PHARMACEUTICAL BIOLOGY
2023, VOL. 61, NO. 1, 1186–1210
https://doi.org/10.1080/13880209.2023.2241518

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REVIEW ARTICLE

Recent advances towards natural plants as potential inhibitors of SARS-Cov-2 targets

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ABSTRACT

Context: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still ongoing and currently the most striking epidemic disease. With the rapid global spread of SARS-CoV-2 variants, new antivirals are urgently needed to avert a more serious crisis. Inhibitors from traditional medicines or natural plants have shown promising results to fight COVID-19 with different mechanisms of action.

Objectives: To provide comprehensive and promising approaches to the medical community in the fight against this epidemic by reviewing potential plant-derived anti-SARS-CoV-2 inhibitors.

Methods: Structural databases such as TCMSP (http://lsp.nwu.edu.cn/tcmsp.php), TCM Database @ Taiwan (http://tcm.cmu.edu.tw/), BATMAN-TCM (http://bionet.ncpsb.org/batman-tcm/) and TCMID (http://www.megabionet.org/tcmid/), as well as PubMed, Sci Finder, Research Gate, Science Direct, CNKI, Web of Science and Google Scholar were searched for relevant articles on TCMs and natural products against SARS-CoV-2.

Results: Seven traditional Chinese medicines formulas have unique advantages in regulating the immune system for treating COVID-19. The plant-derived natural compounds as anti-SARS-CoV-2 inhibitors were identified based on 5 SARS-CoV-2 key proteins, namely, angiotensin-converting enzyme 2 (ACE2), 3 C-like protease (3CLpro), papain-like protease (PLpro), spike (S) protein, and nucleocapsid (N) protein.

Conclusions: A variety of natural products, such as flavonoids, terpenoids, phenols, and alkaloids, were identified, which could be used as potential SASR-Cov-2 inhibitors. These shed new light on the efficient discovery of SASR-Cov-2 inhibitors from natural products.

ARTICLE HISTORY

Received 10 January 2023
Revised 29 May 2023
Accepted 23 July 2023

KEYWORDS

COVID-19; SARS-CoV-2; natural products; traditional chinese medicines; anti-SARS-CoV-2 strategies; phytochemicals

Introduction

At the end of 2019, the novel coronavirus outbreak caused the rapid spread of the epidemic worldwide, posed a substantial challenge to global public health, and devoured numerous lives (Hallowell et al. 2020). The variant of the SARS-CoV-2 virus emerging across the world, including the Alpha, Beta, Gamma, Delta, and Omicron variants, makes the problem more intractable (WTO 1948–2022). To combat the enduring threat of COVID-19, emerging therapeutic approaches have been developed and proposed, such as remdesivir, molnuopiravir, paxlovid, azvudine as well as vaccines (Zhang et al. 2021a; Gottlieb et al. 2022). Although the global distribution and administration of these approved vaccines and antiviral medications have provided a ray of hope in the fight against the pandemic, there have also been challenges regarding adverse reactions and drug resistance (Service 2022; Waters et al. 2022). In addition, the effectiveness of some antivirals is in dispute (Pan et al. 2021; Ader et al. 2022; Burki 2022).

Traditional Chinese medicines (TCMs) have a history of more than 2000 years in the prevention and treatment of epidemics and plagues (Wang and Qi 2020). In the SARS outbreak from 2002 to 2003, TCMs had been used to treat and prevent SARS (Lau et al. 2005). Evidence shows that gene sequences and pathogenic mechanisms are highly similar between SARS-CoV-2 and SARS-CoV (Kirtipal et al. 2020). Thus, the strategy that TCMs had been used in an attempt to combat SARS could be taken as a reference in today's COVID-19 epidemic. Numerous studies have reported that TCMs are remarkably effective in treating COVID-19 by alleviating SARS-CoV-2 pneumonia, reducing the levels of inflammatory cytokines, and protecting target organs from virus-induced damage (Leung et al. 2020). At the same time, further in-depth research on the mechanisms of TCMs has been constantly conducted.

Natural products, mainly plants, remain a rich source of novel therapeutic agents for the treatment of different human illnesses (Newman and Cragg 2020). Plant-derived active compounds often provide lead compounds for further drug discovery due to their special structures compared with synthetic small-molecule

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compounds. Chloroquine, the first small molecule approved by the Food and Drug Administration (FDA) to treat COVID-19, was inspired and developed from quinine, an old antimalarial agent isolated from the bark of *Cinchona officinalis* L. (Rubiaceae) because it shares the same quinoline core (Vandekerckhove and D'Hooghe 2015; Hoffmann et al. 2020). As natural products have been historically used in the treatment of respiratory infections, researchers have proposed to renew attention to natural products to treat COVID-19 (Rahman et al. 2022). The strategies applied to discover plant-derived natural products that inhibit SARS-CoV-2 are summarized including activity-guided fractionation, metabolomics, molecular docking (MD), network pharmacology, and machine learning approaches. We also focused on the latest research progress in targeting key steps in the SARS-CoV-2 replication cycle and the host immune system.

