Coll. Cardiol. 75, 2352–2371.

Dua, V.K., Verma, G., Singh, B., Rajan, A., Bagai, U., Agarwal, D.D., Gupta, N.C., Kumar, S., Rastogi, A., 2013. Anti-malarial property of steroidal alkaloid conessine isolated from the bark of Holarrhena antidysenterica. Malar. J. 12, 194.

Dyall, J., Gross, R., Kindrachuk, J., Johnson, R.F., Olinger, G.G., Hensley, L.E., Frieman, M.B., Jahrling, P.B., 2017. Middle East respiratory syndrome and severe acute respiratory syndrome: current therapeutic options and potential targets for novel therapies. DrugsDrugs 77, 1935–1966. https://doi.org/10.1007/s40265-017-0830-1.

El-Seedi, H.R., Khalifa, S.A.M., Yosri, N., Khatib, A., Chen, L., Saeed, A., Efferth, T., Verpoorte, R., 2019. Plants mentioned in the Islamic Scriptures (Holy Qur'ân and Ahadith): traditional uses and medicinal importance in contemporary times. J. Ethnopharmacol. 243, 112007.

Elfiky, A.A., Mahdy, S.M., Elshemey, W.M., 2017. Quantitative structure-activity relationship and molecular docking revealed a potency of anti-hepatitis C virus drugs against human corona viruses. J. Med. Virol. 89, 1040–1047.

Feinberg, S.M., Feinberg, A.R., Pruzansky, J., Fisherman, E.W., 1957. Methylprednisolone (medrol), a potent new anti-inflammatory steroid: therapeutic results in allergic diseases. J. Am. Med. Assoc. 165, 1560–1562.

Fielding, B.C., 2011. Human coronavirus NL63: a clinically important virus? Future Microbiol 6, 153–159.

Fowler, R.A., Lapinsky, S.E., Hallett, D., Detsky, A.S., Sibbald, W.J., Slutsky, A.S., Stewart, T.E., 2003. Critically ill patients with severe acute respiratory syndrome. JAMAJAMA 290, 367–373.

Galanakis, C.M., 2020. The Food Systems in the Era of the Coronavirus (COVID-19) Pandemic Crisis. Foods 9, 523.
Gao, H., Yao, H., Yang, S., Li, L., 2016. From SARS to MERS: evidence and speculation. Front. Med. 10, 377–382.
Ge, Y., 2020. Prescription for treating pneumonia caused by novel coronavirus infection and application thereof. CN110870402A.
Geleris, J., Sun, Y., Platt, J., Zucker, J., Baldwin, M., Hripcsak, G., Labella, A., Manson, D. K., Kubin, C., Barr, R.G., Sobieszczyk, M.E., Schluger, N.W., 2020. observational study of hydroxychloroquine in hospitalized patients with Covid-19. N. Engl. J. Med. 382, 2411–2418. https://doi.org/10.1056/NEJMoa2012410.
Govindachari, T.R., Viswanathan, N., Radhakrishnan, J., Pai, B.R., Natarajan, S., Subramaniam, P.S., 1973. Minor alkaloids of Tylophora asthmatica: revised structure of tylophorinidine. TetrahedronTetrahedron 29, 891–897.
Hall, E.D., 1992. The neuroprotective pharmacology of methylprednisolone. J. Neurosurg. 76, 13–22.
Hart, B.J., Dyall, J., Postnikova, E., Zhou, H., Kindrachuk, J., Johnson, R.F., Olinger, G. G., Frieman, M.B., Holbrook, M.R., Jahrling, P.B., Hensley, L., 2014. Interferon-B and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays. J. Gen. Virol. 95, 571–577. https://doi.org/10.1099/vir.0.061911-0.
He, F., Deng, Y., Li, W., 2020. Coronavirus Disease 2019 (COVID-19): what we know? J. Med. Virol 92, 719–725.
