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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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 Saed, i, Haged H.R. El-Seedi, j, Chao Zhao, k, Thomas Effertth, l, Hesham R. El-Seedi, a, b, d, m, n

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, Kuala Lumpur, 26500, 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 Pharmaceutical and Biomedical Sciences, Johannes Gutenberg University, Staudinger Weg 5, 55128 Mainz, Germany
m n International Research Center for Food Nutrition and Safety, Jiangsu University, Zhenjiang 212013, China

ARTICLE INFO

Keywords:
1. Natural products
2. Antiviral
3. Clinical trials
4. Patent
5. 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 bulbifera Decne., Cassia tora L., Cibotium barometz (L.’Hèr.), and Cassia tora L. showed a promising effect against SARS-CoV. Out of the listed compound Lycorine, emetine dihydrochloride hydrate, pristimerin, harmine, conessine, berberine, 4-hydroxychalcone, papaverine, mycophenolic acid, mycophenolate mofetil, monensin sodium, cycloheximide, oligomycin and valinomycin show potent activity against human coronaviruses. Additionally, it

Abbreviations: 3CLpro, 3C-like protease; ACE2, Angiotensin-converting enzyme 2; ARDS, Acute respiratory distress syndrome; CC50, 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; EC50, 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; IC50, 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.

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
0944-7113/© 2021 The Authors. Published by Elsevier GmbH. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
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) (Chikara 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 (Chihikara 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, gyspum, *Tricho-santhes*, 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 *Aloe vera* isolated from *Trichosanthes* were reported 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.

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.
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., 2020).

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.
(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
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 (Bussotti 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) (Pillayar 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 a prophylactic agent for gastric and duodenal ulcers, anti-inflammatory, contraceptive, laxative, anti-asthmatic, galactagogue, and antiviral, and expectorant (Damle, 2014; Sato et al., 1996). Cinatli 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 (EC50 of 300 mg/l) and CC50 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 (Cinatli 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. annulata, P. lingua Mirb. and L. aggregate Sims, showed superior activity at EC50 of 2.4, 34.5, 43.2 and 88.2 µg/ml respectively when compared with interferon alpha as a positive control (EC50 = 660.3 IU/ml). Four potent extracts recorded CC50 values ranged between 868.6 ± 35.0 to 2378.0 ± 87.3 µg/ml. CC50 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 EC50 of 15.7 nM and CC50 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 EC50 values ranging from 0.15 µM to 1.63 µM (Shen et al., 2019).

Emetine is a natural plant alkaloid of ipecac (Carpariae ispecacuana L.), emetine dihydrochloride (31), a derivative of emetine inhibiting the viral protein synthesis of coronaviruses, with an EC50 value of 0.12 to 1.43 µM. Emetine dihydrochloride revealed the strongest anti-CoV activities against MERS-CoV and SARS-CoV with the lowest EC50 of 0.014 and 0.05 µM, whilst the activity against HCoV-NL63, HCoV-OC43, MERS-CoV and MHV-A59 showed EC50 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 CC50 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 (Kakum et al., 2014). TSL-1, a fraction of the aqueous extract of the plant leaves showed anti-viral activity against SARS-coronavirus with EC50 of 30 µg/ml and CC50 value >500 µg/ml via inhibition of the viral replication. Determination of CC50 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 IC50 value of 39 and 44 µg/ml respectively. The six plant extracts recorded the same CC50 value of >500 µg/ml in comparison with valinomycin (positive control) that has value of 75.01 µg/ml. The determination of CC50 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 Thub. 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 3CLpro enzyme. Three different extracts (EtOH, EtOAc and water fraction) have been tested against SARS-CoV infection, and exhibited IC50 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 IC50 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 spp. oxy- cedrus, Thuja orientalis, Cupressus sempervirens spp. 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 IC50 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