TCMs treatment strategies for COVID-19

In the eighth edition of the guidelines issued by the National Health Commission of China (NHC, 2020) for the Diagnosis and Treatment of COVID-19, the strategy of TCMs combined with antiviral medications and supportive therapy was adopted to treat patients with COVID-19. With these preventative and therapeutic effects, the cure rate of critically ill patients has increased significantly, therapy time has shortened, and the mortality rate has decreased significantly (Shi et al. 2020; Zhou et al. 2021; Zong et al. 2022).

Chinese medicines regimen plays a key role in all stages of the disease, from prevention to clinical treatment period (confirmed cases), including distinct disease stages of mild, moderate, severe, and critical (Huang et al. 2021). For example, a prospective randomized controlled trial showed a significant decrease in the risks of the common cold by herbal medicine therapy (Jinhaoartemisia antipyretic granules and Huoxiangzhengqi oral liquids) (Xiao et al. 2020). Suspected cases in the medical observation period with fatigue and gastrointestinal discomfort were administered Huxiangzhengqi capsules, and patients with fever and weakness were administered Lianhuaqingwen capsules. For critically ill patients with respiratory distress, TCMs decoctions containing *Rhabarbarum palmatum* L. (Polygonaceae), *Salvia miltiorrhiza* Bunge (Lamiaceae), *Astragalus mongholicus* Bunge (Fabaceae), *Lonicera japonica* Thunb. (Caprifoliaceae), and *Glycyrrhiza glabra* L. (Fabaceae), among other plant materials, were recommended (Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) 2020).

It is important to improve the effective utilization and application of natural products from Chinese medicine. Generally, activity-guided fractionation leads to the isolation of active pure compounds. Crude extracts can be fractionated into subfractions that are more suitable for high-performance liquid chromatography systems and analyzed by using nuclear magnetic resonance (NMR) spectrometry and liquid chromatography-high-resolution mass spectrometry. For example, Jimenez-Aleman et al. (2021) identified the antiviral metabolite as pheophorbide A (PheoA) from *Marchantia polymorpha* L. (Marchantiaceae) by using a bioactivity-guided chromatographic approach. These analytical approaches coupled with computational approaches generate natural product structures or spectral data. Various chemometric methods, such as principal component analysis, support vector machines, artificial neuronal networks and so on, correlate signals in NMR and MS data with the measured activity. These approaches might accelerate the identification of bioactive natural products. For example, Darwish et al. (2022) used UPLC-MS/MS coupled with chemometric analysis to detect chemical composition differences among different *Lantana camara* L. (Verbenaceae) (a widespread plant) cultivars extracts and correlated them to COVID-19 inhibitory activities allowing to determine possible biomarkers (Figure 1).

To greatly improve the efficiency of drug research and development from natural products, technologies in the field of computer-aided drug research, such as MD, and network pharmacology have become effective strategies to fight COVID-19 (Bharadwaj et al. 2021). Besides, the background of high-quality natural product databases and applicable biological analytical methods are also helpful in the analysis and prediction of the treatment effects of single or multiple combined small biological compounds (Zhang et al. 2021b). For example, potential antimalarial hits can be quickly and precisely found from new sets of natural products by using the random forest classifier, sequential minimization optimization, naïve Bayesian classifier and other algorithms (Egieyeh et al. 2018). Due to the complexity of natural product structures, models built for synthetic or drug-like compounds may not be suitable. Drug screening strategies and technologies above could contribute significantly to exploring multi-targeted agents against COVID-19 with cost-effective outcomes as well.

Potential natural products inhibitors targeting SARS-CoV-2

Chinese herbal medicine is rich in antiviral compounds, including flavonoids, polyphenols, terpenes, and alkaloids (Ti 2020). In the past 20 years, with the continuous development of antiviral drugs for SARS-CoV infection, several small molecules extracted from Chinese herbal medicines have been identified as possessing significant anti-CoV activities by some research groups. Recently, small-molecule compounds extracted from Chinese herbal medicines, such as epigallocatechin gallate (EGCG), quercetin, and kaempferol, were shown to exert potential anti-SARS-CoV-2 effects for suppressing the activity of 3CLpro *in vitro* and inhibiting the replication of intracellular viruses (Jang et al. 2020; Sun et al. 2020; Bilginer et al. 2022). In this section, the potential natural small-molecule compounds targeting SARS-CoV-2 are summarized (Figure 2).

Viral entry inhibitors

Four types of coronaviruses have been identified: α, β, γ, and δ. The α and β types infect humans, and SARS-CoV-2 is a β-coronavirus. SARS-CoV-2 is a positive-strand single-stranded RNA coronavirus with a 30 kb-long sequence (Yao et al. 2020). The genome of SARS-CoV-2 includes 14 open reading frames, of which two-thirds encode 16 nonstructural proteins (Nsps), and one-third encode 9 accessory proteins and 4 structural proteins (Harrison et al. 2020). S protein is a crucial structural protein located on the surface of the SARS-CoV-2 envelope and consists of the S1 subunit at the amino terminus (N-terminus) and the S2 subunit at the carboxyl terminus (C-terminus) (Wrappet al. 2020). The receptor binding domain (RBD) of the S1 subunit recognizes and binds to ACE2 to form an RBD-ACE2 complex and is then processed by the cellular protease transmembrane serine protease 2 (TMPRSS2) to enable the S protein to achieve viral infection (Hoffmann et al. 2020; Qiu et al. 2020; Wrapp et al. 2020). According to the above mechanisms, RBD is the primary binding site of current antiviral drugs and vaccines (Tai