He, Y., Zhou, Y., Liu, S., Kou, Z., Li, W., Farzan, M., Jiang, S., 2004. Receptor-binding domain of SARS-CoV spike protein induces highly potent neutralizing antibodies: implication for developing subunit vaccine. Biochem. Biophys. Res. Commun. 324, 773–781.
Hilgenfeld, R., Peiris, M., 2013. From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses. Antiviral Res 100, 286–295.
Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., Cao, B., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497–506.
Ibrahim, I.M., Abdelmalek, D.H., Elshahat, M.E., Elfiky, A.A., 2020. COVID-19 Spike-host cell receptor GRP78 binding site prediction. J. Infect 80, 554–562.
Iciek, M., Kwiecień, I., Włodek, L., 2009. Biological properties of garlic and garlic-derived organosulfur compounds. Environ. Mol. Mutagen. 50, 247–265. https://doi.org/10.1002/em.20474.
Ingwersen, J., Aktas, O., Kuery, P., Kieseier, B., Boyko, A., Hartung, H.-P., 2012. Fingolimod in multiple sclerosis: mechanisms of action and clinical efficacy. Clin. Immunol. 142, 15–24.
Islam, M.T., Sarkar, C., El-Kersh, D.M., Jamaddar, S., Uddin, S.J., Shilpi, J.A., Mubarak, M.S., 2020. Natural products and their derivatives against coronavirus: a review of the non-clinical and pre-clinical data. Phyther. Res. n/a. https://doi.org/10.1002/ptr.6700.
Jarvill-Taylor, K.J., Anderson, R.A., Graves, D.J., 2001. A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. J. Am. Coll. Nutr. 20, 327–336.
Ji, W., Wang, W., Zhao, X., Zai, J., Li, X., 2020. Homologous recombination within the spike glycoprotein of the newly identified coronavirus may boost cross-species transmission from snake to human. J. Med. Virol.
Jiang, F., Deng, L., Zhang, L., Cai, Y., Cheung, C.W., Xia, Z., 2020. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). J. Gen. Intern. Med. 35, 1545–1549. https://doi.org/10.1007/s11606-020-05762-w.
Kahn, J.S., McIntosh, K., 2005. History and recent advances in coronavirus discovery. Pediatr. Infect. Dis. J. 24, S223–S227.
Kakumu, A., Ninomiya, M., Efdi, M., Adfa, M., Hayashi, M., Tanaka, K., Koketsu, M., 2014. Phytochemical analysis and antileukemic activity of polyphenolic constituents of Toona sinensis. Bioorg. Med. Chem. Lett. 24, 4286–4290.
Kam, K.-Q., Yung, C.F., Cui, L., Lin Tzer Pin, R, Mak, T.M, Maiwald, M, Li, J, Chong, C.Y, Nadua, K, Tan, N.W.H, Thoon, K.C, 2020. A well infant with coronavirus disease 2019 (COVID-19) with high viral load. Clin. Infect. Dis. 71, 847–849.
Keyaerts, E., Li, S., Vijgen, L., Rysman, E., Verbeeck, J., Van Ranst, M., Maes, P., 2009. Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. Antimicrob. Agents Chemother. 53, 3416–3421.
Khalifa, S.A.M., Mohamed, B.S., Elashal, M.H., Du, M., Guo, Z., Zhao, C., Musharraf, S.G., Boskabady, M.H., El-Seedi, H.H.R., Efferth, T., El-Seedi, H.R., 2020. Comprehensive Overview on Multiple Strategies Fighting COVID-19. Int. J. Environ. Res. Public Health 17, 5813.
Kim, D.E., Min, J.S., Jang, M.S., Lee, J.Y., Shin, Y.S., Park, C.M., Song, J.H., Kim, H.R., Kim, S., Jin, Y.-H., Kwon, S., 2019. Natural Bis-Benzylisoquinoline Alkaloids-Tetrandrine, Fangchinoline, and Cepharanthine, Inhibit Human Coronavirus OC43 Infection of MRC-5 Human Lung Cells. Biomolecules 9, 696.