| Compound name, chemical class | Origin | Mechanism of action | Virus type | IC₅₀ or EC₅₀ (CC₅₀) value µg/ml | Reference |
|-------------------------------|--------|----------------------|------------|---------------------------------|-----------|
| **Plants**                    |        |                      |            |                                 |           |
| 2,3,4,6,7-pentamethoxy-12,13-dihydro-11H-dibenzo[2,3][1,2,β]isouquinolin-10-ium (ND), alkaloid (1) | *Ficus septic*a L. | Inhibits viral replication | TGEV | 14.906±2.2468 (< 100,000) nM | Yang et al., 2010a |
| 3,14β-hydroxy-6,7-dimethoxy-naphthaloindolizidine (ND), alkaloid (2) | *T. ovata* L. | Inhibits viral replication | TGEV | 8 ± 2 (59.943±2.786) nM | Yang et al., 2010a |
| 3',4'-dihydroxy-6,7-dimethoxy-naphthaloindolizidine (ND), alkaloid (3) | *T. ovata* L. | Inhibits viral replication | TGEV | 18±1 (31.632±1.192) nM | Yang et al., 2010a |
| 3'-O-methylidiploclof (ND), flavonoid (4) | *Paulownia tomentosa* (Thunb.) | Inhibits PL₃₉₃ enzyme | SARS-CoV | 9.5 ± 0.10 µM | Cho et al., 2013 |
| 3'-O-methylidiploclacosine (ND), flavonoid (5) | *P. tomentosa* (Thunb.) | Inhibits PL₃₉₃ enzyme | SARS-CoV | 13.2 ± 0.14 µM | Cho et al., 2013 |
| 3'-O-methylidiploclof (ND), flavonoid (6) | *Broussonetia papyrifera* (ND), flavonoid (6) | Inhibits PL₃₉₃ enzyme | SARS-CoV | 12.7 ± 0.19 µM | Cho et al., 2013 |
| 4'-Hydroxychalcone (ND), flavonoid (8) | *Cinnamomum spp.* | Inhibits viral replication | HCoV-OC43 | 1.52 (< 20) µM | Yang et al., 2010a |
| 4'-O-methylidiploclof (ND), flavonoid (9) | *P. tomentosa* (Thunb.) | Inhibits PL₃₉₃ enzyme | SARS-CoV | 13.9 ± 0.18 µM | Cho et al., 2013 |
| 4'-O-methylidiploclof (ND), flavonoid (10) | *P. tomentosa* (Thunb.) | Inhibits PL₃₉₃ enzyme | SARS-CoV | 12.7 ± 0.19 µM | Cho et al., 2013 |
| 6,7-dehydroxyooleanone (ND), diterpenoid (12) | *Chamaecyparis obtusa var. formosana* (Thunb.) | Inhibits viral replication | SARS-CoV | 5.55 (89.7) µM | Wen et al., 2007 |
| 6-geranyl-4,5,7-trihydroxy-3',5'-dimethoxyflavone (ND), flavonoid (13) | *C. japonica* L. | Inhibits PL₃₉₃ enzyme | SARS-CoV | 1.15 (127) µM | Wen et al., 2007 |
| 8β-hydroxyabiet-9(11),13-dien-12-one (ND), diterpenoid (15) | *C. obtusa var. formosana* (Thunb.) | Inhibits viral replication | SARS-CoV | 1.47 (> 750) µM | Wen et al., 2007 |
| Acetyl-O-methylhydroxylorphanidine (ND), alkaloid (16) | *Isatis indigotica* (Thunb.) | Inhibits enzymatic activity of virus | SARS-CoV | 366 (11,592) µg/ml | Goyindachari et al., 1973; Yang et al., 2010a |
| Basicaolin (ND), flavonoid (18) | *Scutellaria baicalensis* (Thunb.) | Inhibits the enzymatic activity | SARS-CoV | 12.5 (< 100) µg/ml | Chen et al., 2004; Deng et al., 2012 |
| Berhamine (ND), bis-benzyloquinoline alkaloids (19) | *Berberis amurensis* (Thunb.) | Inhibits viral replication | SARS-CoV | 13.14 (< 20) µM | Meng et al., 2013; Shen et al., 2019 |
| Beta-sitosterol (N), steroidal (20) | *I. indigotica* (Thunb.) | Inhibits enzymatic activity of virus | SARS-CoV | 1210 (1475) µg/ml | 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 |
| Broussonachol A (ND), polyphenol (22) | *B. papyrifera* | Inhibits viral replication | SARS-CoV | 42.1 ± 5.0 µM | Park et al., 2017 |
| Broussonachol A (ND), polyphenol (23) | *B. papyrifera* | Inhibits viral replication | SARS-CoV | 88.1 ± 13.0 µM | Park et al., 2017 |
| Broussonachol A (ND), polyphenol (24) | *B. papyrifera* | Inhibits viral replication | SARS-CoV | 112.9 ± 10.1 µM | Park et al., 2017 |
| Cedrane-3β,12-diol (ND), sesquiterpenoid (25) | *J. formosana* L. | Inhibits viral replication | SARS-CoV | 49.1 ± 7.5 µM | Park et al., 2017 |
| Cephalantherine, (ND), (bis-benzyloquinoline alkaloids) (26) | *S. tetrandra* | Inhibits viral replication | SARS-CoV | 92.4 ± 21.1 µM | Park et al., 2017 |
| Chloroquine (S*), alkaloid (27) | *Cinchona spp.* | Inhibits viral replication | SARS-CoV | 1.48 (< 20) µM | Yang et al., 2010a |
| Conessine (ND), steroid alkaldiol (28) | *Holarrhena antidysenterica* | Inhibits viral replication | SARS-CoV | 20.57 (< 20) µM | Dua et al, 2013; Shen et al., 2019 |
| Cryptoponapone (ND), diterpenoid (29) | *Cryptosperma japonica* L. | Inhibits viral replication | SARS-CoV | > 10 (78.5) µM | Wen et al., 2007 |
| Dehydroabieta-7-one, (ND), diterpenoid (30) | *C. obtusa var formosana* | Inhibits viral replication | SARS-CoV | 4 (305.1) µM | Wen et al., 2007 |