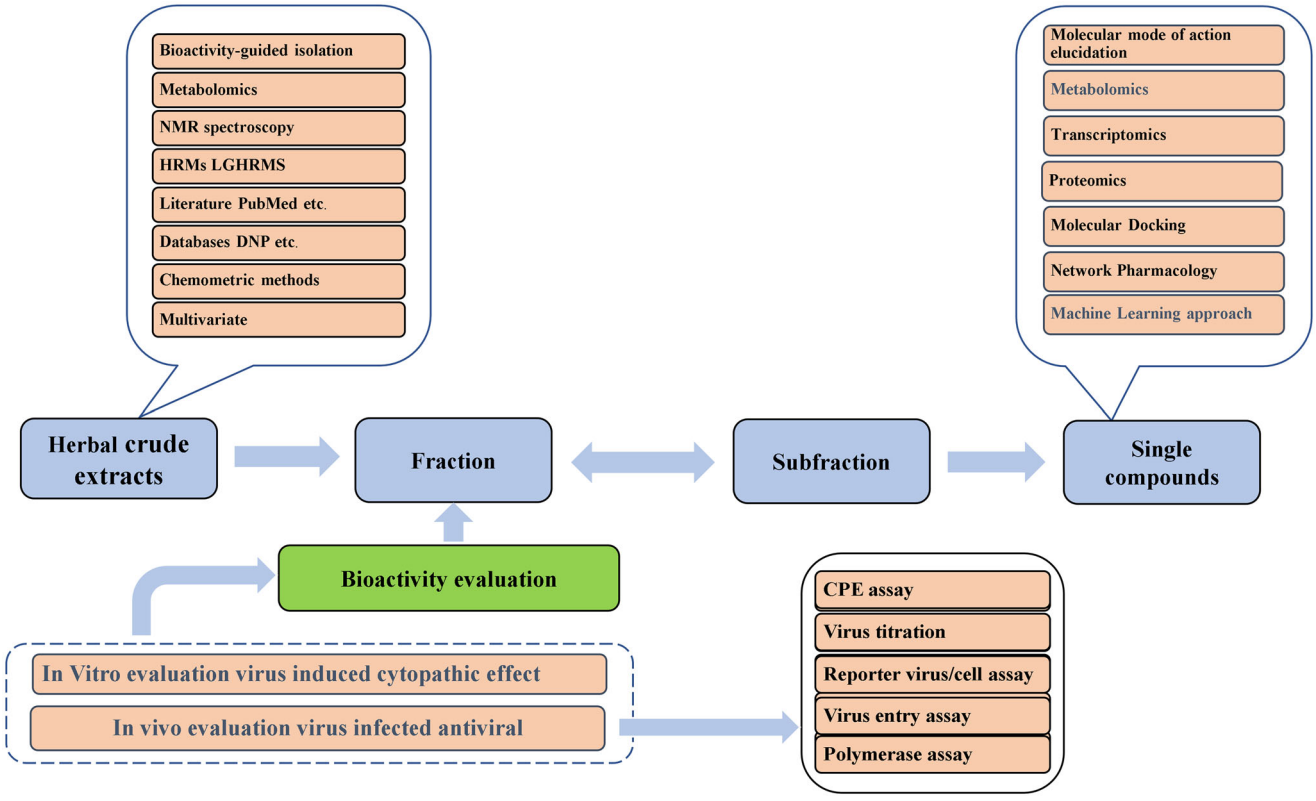


Figure 1. Identification outline of anti-SARS-CoV-2 inhibitors from plant natural products and TCMs (Bharadwaj et al. 2021).

et al. 2020). TMPRSS2 is attracting increasing attention and becoming an attractive therapeutic target for COVID-19 drug discovery (Shapira et al. 2022) (Table 1).

Polyphenols

Polyphenols, which are high in green tea, have a wide range of pharmacological activities, such as antioxidant, anti-tumor and antiviral effects (Xu et al. 2017). EGCG, the most active compound extracted from green tea, is reported to inhibit SARS-CoV-2 production in the cells (Park et al. 2021). *In vitro* experiment reveals that EGCG, with an inhibitory concentration (IC_{50}) of 1.72 μg/mL, blocks the binding and attachment of the S protein RBD to the ACE2 receptor, reducing the infection rate, inhibiting virus infections (Henss et al. 2021). However, by bioinformatics and MD experiments, the binding affinity of EGCG for the S protein was higher than that for the receptor ACE2, indicating that EGCG destroys the stability of the viral S protein to interfere with virus entry and reproduction in host cells (Maiti and Banerjee 2021).

Resveratrol, a naturally occurring polyphenol antioxidant, has attracted attention because of its anticancer, antiaging, and antibacterial properties (Wu SX et al. 2022). It is reported that resveratrol is an effective anti-coronavirus active ingredient *in vitro* with low toxicity, partly through upregulating of ACE2 to ward off SARS-CoV-2 infection and serious disease (Ramdani and Bachari 2020; Pasquereau et al. 2021; Yang et al. 2021).