Koehn, F.E., Sarath, G.P., Neil, D.N., Cross, S.S., 1991. Halitunal, an unusual diterpene aldehyde from the marine alga Halimeda tuna. Tetrahedron Lett. 32, 169–172.
Kumaki, Y., Wandersee, M.K., Smith, A.J., Zhou, Y., Simmons, G., Nelson, N.M., Bailey, K.W., Vest, Z.G., Li, J.K.-K., Chan, P.K.-S., Smee, D.F., Barnard, D.L., 2011. Inhibition of severe acute respiratory syndrome coronavirus replication in a lethal SARS-CoV BALB/c mouse model by stinging nettle lectin, Urtica dioica agglutinin. Antiviral Res. 90, 22–32. https://doi.org/10.1016/j.antiviral.2011.02.003.
Kumar, V., Jung, Y.-S., Liang, P.-H., 2013. Anti-SARS coronavirus agents: a patent review (2008–present). Expert Opin. Ther. Pat. 23, 1337–1348.
Labanca, F., Ovesna, J., Milella, L., 2018. Papaver somniferum L. taxonomy, uses and new insight in poppy alkaloid pathways. Phytochem. Rev 17, 853–871.
Lau, S.K.P., Woo, P.C.Y., Yip, C.C.Y., Tse, H., Tsoi, H., Cheng, V.C.C., Lee, P., Tang, B.S.F., Cheung, C.H.Y., Lee, R.A., So, L., Lau, Y., Chan, K., Yuen, K., 2006. Coronavirus HKU1 and other coronavirus infections in Hong Kong. J. Clin. Microbiol. 44, 2063–2071.
Lei, M., Yang, L., 2020. Traditional Chinese medicine composition and application thereof. CN111184805A.
Lei, J., Li, J., Li, X., Qi, X., 2020. CT imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia. RadiologyRadiology 295, 18.
Lessler, J., Reich, N.G., Brookmeyer, R., Perl, T.M., Nelson, K.E., Cummings, D.A.T., 2009. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect. Dis. 9, 291–300.
Leung, C.C., Lam, T.H., Cheng, K.K., 2020. Mass masking in the COVID-19 epidemic: people need guidance. Lancet 395, 945.
Li, J., Yan, Y., Sun, H., Liu, Y., Su, C., Chen, H., Zhang, J., 2019. Anti-Cancer Effects of Pristimerin and the Mechanisms: a Critical Review. Front. Pharmacol. 10, 746.
Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., Ren, R., Leung, K.S.M., Lau, E.H.Y., Wong, J.Y., et al., 2020a. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N. Engl. J. Med. 382, 1199–1207.
Li, S., Chen, C., Zhang, H., Guo, H., Wang, H., Wang, L., Zhang, X., Hua, S., Yu, J., Xiao, P., Li, R., Tan, X., 2005. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antiviral Res. 67, 18–23.
Li, W., Moore, M.J., Vasilieva, N., Sui, J., Wong, S.K., Berne, M.A., Somasundaran, M., Sullivan, J.L., Luzuriaga, K., Greenough, T.C., Choe, H., Farzan, M., 2003. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. NatureNature 426, 450–454.
Li, Z., Wu, M., Guo, J., Yao, J., Liao, X., Song, S., Han, M., Li, J., Duan, G., Zhou, Yuanxiu, Wu, X., Zhou, Z., Wang, T., Hu, M., Chen, X., Fu, Y., Lei, C., Dong, H., Zhou, Y, Jia, H., Chen, X., Yan, J., 2020b. Caution on kidney dysfunctions of 2019-nCoV patients. MedRxiv.
Liang, Y., Hu, J., Chen, H., Zhang, T., Ito, Y., 2007. Preparative isolation and purification of four compounds from Chinese medicinal herb Gentiana scabra Bunge by high-speed countercurrent chromatography. J. Liq. Chromatogr. Relat. Technol. 30, 509–520.