(continued on next page)
| Compound name, chemical class | Origin | Mechanism of action | Virus type | IC₅₀ or EC₅₀ (CC₅₀) value µg/ml | Reference |
|-------------------------------|--------|---------------------|------------|--------------------------------|-----------|
| Emetine dihydrochloride hydrate (S*), alkaloid (31) | Carapa incana L. | Inhibits RNA, DNA, and protein synthesis | HCoV-OC43 | 0.30 (2.69) µM | Dyall et al., 2017; Pillaiyar et al., 2020; Shen et al., 2019 |
| | | | HCoV-NL63 | 1.43 (3.63) µM | |
| | | | MERS-CoV | 0.34 (3.08)/ 0.014 µM | |
| | | | MHV-AS9 | 0.12 (3.51) µM | 0.05 µM |
| | | | SARS-CoV | 919.2 nM | Kim et al., 2019 |
| Fangchinoline, (N), (Bis-benzylisoquinoline alkaloids) (32) | S. tsoana | Inhibits viral S and N protein expression | HCoV-229E | 1.90 (> 20) µM | Moloudazarzarghi et al., 2013; Shen et al., 2019 |
| Ferruginol, (N), diterpenoid (33) | C. obtus var. formosana | Inhibits viral replication | SARS-CoV | 4.93 (> 20) 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-CoV | 8.3 (2718 µM) | Cinatl et al., 2003 |
| Harmine (N), alkaloid (35) | Peganum harmala | Inhibits viral replication | HCoV-OC43 | 1.90 (> 20) µM | |
| | | | HCoV-NL63 | 13.46 (> 20) µM | |
| | | | MERS-CoV | 4.93 (> 20) µM | |
| | | | MHV-AS9 | 13.77 (> 20) µM | |
| Hesperetin, (N), flavonoid (36) | Citrus aurantium | Inhibits viral replication | SARS-CoV | 8.3 (> 750) µM | Lin et al., 2005 |
| Hinoxin (N), lignoid (37) | C. obtus 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 | 88.5 ± 3.9 µM | Park et al., 2017 |
| Kazinol B (N), flavonoid (41) | B. papyrifera | Inhibits coronavirus proteases enzyme | MERS-CoV | 84.8 ± 10.4 µM | Park et al., 2017 |
| Kazinol F (N), flavonoid (42) | B. papyrifera | Inhibits coronavirus proteases enzyme | MERS-CoV | 94.9 ± 13.1µM | Park et al., 2017 |
| Kazinol J (N), flavonoid (43) | B. papyrifera | Inhibits coronavirus proteases enzyme | MERS-CoV | 233.3 ± 6.7 µM | Park et al., 2017 |
| Luteolin (N), flavonoid (44) | Rhodiala 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 | 0.15 (4.37) µM | Li et al., 2005; Pillaiyar et al., 2020; Shen et al., 2019 |
| | | | HCoV-NL63 | 0.47 (3.81) µM | |
| | | | MERS-CoV | 1.63 (3.14) µM | |
| | | | MHV-AS9 | 0.31 (3.51) µM | |
| | | | SARS-CoV | 0.0157 (14.98) µM | |
| Mimulone, (N), flavonoid (46) | P. tomentosa | Inhibits PL₃₉₀ enzyme | SARS-CoV | 14.4 ± 0.27 µM | Cho et al., 2013 |
| N-acetylglucosamine, (N), alkaloid (47) | Urtica dioica aggutinulin | Inhibits viral replication | SARS-CoV | 2.6 ± 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 | 1.61 (12.11) µM | Labanca et al., 2018; Shen et al., 2019 |
| | | | HCoV-NL63 | 7.32 (11.71) µM | |
| | | | MERS-CoV | 9.45 (11.98) µM | |
| | | | MHV-AS9 | 11.46 (12.44) µM | |
| | | | SARS-CoV | 112.5 ± 7.3 µM | |
| Papyriflavonol A (N), flavonoid (49) | B. papyrifera | Inhibits coronavirus proteases enzyme | SARS-CoV | 103.6 ± 17.4µM | Park et al., 2017 |
| Pinusulic acid, (N), diterpenoid (50) | C. obtus var. | Inhibits viral replication | SARS-CoV | 4.71 (> 750) µM | Wen et al., 2007 |
| Pristimerin (N), triterpenoid (51) | Pristimerin indica, Tripterygium regelii | Inhibits viral replication | SARS-CoV | 1.99 (> 20) µM | Li et al., 2019; Ryu et al., 2010; Shen et al., 2019 |
| | | | HCoV-OC43 | 1.63 (> 20) µM | |
| | | | HCoV-NL63 | 13.87 (> 20) µM | |
| | | | MERS-CoV | 5.91 (> 20) µM | |
| | | | MHV-AS9 | 0.19 (3.51) µM | |
| | | | SARS-CoV | 5.5 µM | |
| Saikosaponin A (N), triterpenoid saponins (52) | Bupleurum spp., Hetetmora 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., Hetetmora 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., Hetetmora 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., Hetetmora 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. obtus var. | Inhibits viral replication | 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)
| Compound name, chemical class | Origin | Mechanism of action | Virus type | IC50 or EC50 (CC50) value µg/ml | Reference |
|-----------------------------|--------|---------------------|------------|---------------------------------|-----------|
| Tetrandrine, (N), (bis-benzylisoquinoline alkaloids) (58) | *Stephania tetrandra* | Inhibits viral S and N protein expression | HCoV-OC43 | 1.65 (3.62) µg/ml | Shen et al., 2019; Van Tamelen et al., 1961 |
| Tetra-O-galloyl-β-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 PLpro enzyme | SARS-CoV | 6.2 ± 0.04 µM | Cho et al., 2013 |
| Tomentin B (N), coumarin (61) | *P. tomentosa* (Thunb.) | Inhibits PLpro enzyme | SARS-CoV | 6.1 ± 0.02 µM | Cho et al., 2013 |
| Tomentin C (N), coumarin (62) | *P. tomentosa* (Thunb.) | Inhibits PLpro enzyme | SARS-CoV | 11.6 ± 0.13 µM | Cho et al., 2013 |
| Tomentin D (N), coumarin (63) | *P. tomentosa* (Thunb.) | Inhibits PLpro enzyme | SARS-CoV | 12.5 ± 0.22 µM | Cho et al., 2013 |
| Tomentin E (N), coumarin (64) | *P. tomentosa* (Thunb.) | Inhibits PLpro enzyme | SARS-CoV | 5.0 ± 0.06 µM | Cho et al., 2013 |
| Tylephorine (N), alkaloid (65) | *T. indica* L. | Inhibits viral replication | TGEV | 95±17 (100.000) nM | Yang et al., 2010a |
| Tylephorine (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 |
| Esculetin-4-carboxylic acid ethyl ester (N), marine (68) | *Axinella cf. corregata*, Sponge | Inhibits enzymatic activity of virus | SARS-CoV | > 800 µmol l⁻¹, 112 µmol l⁻¹ | Lira et al., 2007 |
| Halitunal (N), diterpene aldehyde (69) | *Halimeda 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 Hammam, 2003 |
| **Microorganisms** | | | | | |
| Antibiotic (N), alkaloid (71) | *Streptomyces spp.*, Bacteria | Antibiotic | HCoV-OC43 | 1.65 (3.62) µg/ml | Shen et al., 2019; Van Tamelen et al., 1961 |
| Antibiotic (N), alkaloid (72) | *Streptomyces spp.*, Bacteria | Protein synthesis inhibitor | HCoV-OC43 | 0.43 (3.12) µg/ml | Shen et al., 2019; Sider and Siegel, 1967 |
| Antibiotic (N), alkaloid (73) | *Streptomyces cinnamomensis*, Bacteria | Inhibit viral replication | HCoV-OC43 | 3.81 (<20) µg/ml | Lowicki and Huczyński, 2013; Pillaiyar et al., 2020; Shen et al., 2019 |
| Antibiotic (N), alkaloid (74) | *Penicillium spp.*, Fungus | Immune suppressant, antineoplastic, antiviral | HCoV-OC43 | 1.58 (3.43) µg/ml | Bittercourt et al., 2000; Pillaiyar et al., 2020; Shen et al., 2013; Sollinger, 2004 |
| Antibiotic (N), alkaloid (75) | *Penicillium spp.*, Fungus | Immune suppressant, antineoplastic, antiviral | HCoV-OC43 | 1.95 (3.55) µg/ml | Canetti et al., 2003; Hart et al., 2014; Pillaiyar et al., 2020; Shen et al., 2014; Sollinger, 2004 |
| Antibiotic (N), Peptide (76) | *Streptomyces sp.*, Bacteria | Antibiotic | HCoV-OC43 | 4.43 (6.15) µg/ml | Cheng, 2006; Shen et al., 2019 |
| Antibiotic (N), Peptide (77) | *Streptomyces sp.*, Bacteria | Inhibits viral replication | HCoV-OC43 | 1.89 (4.12) µg/ml | Shen et al., 2019; Yang et al., 2010b |