Curcumin, one of the diketones extracted from *Curcuma longa* L. (Zingiberaceae), has been studied extensively. It was found to interfere with the attachment of SARS-CoV-2 virus particles to stressed cells by competing for the glucose-regulating protein 78, one of the binding sites of the S protein (Allam et al. 2020; Urošević et al. 2022).

Fisetin is a modified flavonol extracted from *Rhus succedanea* L. (Anacardiaceae). By using MD simulation, Pandey et al. (2021) concluded that fisetin and quercetin have similar binding energies and a higher binding affinity for the S2 domain, which may interfere with the interactions of the ACE2-S protein complex.

Flavonoids

Baicalein is the major active component of *Scutellaria baicalensis* Georgi (Lamiaceae), which has antiviral, antitumor, and antioxidative stress effects (Chen Y et al. 2021; Liu et al. 2021; Zandi et al. 2021). Song et al. (2021) investigated the effect of baicalein on 2019-nCoV by performing *in vitro* and *in vivo* experiments, respectively. In an *in vitro* cell-based experiment with baicalein at a concentration greater than or equal to 0.1 μmol/L, baicalein protected Vero E6 cells from damage induced by SARS-CoV-2 and directly killed SARS-CoV-2. The result of an *in vivo* experiment shows that baicalein alleviated the infiltration of inflammatory cells in lung tissues and respiratory function of SARS-CoV-2-infected mice, accompanied by decreased serum the cytokine interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) levels, and downregulated the level of serum inflammatory cytokines induced by sepsis in mice. In addition, TMPRSS2 enzyme might be inhibited by baicalein, which might be another mechanism of action by which baicalein exerts its anti-SARS-CoV-2 effect (Pooja et al. 2021).

Baicalin is another main bioactive component of *Scutellaria baicalensis*. It has a wide range of clinical applications because of its antiviral, anti-inflammatory and other pharmacological activities (An et al. 2022; Qin et al. 2022). Scutellarin is the major effective ingredient of *Erigeron breviscapus* (Vaniot) Hand.-Mazz. (Asteraceae), and has anti-inflammatory efficacy (Nie et al. 2018). Chen and Du (2000) used MD simulations to evaluate the