Lin, C.-W., Tsai, F.-J., Tsai, C.-H., Lai, C.-C., Wan, L., Ho, T.-Y., Hsieh, C.-C., Chao, P.-D. L., 2005. Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antiviral Res. 68, 36–42.
Lin, L.-T., Hsu, W.-C., Lin, C.-C., 2014. Antiviral natural products and herbal medicines. J. Tradit. Complement. Med. 4, 24–35.
Lin, L., Lu, L., Cao, W., Li, T., 2020. Hypothesis for potential pathogenesis of SARS-CoV-2 infection——a review of immune changes in patients with viral pneumonia. Emerg. Microbes Infect. 9, 727–732.
Lira, S.P.de, Seleghim, M.H.R., Williams, D.E., Marion, F., Hamill, P., Jean, F., Andersen, R.J., Hajdu, E., Berlinck, R.G.S., 2007. A SARS-coronovirus 3CL protease inhibitor isolated from the marine sponge Axinella *cf.* corrugata: structure elucidation and synthesis. J. Braz. Chem. Soc 18, 440–443.
Liu, Y., Li, Z., Liu, G., Jia, J., Li, S., Yu, C., 2008. Liquid chromatography–tandem mass spectrometry method for determination of N-acetylglucosamine concentration in human plasma. J. Chromatogr. B 862, 150–154. https://doi.org/10.1016/j.jchromb.2007.11.043.
Loizzo, M.R., Saab, A.M., Tundis, R., Statti, G.A., Menichini, F., Lampronti, I., Gambari, R., Cinatl, J., Doerr, H.W., 2008. Phytochemical analysis and *in vitro* antiviral activities of the essential oils of seven Lebanon species. Chem. Biodivers. 5, 461–470.
Łowicki, D., Huczyński, A., 2013. Structure and antimicrobial properties of monensin A and its derivatives: summary of the achievements. Biomed Res. Int 2013.
Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., et al., 2020. . Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395, 565–574.
Luo, H., Tang, Q., Shang, Y., Liang, S., Yang, M., Robinson, N., Liu, J., 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. Chin. J. Integr. Med 26, 243–250.
Maxmen, A., 2020. Slew of trials launch to test coronavirus treatments in China. NatureNature 578, 347–348.
McLean, J.A.Y., 1959. The discovery of heparin. CirculationCirculation 19, 75–78.
Meng, Z., Li, T., Ma, X., Wang, X., Van Ness, C., Gan, Y., Zhou, H., Tang, J., Lou, G., Wang, Y., Wu, J., Yen, Y., Xu, R., Huang, W., 2013. Berbamine inhibits the growth of liver cancer cells and cancer-initiating cells by targeting Ca2+/calmodulin-dependent protein kinase II. Mol. Cancer Ther. 12, 2067–2077.
Moloudizargari, M., Mikaili, P., Aghajanshakeri, S., Asghari, M.H., Shayegh, J., 2013. Pharmacological and therapeutic effects of Peganum harmala and its main alkaloids. Pharmacogn. Rev. 7, 199–212.
Newman, D.J., Cragg, G.M., 2020. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. J. Nat. Prod. 83, 770–803.
Ng, D.L., Al Hosani, F, Keating, M.K, Gerber, S.I, Jones, T.L, Metcalfe, M.G, Tong, S, Tao, Y, Alami, N.N, Haynes, L.M, Mutei, M.A, Abdel-Wareth, L, Uyeki, T.M, Swerdlow, D.L, Barakat, M, Zaki, S.R, 2016. Clinicopathologic, immunohistochemical, and ultrastructural findings of a fatal case of Middle East respiratory syndrome coronavirus infection in the United Arab Emirates, April 2014. Am. J. Pathol 186, 652–658.