TGEV: Coronavirus infected Pigs.
Table 2
List of plants extracts used as anti-coronaviruses.

| Plants                  | Type of extract | Organism/ Mechanism | IC50 or EC50 (µM) | References |
|-------------------------|----------------|---------------------|-------------------|------------|
| Artemisia annua          | EtOH           | SARS-CoV Reduces RNA replication | 34.5 (1053)       | Li et al., 2005 |
| L., Whole plant         |                |                     |                   |            |
| Cuscuta australis        | EtOH           | SARS-CoV Inhibits viral replication | 8.43 (> 500) > 50 | Wen et al., 2011 |
| (CHI)                   |                |                     |                   |            |
| Celastrus orbiculatus   | EtOH           | SARS-CoV Inhibits enzymatic activity | 19.4               | Kumar et al., 2013 |
| Thunb.                  | EtOAc          | SARS-CoV NR          | 17.8              |            |
| Cibotium barometz        | EtOH           | SARS-CoV Inhibits viral replication, Inhibits enzymatic activity | 8.42 (> 500) > 50 | Wen et al., 2011 |
| (CBE)                   |                |                     |                   |            |
| C. barometz             | EtOH           | SARS-CoV Inhibits viral replication Inhibits enzymatic activity | > 10 (> 500) 39    | Wen et al., 2011 |
| (CBM)                   |                |                     |                   |            |
| Dioscorea batatas       | EtOH           | SARS-CoV Inhibits viral replication Inhibits enzymatic activity | 8.06 (> 500) 44    | Wen et al., 2011 |
| (DBM)                   |                |                     |                   |            |
| Echinacea purpurea      | Aqueous ethanol | SARS-CoV Inhibits viral replication | 50              | Signer et al., 2020 |
| Roots                   |                |                     |                   |            |
| Gentiana scabra         | EtOH           | SARS-CoV Inhibits viral replication Inhibits enzymatic activity | 8.70 (> 500) > 50  | Wen et al., 2011 |
| (GSH), Rhizomes         |                |                     |                   |            |
| J. oxycedrus, 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 aggregata       | EtOH           | SARS-CoV Reduces RNA replication | 88.2 (1374)      | Li et al., 2005 |
| Sims, Roots             |                |                     |                   |            |
| Lycoris radiata         | EtOH           | SARS-CoV Reduces RNA replication | 2.4            | Li et al., 2005 |
| (L’Hér.), Stem          |                |                     | (886.6)          |            |
| P. palpebina, Fruits    | Essential oil  | SARS-CoV Inhibits viral replication | > 1000         | Loizzo et al., 2008 |
| Pyroisling lingua       | CHCs           | SARS-CoV Reduce RNA replication | 43.2 (2378)     | Li et al., 2005 |
| Mirb., Leaves           |                |                     |                   |            |
| T. orientalis, Fruits   | Essential oil  | SARS-CoV Inhibits viral replication | 130            | Loizzo et al., 2008 |
| Taraxacum chinensis     | EtOH           | SARS-CoV Inhibits viral replication Inhibits enzymatic activity | 5.39 (> 500) > 50 | Wen et al., 2011 |
| (TCH)                   |                |                     |                   |            |
| Toona sinensis          | Aqueous        | SARS-CoV Inhibits viral replication | 30 (> 500)      | Chen et al., 2008 |
| Roem Leaves             |                |                     |                   |            |