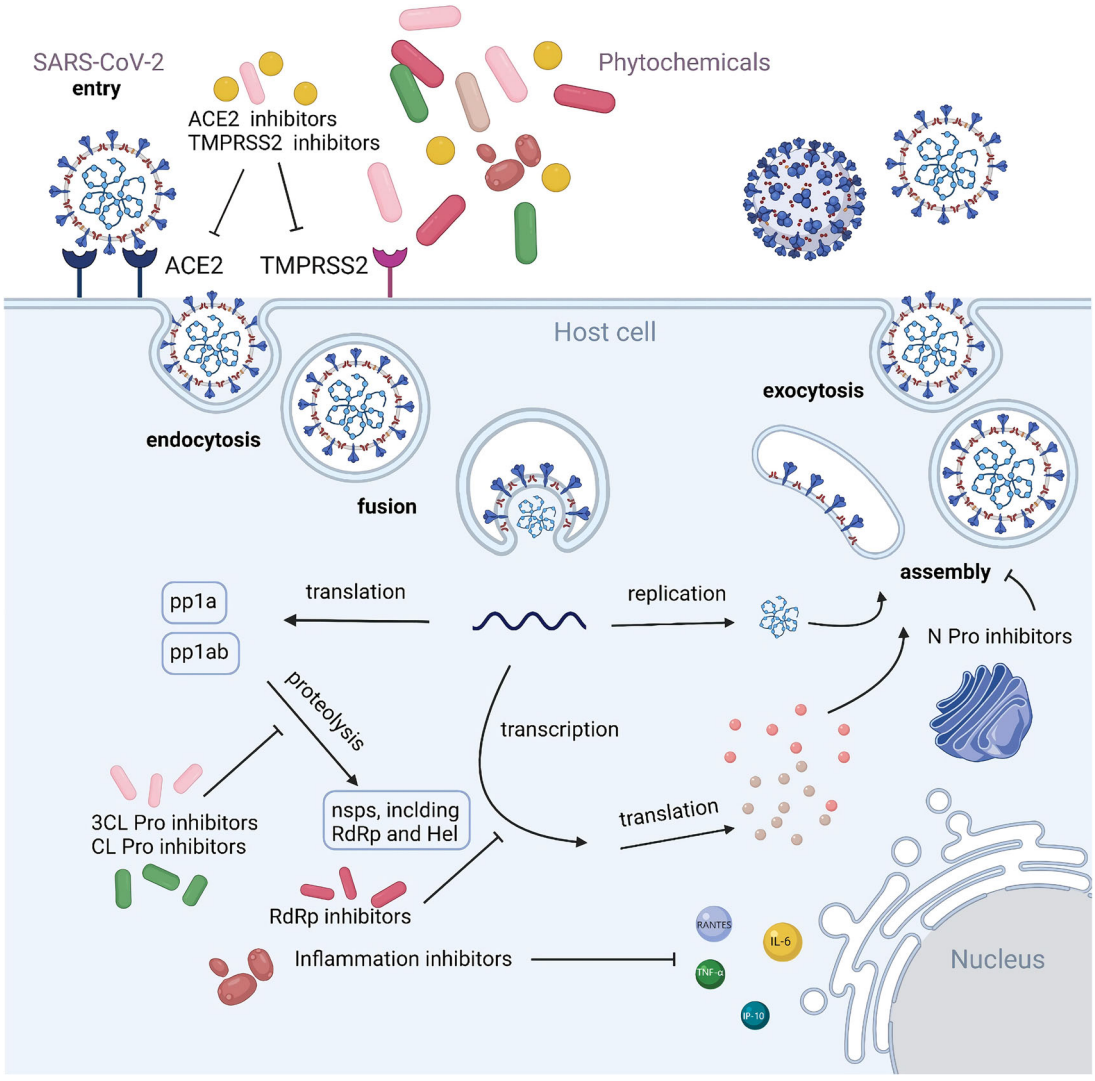


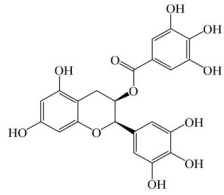
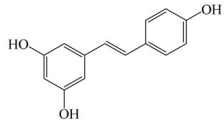
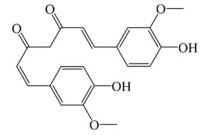
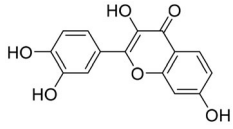
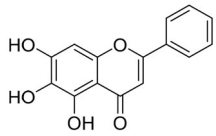
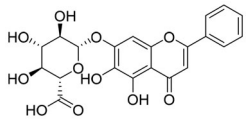
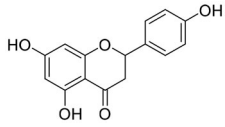
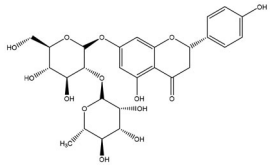
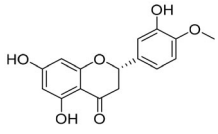
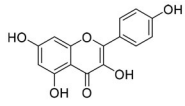
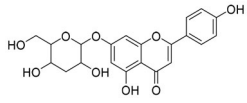
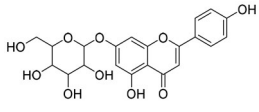
Figure 2. Schematic diagram of SARS-CoV-2 inhibitors from plant natural products and TCMs in relation to the viral replication cycle (Bilginer et al. 2022).

binding ability of baicalin and scutellarin with ACE2. The results revealed two molecules have good binding ability with the ACE2 enzyme.

Naringenin, naringin, and hesperetin are flavonoids in *Citrus* compounds, all of which have the potential to anti-SARS-CoV-2 through binding to the ACE2 enzyme (Liu et al. 2022b). Conducted by MD, naringenin is also a potential inhibitor of 3CLpro (Khaerunnisa et al. 2020). Naringin could inhibit the expression of the proinflammatory cytokines (cyclooxygenase-2, nitric oxide synthase, IL-1β and IL-6) *in vitro* induced by lipopolysaccharide (LPS), and has a strong binding affinity with the ACE2 by simulating MD (Liu et al. 2022b). Kaempferol, luteolin-7-glucoside, and apigenin-7-glucoside are potential main Protease (Mpro) inhibitors and have similar pharmacophores to nelfinavir, which was used to treat patients with new coronavirus-induced pneumonia (Khaerunnisa et al. 2020). Rutin is a natural antioxidant widely found in tea, apples, grapes, oranges, cherries and other plants (Rahman F et al. 2021). Rutin has antiviral activity on SARS-CoV-2 3CLPro and RNA-dependent RNA polymerase (RdRp) by docking analysis (da Silva et al. 2020). The residues of the SARS-CoV-2 protein substrate binding pocket and rutin are closely interactive, which helps to lock rutin in the substrate binding pocket and effectively inhibits the SARS-CoV-2 protein (Jain et al. 2021). Alagu Lakshmi et al. (2021) screened the active ligands of medicinal plants and found that orientin and vitexin have high binding affinities for the 3CLpro, the S protein of SARS-CoV-2 and human (h)ACE2. In their study, the binding energy of orientin with 3CLpro, S protein and hACE2 ranged from −90.2 to −70.6 kcal/mol. Vitexin is an apigenin flavonoid glycoside, and its docking scores for 3CLpro, S protein, and hACE2 ranged from −98.34 to −95.24 kcal/mol.