Niemann, H., Boschek, B., Evans, D., Rosing, M., Tamura, T., Klenk, H.D., 1982. Post-translational glycosylation of coronavirus glycoprotein E1: inhibition by monensin. EMBO J 1, 1499–1504.
Oh, M.H., Houghton, P.J., Whang, W.K., Cho, J.H., 2004. Screening of Korean herbal medicines used to improve cognitive function for anti-cholinesterase activity. Phytomedicine 11, 544–548.

Oliveira, A.B., Dolabela, M.F., Braga, F.C., Jácome, R.L.R.P., Varotti, F.P., Póvoa, M.M., 2009. Plant-derived antimalarial agents: new leads and efficient phythomedicines. Part I. Alkaloids. An. Acad. Bras. Cienc. 81, 715–740.
Orlikova, B., Tasdemir, D., Golais, F., Dicato, M., Diederich, M., 2011. The aromatic ketone 4'-hydroxychalcone inhibits TNFalpha-induced NF-kappaB activation via proteasome inhibition. Biochem. Pharmacol. 82, 620–631. https://doi.org/10.1016/j.bcp.2011.06.012.
Ou, X., Liu, Y., Lei, X., Li, P., Mi, D., Ren, L., Guo, L., Guo, R., Chen, T., Hu, J., Xiang, Z., Mu, Z., Chen, X., Chen, J., Hu, K., Jin, Q., Wang, J., Qian, Z., 2020. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat. Commun. 11, 1–12.
Pan, Y., Wang, H., Zhang, D., Zhang, B., Li, Q., Luo, N., Cao, Z., Zhai, Y., 2020. Chinese medicine composition for preventing and treating viral diseases and application thereof. CN111150755A.
Pan, X., Chen, D., Xia, Y., Wu, X., Li, T., Ou, X., Zhou, L., Liu, J., 2020b. Asymptomatic cases in a family cluster with SARS-CoV-2 infection. Lancet Infect. Dis. 395, 514–523.
Park, J.-Y., Yuk, H.J., Ryu, H.W., Lim, S.H., Kim, K.S., Park, K.H., Ryu, Y.B., Lee, W.S., 2017. Evaluation of polyphenols from Broussonetia papyrifera as coronavirus protease inhibitors. J. Enzyme Inhib. Med. Chem. 32, 504–512.
Pawar, H.A., D'mello, P.M., 2011. Cassia tora Linn.: an overview. Int. J. Pharm. Sci. Res. 2, 2286–2291.
Peiris, J.S.M., Lai, S.T., Poon, L.L.M., Guan, Y., Yam, L.Y.C., Lim, W., Nicholls, J., Yee, W. K.S., Yan, W.W., Cheung, M.T., 2003. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 361, 1319–1325.
Pillaiyar, T., Meenakshisundaram, S., Manickam, M., 2020. Recent discovery and development of inhibitors targeting coronaviruses. Drug Discov. Today 25, 668–688. https://doi.org/10.1016/j.drudis.2020.01.015.
Ravina, E., 2011. The Evolution of Drug discovery: from Traditional Medicines to Modern Drugs. John Wiley & Sons.
Ray, A., Banerjee, B.D., Sen, P., 1996. Modulation of humoral and cell-mediated immune responses by Azadirachta indica (Neem) in mice. Indian J. Exp. Biol. 34, 698–701.
Rodrigues, T., Reker, D., Schneider, P., Schneider, G., 2016. Counting on natural products for drug design. Nat. Chem. 8, 531–541.
Rothan, H.A., Byrareddy, S.N., 2020. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J. Autoimmun. 109, 102433.
Ryu, Y.B., Park, S.-J., Kim, Y.M., Lee, J.-Y., Seo, W.D., Chang, J.S., Park, K.H., Rho, M.-C., Lee, W.S., 2010. SARS-CoV 3CLpro inhibitory effects of quinone-methide triterpenes from Tripterygium regelii. Bioorg. Med. Chem. Lett. 20, 1873–1876.