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®, Blilive®, Anflu®, Afluria® and Optaflu®, and are used against the influenza virus, 26 are synthetic but the pharmaco- phores 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 myr- locin (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. Fingoli- mod 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. Tetran- drine 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 Chandrasekhar, 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 values ranging from 0.18 to 1.95 µM). The value of CC50 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 EC50 of 1.58, 0.23, 1.54 and 0.27 µM. The CC50 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 (EC50 = 0.17 µM) (Shen et al., 2019).
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$_2$O, 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
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 anti-cancer 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
stage of infection with EC_{50} of 3.0 \, \mu M, 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).
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. 4.** (continued).

**Fig. 5.** Structures of isolated anti-viral compounds of marine origin or their derivatives.
Twig, 9 parts of Rhizoma Alismatis, 9 parts of Frifola, 9 parts of bighed 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 sweetseed, 20 parts of wrinkled Gianthyssop herb, 20 parts of Rhizoma Atractylodis, 20 parts of Radix Bupleuri, 2 parts of Calculus Bovis Fac-titius, 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 COVID-19.
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, 15–15 parts of Cortex Moutan, 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

| Compounds | Natural products origin | Clinical trials/phase/ Type of the study/ No of participants | Dose/ administration route/ Mechanism of action | Reference/ ClinicalTrials.gov Identifier |
|-----------|------------------------|--------------------------------------------------------------|------------------------------------------------|----------------------------------------|
| (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 SARS-CoV, Severe Acute Respiratory Syndrome (SARS) Pneumonia/ Phase 2/ Interventional / 440 P | 10 mg/kg followed by 155 mg daily (250 mg chloroquine phosphate salt or 200 mg of or hydroxychloroquine sulphate)/ for 3 m 150 mg/ twice daily/ 10 days | (https://clinicaltrials.gov, NCT04303507) |
| 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, NCT04273221) |
| Tetrandrine (N), alkaloid (58) | Stephania tetrandra, Plant | Corona Virus Disease 2019, COVID-19/ Phase 4/ Interventional/ 60 P | 40 mg/ 12 h for 5 days | (https://clinicaltrials.gov, NCT04244591) |
| 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) |
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: | 9 parts of ephedra, 6 parts of honey-fried licorice root, 9 parts of almond, 15–30 parts of Gypsum, 9 parts of Cauis Twig, 9 parts of Rhizoma Alismatis, 9 parts of Griffola, 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 arse, 9 parts of Flos Farane, 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: | 40 parts of Folium Iastidis, 40 parts of the wild Chrysanthemum flower, 20 parts of Coptis chinensis, 30 parts of sweetseed seed, 20 parts of wrinkled Gianthyssop herb, 20 parts of Rhizoma Atractylodis, 20 parts of Radix Bupleuri, 2 parts of Calculus Bovis Fisiculitum, 20 parts of Houtymina 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 milirostris, 15 parts of Bulbus Fritiliarae Cirrhosum, 10 parts of Sausarea involucrate, 60 parts of Astragulus 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: | 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 Peristeromucicicada, 4–12 parts of Codonopsis piloula, 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: | 30–60 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 flowers, 10–30 parts of Fructus Forsythiae, 10–30 parts of Iastidis root, 10–30 parts of reed rhizome, 15–30 parts of Folium Iastidis, 20–240 parts of Gypsum, 10–30 parts of Iangang grass rhizome, 15–10 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 Rhum officinale, 15–45 parts of ginger, 10–30 parts of Chinese date and 5–9 parts of musk/ Liquid | Traditional Chinese medicine composition 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: | 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: | 50–80 parts of clove, 20–30 parts of Cacumen Biotae and 15–20 parts of Angelica dahuica, 10–15 parts of honeysuckle, 10–15 parts of Agastache rugous, 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./ (CN111214695A)/ CN | SARS-CoV-2/ Not reported/ Preventing novel coronavirus pneumonia and preventing and treating respiratory diseases | Wang et al., 2020a |