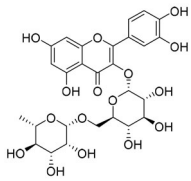
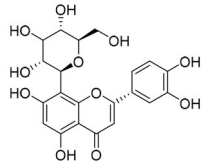
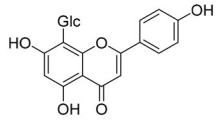
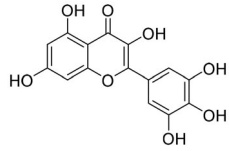
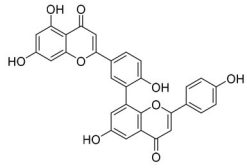
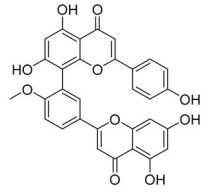
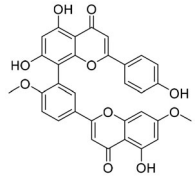
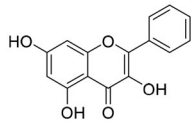
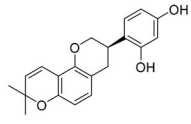
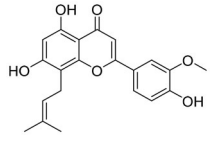
Myricetin is high in the Chinese speciality fruit bayberry, as well as *Isatis tinctoria* L. (Brassicaceae) and *Torreya grandis* Fortune ex Lindl. (Taxaceae). Myricetin has many pharmacological activities, such as antiviral and anti-inflammatory effects (Hou et al. 2018; Hu et al. 2022b). Research confirms that myricetin has a strong affinity for the 6 key residues of the active site of nonstructural protein 15 (Nsp15) and a low binding energy, thus forming a stable complex (Sharma et al. 2021). Amentoflavone, bilobetin, and ginkgetin are the biflavonoids in *Torreya grandis* screened by Ghosh et al. (2022). They all interacted with the two most important catalytic residues (His41 and Cys145) of Mpro without changing the conformation of Mpro after binding. Glabridin is one of the unique isoflavones in *Glycyrrhiza glabra* and has a wide range of biological activities. In terms of its binding mode, glabridin formed a strong noncovalent interaction with the main protease of SARS-CoV-2 (Islam et al. 2021). *In vitro*, Sberna et al. (2022) found that galangin,

Table 1. SARS-CoV-2 inhibitors targeting ACE2 and TMPRSS2.

Natural products	Category	Structure	References
Epigallocatechin gallate (EGCG)	Polyphenols		Henss et al. 2021; Park R et al. 2021; Maiti and Banerjee et al. 2021
Resveratrol	Polyphenols		Pasquereau et al. 2021; Ramdani and Bachari 2020; Wu SX et al. 2022; Yang et al. 2021
Curcumin	Polyphenols		Allam et al. 2020; Urošević et al. 2022
Fisetin	Polyphenols		Pandey et al. 2021
Baicalein	Flavonoids		Chen Y et al. 2021; Song et al. 2021 Pooja et al. 2021
Baicalin	Flavonoids		An et al. 2022; Qin et al. 2022; Nie et al. 2018; Chen and Du 2020
Naringenin	Flavonoids		Liu et al. 2022b
Naringin	Flavonoids		Liu et al. 2022b
Hesperetin	Flavonoids		Liu et al. 2022b
Kaempferol	Flavonoids		Bilginer et al. 2022; Khaerunnisa et al. 2020
Luteolin-7-glucoside	Flavonoids		Khaerunnisa et al. 2020
Apigenin-7-glucoside	Flavonoids		Khaerunnisa et al. 2020

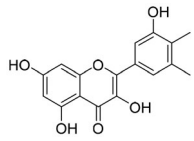
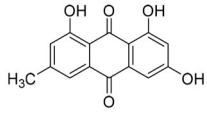
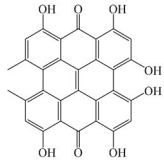
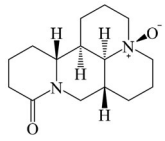
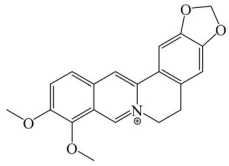
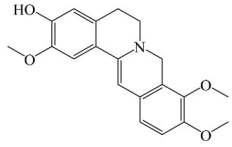
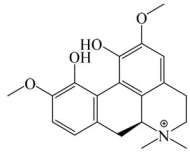
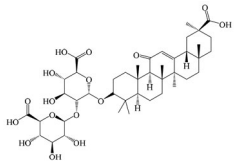
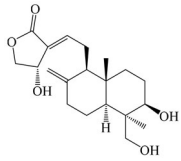
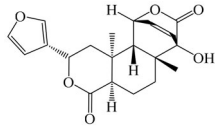
(*continued*)

Table 1. Continued.

Natural products	Category	Structure	References
Rutin	Flavonoids		da Silva et al. 2020; Jain et al. 2021; Rahman F et al. 2021
Orientin	Flavonoids		Alagu Lakshmi et al. 2021
Vitexin	Flavonoids		Alagu Lakshmi et al. 2021
Myricetin	Flavonoids		Hou et al. 2018; Hu et al. 2022b; Sharma et al. 2021
Amentoflavone	Flavonoids		Ghosh et al. 2022
Bilobetin	Flavonoids		Ghosh et al. 2022
Ginkgetin	Flavonoids		Ghosh et al. 2022
Galangin	Flavonoids		Sberna et al. 2022
Glabridin	Flavonoids		Islam et al. 2021
Caflanone	Flavonoids		Ngwa et al. 2020

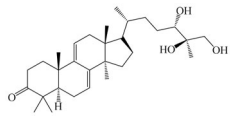
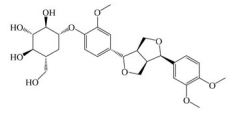
(*continued*)

Table 1. Continued.