Sahin, A.R., Erdogan, A., Agaoglu, P.M., Dineri, Y., Cakirci, A.Y., Senel, M.E., Okyay, R. A., Tasdogan, A.M., 2020. 2019 Novel Coronavirus (COVID-19) Outbreak: a Review of the Current Literature. EJMO 4, 1–7.
Sato, H., Goto, W., Yamamura, J., Kurokawa, M., Kageyama, S., Takahara, T., Watanabe, A., Shiraki, K., 1996. Therapeutic basis of glycyrrhizin on chronic hepatitis B. Antiviral Res 30, 171–177.
Shen, L., Niu, J., Wang, C., Huang, B., Wang, W., Zhu, N., Deng, Y., Wang, H., Ye, F., Cen, S., Wenjie, T., 2019. High-throughput screening and identification of potent broad-spectrum inhibitors of coronaviruses. J. Virol. 93 e00023-19.
Shirato, K., Kanou, K., Kawase, M., Matsuyama, S., 2017. Clinical isolates of human coronavirus 229E bypass the endosome for cell entry. J. Virol. 91 e01387-16.
Signer, J., Jonsdottir, H.R., Albrich, W.C., Strasser, M., Züst, R., Ryter, S., Ackermann-Gäumann, R., Lenz, N., Siegrist, D., Suter, A., Schoop, R., Engler, O.B., 2020. *In vitro* antiviral activity of Echinaforce®, an Echinacea purpurea preparation, against common cold coronavirus 229E and highly pathogenic MERS-CoV and SARS-CoV. Virology.
Singhal, T., 2020. A Review of Coronavirus Disease-2019 (COVID-19). Indian J. Pediatr 1–6.
Sisler, H.D., Siegel, M.R., 1967. Cycloheximide and Other Glutarimide antibiotics, in: Mechanism of Action. Springer, pp. 283–307.
Sohrabi, C., Alsafi, Z., O'Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., Iosifidis, C., Agha, R., 2020. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). Int. J. Surg. 76, 71–76.
Sollinger, H.W., 2004. Mycophenolates in transplantation. Clin. Transplant. 18, 485–492.
Sultan, M.T., Buttxs, M.S., Qayyum, M.M.N., Suleria, H.A.R., 2014. Immunity: plants as Effective Mediators. Crit. Rev. Food Sci. Nutr. 54, 1298–1308. https://doi.org/10.1080/10408398.2011.633249.
Talbot, H.K., Shepherd, B.E., Crowe Jr, J.E, Griffin, M.R, Edwards, K.M, Podsiad, A.B, Tollefson, S.J, Wright, P.F, Williams, J.V, 2009. The pediatric burden of human coronaviruses evaluated for 20 years. Pediatr. Infect. Dis. J. 28, 682.
Touret, F., de Lamballerie, X., 2020. Of chloroquine and COVID-19. Antiviral Res 177, 104762.
Tsui, P.T., Kwok, M.L., Yuen, H., Lai, S.T., 2003. Severe acute respiratory syndrome: clinical outcome and prognostic correlates. Emerg. Infect. Dis. 9, 1064.
van der Hoek, L., Pyrc, K., Jebbink, M.F., Vermeulen-Oost, W., Berkhout, R.J.M., Wolthers, K.C., Wertheim-van Dillen, P.M.E., Kaandorp, J., Spaargaren, J., Berkhout, B., 2004. Identification of a new human coronavirus. Nat. Med. 10, 368–373.
Van Tamelen, E.E., Dickie, J.P., Loomans, M.E., Dewey, R.S., Strong, F.M., 1961. The Chemistry of Antimycin AX Structure of the Antimycins1. J. Am. Chem. Soc. 83, 1639–1646.
Walls, A.C., Park, Y.-J., Tortorici, M.A., Wall, A., McGuire, A.T., Veesler, D., 2020. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. CellCell 181, 281–292.