(continued on next page)
S.A.M. Khalifa et al.  
Phytomedicine 85 (2021) 153311

| Invention | 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: 张庆芳, 何玉华 and 饶勇 | isatis root, 10-15 parts of folium Artemisiae argyi and 10-15 parts of borneol/ Capsule 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 Cynula 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 astier, 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 Aegaturtug rosaos/ Tablets, powder, soft capsules, syrup, pills and granules. 6–30 parts of Astragalus membracens, 6–30 parts of Codonopsis pilularis, 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 | Traditional Chinese medicine composition and preparation method and pharmaceutical application thereof/ (CN111214657A)/ CN | SARS-CoV-2/ not reported/ Treating or preventing the new coronavirus 2019-nCoV | Zhang et al., 2020 |
| Chinese name: 韩赛斯, 杜维勇 and 倪浩 | 8–12 parts of semliguidiambar cathayensis, 8–12 parts of cinnamomum camphora root, 8–12 parts of citronella, 8–12 parts of Scutellaria 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 Chamaecium glaucescens, 8–12 parts of bitter apricot kernel, 8–12 parts of astier, 8–12 parts of reed rhizome and 8–12 parts of euphoria lathyrism/ 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 杨仪德尔 | 20–100 g of Lagerra pterodonota, 10–50 g of dried ginger, 10–40 g of divaricate saposhnikovia root, 10–50 g of Officinal magnolia bark and 10–60 g of pilose asialbell root/ liquid | Lagerra pterodonota 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 |

Table 4 (continued)
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 EC50 and C50 values. Other therapeutic agents have also been reported and are already moving into clinical trials including Xiyueping, 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., Matsuoaka, Y., Wilcox, G.E., Companis, 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.
Astiri, A., Al-Tawfiq, J.A., Al-Rabiah, A.F., Al-Rabiah, F.A., Al-Menhali, S., Al-Rabiah, Y., Al-Sayari, A., Al-Sayari, E., Al-Sayari, M., Al-Sayari, S., Al-Sayari, T., 2019. 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. JAMA JAMA 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. BioMed. J. Clin. Invest. 50, e13209.
Bittencourt, V.R.E.P., Mascarenhas, A.G., de Menezes, G.C.R., Monteiro, S.G., 2000. Clinical and Epidemiological Aspects of Respiratory Diseases. Pharm. Biol. 38, 251–257.
Bhagya, N., Chandrashekar, K.R., 2016. Tetrandrine: a potent medicinal herb. Int. J. Herb. Pharm. Med. 2, 132–136.
Day, M., 2020. Covid-19: ibuprofen should not be used for managing symptoms, says doctors and scientists. BMJ 368, m1086.
Deng, J., Jin, Yipeng, Liu, Y., Sun, J., Hui, L., 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.
Donia, M., Afsho, R.E., Jin, Y., Liu, D., 2018. Inhibitory activities of baicalin against renin and angiotensin-converting enzyme. Pharm. Biol. 56, 401–406.
Donia, M., Hamann, M.T., 2003. Marine natural products and their potential applications as anti-infective agents. Adv. Drug. Deliv. Rev. 55, 338–348.
Dring, J., Madhavan, M.V., Bikdeli, B., Chuich, T., Laracy, J., Bondi-Zoccai, G., Brown, T.S., Der Gigiohannis, 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, 253–257.
Dua, V.K., Verma, G., Singh, B., Rajan, A., Bagai, U., Agarwal, D., Gupta, N.C., Kumar, S., Rastogi, A., 2013. Anti-malathal property of steroidal alkaloid connexone isolated from the bark of Holarrhena antidysenterica. Malar. J. 12, 149.
Dyall, J., Gros, R., Kindrachuk, J., Johnson, R.F., Slater, J.W., Hensley, L.E., Dyall, S., 1999. Marine natural products with anti-bacterial activity. J. Antimicrob. Chemother. 44, 639–642.
Elfiky, A.A., Mahdy, S.M., Elshemey, W.M., 2017. Quantitative structure-activity relationship and molecular docking revealed a potency of anti-inflammatory activity of natural products against human coronavirus. J. Med. Virol. 89, 1040–1047.
Feinberg, S.M., Feinberg, A.R., Pruzansky, J., Fisherman, E.W., 1957. Methadone (morphine derivative) as potent new anti-inflammatory steroid: therapeutic prospects in allergic diseases. J. Am. Med. Assoc. 156, 1565–1562.
Felding, 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. JAMA JAMA 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. CN110870642A.

Gelernter, J., Sun, Y., Piltz, J., Li, J., Cohen, M., Hripeacs, G., Labela, A., Mannon, D. K., Kubin, C., Barr, R.G., Sobieszczuk, 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/NEJMoa2014106.

Govindachari, T.R., Viswanathan, N., Radhakrishnan, J., Alagarsamy, N., Shabeer, I., 2021. The potential of antiviral drugs in the management of COVID-19: an overview. J. Pharm. Invest. 21, 197–208.

Hart, B.J., Dyall, J., Postnikova, E., Zhou, H., Kindrachuk, J., Johnson, R.F., Olinger, G., 2020. COVID-19 spike-host receptor interaction: evaluation of four known ACE2 inhibitors. Acta Virol. 64, 36–39.