Natural products	Category	Structure	References
Linebacker	Flavonoids		Ngwa et al. 2020
Emodin	Anthraquinones		Basu et al. 2020
Hypericin	Anthraquinones		Romeo et al. 2020
Oxosophoridine	Alkaloids		Cao et al. 2018; Jin SJ et al. 2017; Zhang YN et al. 2020
Berberine	Alkaloids		Narkhede et al. 2020; Pizzorno et al. 2020; Varghese et al. 2016
Jatrorrhizine	Alkaloids		Pooja et al. 2021
Magnoflorine	Alkaloids		Alagu Lakshmi et al. 2021
Glycyrrhizin	Terpenoids		Yu S et al. 2021; Chen R et al. 2020
Andrographolide	Terpenoids		Dai et al. 2019; Enmozhi et al. 2021; Maurya et al. 2020; Sa-Ngiamsuntorn et al. 2021
Columbin	Terpenoids		Pooja et al. 2021

(*continued*)

Table 1. Continued.

Natural products	Category	Structure	References
Ganodermanontriol	Terpenoids		Pooja et al. 2021
Phillyrin	lignans		Yu JW et al. 2020

one of the main constituents of propolis, with caffeic acid phenethyl ester and pinocembrin, have a remarkable ability to hinder the replication of SARS-CoV-2, and suggested that mechanism of the antiviral activity is probably the result of a synergistic effect, which encourages further investigations. Galangin displayed strong a binding energy with the ACE2 receptor protein and S protein of −7.60 and −7.89 kcal/mol, respectively. *In silico* studies show that caflanone and linebacker bind to the S protein, helicase and protease sites on the ACE2 receptor with high affinity to cause conformational changes, thereby inhibiting the invasion of coronavirus (Ngwa et al. 2020).

Anthraquinones

Other scientists through MD studies also found that emodin blocked the interaction between the S protein and ACE2, and 0.05 mM emodin produced an inhibition rate of 94.12%. Emodin noncompetitively binds to the host protein ACE2 and effectively inhibits the entry of SARS-CoV-2 into cells by destroying the stability of the S protein binding to the host ACE2 receptor (Basu et al. 2020).

Hypericin, a dianthrone extracted from *Hypericum perforatum* L. (Hypericaceae), induces strong antiviral and antitumor effects. Romeo et al. (2020) found that hypericin shows a high affinity for the heptad repeats 1 region of the S protein with a binding affinity of −13.7 kcal/mol.

Alkaloids

Alkaloids, nitrogen-containing basic organic compounds in plants, are classified into many categories with unique chemical structures and various biological activities, such as antiviral and anti-inflammatory activities (Ti et al. 2021). The antiviral activity includes anti-influenza virus, anti-Zika virus, etc (Wu Y et al. 2011; Quintana et al. 2020).

Oxosophoridine, extracted and separated from the leguminous plant *Sophora alopecuroides* L. (Leguminosae), has anti-inflammatory, antioxidative stress, antiapoptotic, and anticancer effects (Jin SJ et al. 2017; Cao et al. 2018). Zhang YN et al. (2020) researched the effects of lycorine and oxosophoridine in Vero E6 cells infected with SARS-CoV-2 and found that lycorine and oxosophoridine both inhibited the replication of the virus in Vero E6 cells with the effective concentration values of 0.3 μM and 0.18 μM, respectively. In addition, oxosophoridine might be a broad-spectrum antiviral molecule because it effectively inhibits the replication of flaviviruses and alphaviruses.

Berberine, an isoquinoline alkaloid extracted from *Coptis chinensis* Franch. (Ranunculaceae), has broad-spectrum antiviral activity, especially against yellow fever virus and alphavirus (Varghese et al. 2016). Pizzorno et al. (2020) evaluated the antiviral effect of berberine in Vero E6 cells infected with SARS-CoV-2, and its IC_{50} was 10.6 μM, showing a dose-dependent response. Varghese et al. (2021) proposed that berberine with good safety is suitable as a potential treatment for SARS-CoV-2. According to their experimental results, low concentrations of berberine inhibit SARS-CoV-2 replication in Vero E6 cells, possibly by altering the assembly of the virus and regulating the pathways required for virus infection, which are related to the later stages of the virus life cycle. Narkhede et al. (2020) found that berberine binds tightly to 3CLpro through MD, and its affinity is −8.1 kcal/mol, which may inhibit viral replication. Thus, further evaluations of berberine as a treatment for SARS-CoV-2 should be considered.

Jatrorrhizine is a tetrahydroisoquinoline alkaloid isolated from *Tinospora sagittata* (Oliv.) Gagnep. (Menispermaceae) and *Coptis chinensis* with anticancer, cholesterol-lowering, and antioxidant effects. Pooja et al. (2021) reported that good affinity of jatrorrhizine for the active site of TMPRSS2, with a binding energy of −7.5 kcal/mol. Magnoflorine is an important aporphine-type alkaloid in *Coptis chinensis*. Alagu Lakshmi et al. (2021) found that magnoflorine displayed a good binding to 3CLpro and S protein of SARS-CoV-2 and ACE2.