Walsh, E.E., Shin, J.H., Falsey, A.R., 2013. Clinical impact of human coronaviruses 229E and OC43 infection in diverse adult populations. J. Infect. Dis. 208, 1634–1642.
Wan, Y., Shang, J., Graham, R., Baric, R.S., Li, F., 2020b. Receptor recognition by the novel coronavirus from wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J. Virol 94.
Wang, X., Zhang, D., Cheng, S., 2020. Sachet for efficiently preventing novel coronavirus pneumonia and influenza. CN111214689A.
Wan, S., Xiang, Y., Fang, W., Zheng, Y., Li, B., Hu, Y., Lang, C., Huang, D., Sun, Q., Xiong, Y., et al., 2020a. Clinical Features and Treatment of COVID-19 Patients in Northeast Chongqing. J. Med. Virol. 92, 797–806.
Wang, L., Wang, Y., Ye, D., Liu, Q., 2020b. A review of the 2019 Novel Coronavirus (COVID-19) based on current evidence. Int. J. Antimicrob. Agents 55, 105948.
Wen, C.-C., Kuo, Y.-H., Jan, J.-T., Liang, P.-H., Wang, S.-Y., Liu, H.-G., Lee, C.-K., Chang, S.-T., Kuo, C.-J., Lee, S.-S., Hou, C.-C., Hsiao, P.-W., Chien, S.-C., Shyur, L.-F., Yang, N.-S., 2007. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. J. Med. Chem. 50, 4087–4095.
Wen, C.-C., Shyur, L.-F., Jan, J.-T., Liang, P.-H., Kuo, C.-J., Arulselvan, P., Wu, J.-B., Kuo, S.-C., Yang, N.-S., 2011. Traditional Chinese medicine herbal extracts of Cibotium barometz, Gentiana scabra, Dioscorea batatas, Cassia tora, and Taxillus chinensis inhibit SARS-CoV replication. J. Tradit. Complement. Med. 1, 41–50.
Woo, P.C.Y., Lau, S.K.P., Chu, C., Chan, K., Tsoi, H., Huang, Y., Wong, B.H.L., Poon, R.W. S., Cai, J.J., Luk, W., 2005. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. J. Virol. 79, 884–895.
World Health Organization, 2020a. Coronavirus disease (COVID-19): situation Report–176.
World Health Organization, 2020b. Coronavirus disease (COVID-19): situation Report – 146.
World Health Organization, 2003. Consensus document on the epidemiology of severe acute respiratory syndrome (SARS). World Health Organization.
Wrapp, D., Wang, N., Corbett, K.S., Goldsmith, J.A., Hsieh, C.-L., Abiona, O., Graham, B. S., McLellan, J.S., 2020. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science (80-.) 367, 1260–1263.
Wu, S., Sun, C., Wang, K., Pan, Y., 2004. Preparative isolation and purification of celastrol from Celastrus orbiculatus Thunb. by a new counter-current chromatography method with an upright coil planet centrifuge. J. Chromatogr. A 1028, 171–174.
Wu, T., Liang, L., Zhang, T., Liang, H., 2020. Traditional Chinese medicine formula for treating or preventing novel coronavirus pneumonia and viral influenza. CN111110819A.
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. JAMAJAMA 323, 1239–1242.
Xi, Z., Shu, Y., Liu, Z., Ma, C., Wang, Y., Shi, S., Qiao, F., Wu, L., Wu, X., 2020. Epidemic prevention traditional Chinese medicine composition and preparation method and application thereof. CN111214566A.
Xiao, X.-W., Fu, H.-Z., Luo, Y.-H., Wei, X.-Y., 2013. Potential anti-angiogenic sulfates of andrographolide. J. Asian Nat. Prod. Res. 15, 809–818.