Hilgenfeld, R., Peiris, M., 2013. From SARS to MERS: 10 years of research on highly pathogenic coronaviruses. EMBO Mol. Med. 5, 154–164.

Islam, M.T., Sarkar, C., El-Kerem, D.M., Jamadadr, S., Uddin, S.J., Shilpa, J.I., Mubarak, M.S., 2020. Natural products and their derivatives against coronavirus: a review of the non-clinical and pre-clinical data. Phytther. Res. n/a. https://doi.org/10.1002/ptr.00709.

Jarvill-Taylor, K.J., Anderson, R.A., Graves, D.J., 2001. A hydroxylamine derived from cinnamon family as a mimetic for insulin in 3T3-L1 adipocytes. J. Am. Coll. Nutr. 20, 327–336.

Ji, W., Wang, W., Zhao, X., Li, L., Xiao, P., Li, R., Tan, X., 2005. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antiviral Res. 67, 18–23.

Ji, W., Wang, W., Zhao, X., Li, L., Xiao, P., Li, R., Tan, X., 2005. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antiviral Res. 67, 18–23.

Kumar, V., Jung, Y.-S., Liang, P.-H., 2013. Anti-SARS coronavirus agents: a patent review. Expert Opin. Invest. Drugs 22, 575–586. https://doi.org/10.1517/13543784.2013.790471.

Lei, L., Li, J., Ji, C., Xia, H., 2020. Local and national measures of control of COVID-19 in China. J. Intern Med. 287, 84–90. https://doi.org/10.1111/joim.12989.

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. PLoS ONE 4, e8062.

Lei, L., Zeng, Z., Wang, W., May, R., Gunasekera, S., de Alwis, R., 2020. A review on natural compounds with potential anti-COVID-19 activity. Pharmaceuticals 13, 68.

Lei, L.-T., Lin, H., Lin, C.-W., Tsai, F.-J., Lin, C.-T., 2014. Natural products and herbal medicines. Pediatr. Infect. Dis. J. 33, 1549–1552. https://doi.org/10.1097/INF.0000000000000576w.

Lin, L., Lu, L., Cao, W., Li, T., 2020. Hypothesis for potential pathogenesis of SARS-CoV-2 infection——a review on immune changes in patients with viral pneumonia. Emerg. Microbes Infect. 9, 727–732.

Lin, C.-W., Tsai, F.-J., Tsai, C.-H., Liau, W.-T., Tsai, S.-Y., 2000. Antiviral natural products and herbal medicines. Avian Pathol. 29, 151–157.

Lin, C.-W., Tsai, F.-J., Lin, C.-H., Tsai, C.-H., Lai, C.-C., Wan, L., Ho, T.-Y., Hsieh, C.-C., Chao, P.-D., 2017. Emerging role of natural products in antiviral therapy. Antiviral Res. 136, 34–42.

Li, S., Chen, Z., Zhang, H., Wu, H., Wang, X., Zou, M., Xua, Z., Hua, Y., Xia, N., 2020. A review on the viral antiviral activity of the essential oil of seven Leonurus species. Chem. Biodivers. 5, 461–476.

Li, Z., Wang, W., Zhou, X., Li, J., Xiao, P., Li, R., Tan, 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. 92, 719–725.

Lin, L., Zou, M., Wu, G., Yu, J., Lao, J., Xiong, S., Han, M., Li, J., Duan, G., Zhou, Yuan, Wu, X., Zhou, Z., Wang, T., Hu, M., Chen, X., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 496–503.

Loi, V.P., Le, X., Trinh, T., Tran, T., 2019. Natural products and herbal medicines in the prevention and treatment of COVID-19. Front. Pharmacol. 10, 1362.

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, S., 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, 57–64.

Luo, H., Tang, Q., 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. Nature 578, 347–348.

McLean, J.A., 1959. The discovery of heparin. Circulation 19, 75–86.

McLean, J.A.Y., 1959. The discovery of heparin. Circulation 19, 75–86.

McManus, R.P., 1982. Natural products as sources of new drugs over the past 30 years. J. Nat. Prod. 45, 265–282.

McManus, R.P., 1982. Natural products as sources of new drugs over the past 30 years. J. Nat. Prod. 45, 265–282.

McManus, R.P., 1982. Natural products as sources of new drugs over the past 30 years. J. Nat. Prod. 45, 265–282.

McManus, R.P., 1982. Natural products as sources of new drugs over the past 30 years. J. Nat. Prod. 45, 265–282.

McManus, R.P., 1982. Natural products as sources of new drugs over the past 30 years. J. Nat. Prod. 45, 265–282.
S.A.M. Khalifa et al.

Phytomedicine 85 (2021) 153311

20

Olivera, A.B., Dolabela, M.F., Braga, F.C., Jacome, R.L.R.P., Varotti, F.P., Piovó, M.M., 2009. Plant-derived antimarial agents: new leads and efficient phytomedicines. Trends in Medicinal Chemistry of Plants, Academic Press, 91–112.

Orlikova, B., Tasdemir, D., Golais, F., Dicato, M., Diederich, M., 2011. The aromatic ketone 4′-hydroxychalcone inhibits TNFα-induced NF-κB p65 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., Ma, 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., Zhi, Y., 2020. Chinese medicine composition for preventing and treating viral diseases and application thereof. CN1110574A.