Yang, C.-W., Lee, Y.-Z., Kang, I.-J., Barnard, D.L., Jan, J.-T., Lin, D., Huang, C.-W., Yeh, T.-K., Chao, Y.-S., Lee, S.-J., 2010a. Identification of phenanthroindolizines and phenanthroquinolizidines as novel potent anti-coronaviral agents for porcine enteropathogenic coronavirus transmissible gastroenteritis virus and human severe acute respiratory syndrome coronavirus. Antiviral Res 88, 160–168.
Yang, P.W., Li, M.G., Zhao, J.Y., Zhu, M.Z., Shang, H., Li, J.R., Cui, X.L., Huang, R., Wen, M.L., 2010b. Oligomycins A and C, major secondary metabolites isolated from the newly isolated strain Streptomyces diastaticus. Folia Microbiol. (Praha). 55, 10–16.
Yang, Y., Islam, M.S., Wang, J., Li, Y., Chen, X., 2020b. Traditional Chinese Medicine in the Treatment of Patients Infected with 2019-New Coronavirus (SARS-CoV-2): a Review and Perspective. Int J Biol Sci 16, 1708–1717. https://doi.org/10.7150/ijbs.45538.
Ye, Z.-W., Yuan, S., Yuen, K.-S., Fung, S.-Y., Chan, C.-P., Jin, D.-Y., 2020. Zoonotic origins of human coronaviruses. Int J Biol Sci 16, 1686–1697.
Yeager, C.L., Ashmun, R.A., Williams, R.K., Cardellichio, C.B., Shapiro, L.H., Look, A.T., Holmes, K.V, 1992. Human aminopeptidase N is a receptor for human coronavirus 229E. NatureNature 357, 420–422.
Yi, L., Li, Z., Yuan, K., Qu, X., Chen, J., Wang, G., Zhang, H., Luo, H., Zhu, L., Jiang, P., Chen, L., Shen, Y., Luo, M., Zuo, G., Hu, J., Duan, D., Nie, Y., Shi, X., Wang, W., Han, Y., Li, T., Liu, Y., Ding, M., Deng, H., Xu, X., 2004. Small Molecules Blocking the Entry of Severe Acute Respiratory Syndrome Coronavirus into Host Cells. J. Virol 78. https://doi.org/10.1128/JVI.78.20.11334-11339.2004, 11334 LP – 11339.
Yuan, Y., Cao, D., Zhang, Y., Ma, J., Qi, J., Wang, Q., Lu, G., Wu, Y., Yan, J., Shi, Y., 2017. Cryo-EM structures of MERS-CoV and SARS-CoV spike glycoproteins reveal the dynamic receptor binding domains. Nat. Commun. 8, 15092.
Zhang, L., Koyyalamudi, S.R., Jeong, S.C., Reddy, N., Bailey, T., Longvah, T., 2013. Immunomodulatory activities of polysaccharides isolated from Taxillus chinensis and Uncaria rhyncophylla. Carbohydr. Polym. 98, 1458–1465.
Zhang, N., Yang, H., 2020. Traditional Chinese medicine composition with function of resisting novel coronavirus sars-cov-2 and preparation method and application thereof. CN111150792A.
Zhang, T., He, L., Peng, Y., 2020. Traditional chinese medicine composition and preparation method and pharmaceutical application thereof. CN111214637A.
Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., Si, H.-R., Zhu, Y., Li, B., Huang, C.-L., et al., 2020. . A pneumonia outbreak associated with a new coronavirus of probable bat origin. NatureNature 579, 270–273.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., et al., 2020. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med 382, 727–733.

Zingone, F., Buda, A., Savarino, E.V., 2020. Screening for active COVID-19 infection and immunization status prior to biologic therapy in IBD patients at the time of the pandemic outbreak. Dig. Liver Dis. 52, 604–605. https://doi.org/10.1016/j.dld.2020.04.004.

Yang, H., Chen, C., Chen, T., Yang, Y., 2020. Fumigation bath preparation for preventing and treating plague and use method and application thereof. CN111184823A.