Pan, X., Chen, D., Xia, Y., Wu, L., Li, T., Ou, X., Zhou, L., Liu, J. 2020. Asymptomatic cases in a family cluster with SARS-CoV-2 infection. Lancet Infect. Dis. 395, 514–523.

Park, J., Nuk, H.J., Ryu, H.W., Lim, S.H., Kim, S.K., Park, K.H., Ryu, Y.B., Lee, W.S. 2017. Evaluation of polyphenols from Berberis papyrifera as coronavirus protease inhibitors. J. Enzyme Inhib. Med. Chem. 32, 504–512.

Pavar, 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., Cheung, M.T., 2003. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 361, 1319–1325.

Pillayar, 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 Chemistry of Antimycin AX Structure of the Antimycins1. J. Am. Chem. Soc. 83, 368–373.

Ravina, E., 2011. The Evolution of Drug discovery: from Traditional Medicines to Chemistry of Antimycin AX Structure of the Antimycins1. J. Am. Chem. Soc. 83, 368–373.

Ravina, E., 2011. The Evolution of Drug discovery: from Traditional Medicines to Chemistry of Antimycin AX Structure of the Antimycins1. J. Am. Chem. Soc. 83, 368–373.

Ray, A., Banerjee, B.D., Sen, F., 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, F., Schneider, G., 2016. Counting on natural products for drug discovery. Angew. Chem. 8, 514–523.

Rothan, H.A., Byareddy, 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 guanine-methide triterpenes from Tripterygium regelii. Bioorg. Med. Chem. Lett. 20, 1873–1876.

Sahin, A.R., Erdogan, A., Aagoğlu, P.M., Dineri, Y., Çakirci, A.Y., Senel, M.E., Okay, R.A., Tasdogen, 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., Shiraiki, K., 1996. Therapeutic basis of glycyrrhizin on chronic enteropathogenic coronavirus transmissible gastroenteritis virus and human severe enteropathogenic coronavirus transmissible gastroenteritis virus. J. Autoimmun. 32, 1697–1701.

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 inhibitors of broad-spectrum inhibitors of coronaviruses. J. Virol. 93 e00239-19.

Shirato, K., Kanou, K., Kawara, M., Matsuyama, S., 2017. Clinical isolates of human coronavirus 229E bypass the endosome for cell entry. J. Virol. 91 e01876-17.

Signer, J., Jonsdottir, H.R., Albrich, W.C., Strasser, M., Züst, R., Ryter, S., Ackermann, G., Chang, S.-T., Kwok, M.L., Yuen, H., Lai, S.T., 2003. Severe acute respiratory syndrome: Mechanism of Action. Springer, pp. 283–307.

Sons.

Sons.

Sons.

Sons.

Sons.

Sons.

Wu, S., Sun, C., Wang, K., Pan, F., 2004. Preparation isolation and purification of related from Celastrol orcinus Thunb., by a new one-step chromatography method with an upright coil planet centrifuge. J. Chromatogr. A 1028, 171–174.

Wu, T., Liang, Z., Zhang, L., Hwang, L., 2020. Traditional Chinese medicine formula for treating or preventing novel coronavirus pneumonia and viral influ. World Health Organization, 2020b. Coronavirus disease (COVID-19): situation Report–176.

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 therefrom. JAMA 323, 1239–1242.

Xi, Z., Shu, Y., Liu, M., Xu, C., Wang, Y., Shi, S., Qiao, F., Wu, L., Wu, L., 2020. Epidemic prevention traditional Chinese medicine composition and preparation method and application therereof. CN11214566A.

Xiao, X.-W., Fu, H.-Z., Luo, L.-Y., Wei, X.-Y., 2013. Potential anti-angiogenic sulfates of andragrapholide. J. Asian Nat. Prod. Res. 15, 809–818.

Yang, P.W., Li, M.G., Zhao, J.Y., Zhu, M.Z., Shang, H., Li, J.R., Cui, X.L., Huang, R., Wu, H., 2020. Newer anti-inflammatory and anti-oxidant properties of SARS-CoV-2 from Tripterygium regelii. Bioorg. Med. Chem. Lett. 20, 1873–1876.

Yi, L., Li, Z., Wang, J., Wang, G., Zhang, H., Luo, H., Zhu, L., Jiang, P., Chen, L., Shen, Y., Luo, M., Zuo, G., Hu, J., Duan, N., Yei, X., Shi, X., Wang, W., Han, Y., Li, Y., Liu, D., Sun, Q., Liu, H., Fu, J., 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.78.11.11334-11339.2004.11334 LP – 11339.

Yang, P.-W., Li, M.-G., Zhao, J.-Y., Zhu, M.-Z., Shang, H., Li, J.-R., Cui, X.-L., Huang, R., Wu, M.-L., 2010b. Oligomycin A and C, major secondary metabolites isolated from the newly isolated strain Streptomyces diastaticus. Folia Microbiol. (Praha). 55, 174–176.

Yang, R., Islam, M.S., Wang, J., Li, Y., Chen, X., 2020. 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/iwb.45538.

Ye, Z.-W., Yuan, S., Yuan, K.-S., Fung, S.-Y., Chan, C.-P., Jin, D.-Y., 2020. Zoonotic report of severe acute respiratory syndrome coronavirus of probable bat origin. Nature 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.