Cepharanthine, a naturally occurring alkaloid, has excellent antiviral effects on SARS-CoV-2 either *in silico* or *in vitro* (Zhang S et al. 2022). The result of MD indicated cepharanthine has a strong binding activity with ACE2 (−12.44 kcal/mol) and found it inhibits the entry phase in viral infection (Liu et al. 2022a). Hijikata et al. (2022) suggested diphenyl ester moiety of the molecules was the putative pharmacophore. It was thought to interfere with the ACE2-S-pro interaction. However, for now, whether it is expected to be a therapeutic agent for COVID-19 still needs more research.

Terpenoids

Terpenoids, a type of natural hydrocarbon, exist in plants widely, particularly in conifers. According to the number of isoprene units included in the molecule, these small molecules are divided into monoterpenes, sesquiterpenes, diterpenes, sesquiterpenes, triterpenes, tetraterpenes, and polyterpenes, which have antibacterial, anti-inflammatory, and insect repellent activities (Ludwiczuk and Asakawa 2019).

Glycyrrhizin, also known as glycyrrhizic acid, is a triterpenoid saponin compound that is mainly derived from *Glycyrrhiza uralensis* Fisch. ex DC. (Fabaceae), *G. glabra* (Fabaceae), and *G. inflata* Batalin (Fabaceae). In an *in vitro* study of the antiviral activities of glycyrrhizin, ginsenoside Ra2, ginsenoside Rb1, and ginsenoside Rb3, Yu S et al. (2021) found that both ginsenoside

Rb3 and glycyrrhizin blocked the interaction between the S protein RBD of SARS-CoV-2 and ACE2, but only glycyrrhizin inhibited this interaction at low concentrations (IC_{50} = 22 μmol/L). Ginsenoside Ra2, ginsenoside Rb3, and glycyrrhizin were not cytotoxicity to mouse aortic smooth muscle cells at high concentrations (100 μmol/L) but displayed lower cytotoxicity to normal human lung cells. High-affinity binding of the S1 subunit of SARS-CoV-2 (*in silico*) was observed for glycyrrhizin and the ligands ginsenoside Ra2, ginsenoside Rb1, and ginsenoside Rb3, which blocked the interaction between the S protein and ACE2 protein and can be used as potential anti-SARS-CoV-2 candidate drugs. High-mobility group box 1 (HMGB1), a nuclear protein involved in DNA replication, transcription, recombination, and repair, is an early marker of inflammation, playing a vital role in the occurrence and persistence of inflammation (Sims et al. 2010). Inhibition of the HMGB1-AGE pathway suppresses the expression of ACE2 during SARS-CoV-2 infection by studying the serum HMGB1 levels in COVID-19 patients. Therefore, HMGB1 can be studied as a therapeutic target (Chen R et al. 2020). Gowda et al. (2021) reported a significant effect of glycyrrhizin on alleviating increased inflammatory processes and inhibiting virus replication in Vero E6 cells. Glycyrrhizin exhibits low cytotoxicity and inhibits the upregulation of HMGB1 to block the interaction of SARS-CoV-2 S protein and ACE2, thereby preventing SARS-CoV-2 from entering cells. It not only inhibits the release of cytokines and ferritin from macrophages induced by SARS-CoV-2 but also the replication of SARS-CoV-2 in a dose-dependent manner.

Andrographolide, a natural antibiotic drug, is a diterpenoid lactone extracted from *Andrographis paniculata* (Burm.f.) Nees (Acanthaceae). It has been proven to possess anti-inflammatory, anticancer, antiobesity, and anti-diabetes activities (Dai et al. 2019). Sa-Ngiamsuntorn et al. (2021) found that the replication of SARS-CoV-2 in CALU-3 cells was inhibited by andrographolide in a dose-dependent manner, and the inhibitory activity of andrographolide was equivalent to that of the positive control remdesivir, with an IC_{50} of 0.034 μmol/L. Andrographolide might participate in inhibiting many stages of the virus life cycle, such as virus entry, RNA replication, and protein synthesis, with a particularly stronger interference effect on the later stage of the virus life cycle. After predicting the toxicity of andrographolide, Enmozhi et al. (2021) found that andrographolide was a safe molecule with no obvious adverse reactions and low toxicity. In addition, andrographolide also shows a significant affinity for the S protein, which might achieve an antiviral effect by restricting the entry of the virus into host cells (Maurya et al. 2020).

Columbin from *Tinospora cordifolia* (Willd.) Hook & Thomson (Menispermaceae) and ganodermanontriol from *Ganoderma lucidum* (Curtis) P. Karst (Ganodermataceae) bind tightly to the TMPRSS2 protein with binding energies of −8.1 and −8.2 kcal/mol. They may be able to prevent the virus from entering the host cells and become potential agents to prevent virus infection (Pooja et al. 2021).

Lignans

Phillyrin formed hydrogen bonds with Gln325/Glu329 of ACE2, while chlorogenic acid formed hydrogen bonds with Gln42/Asp38 (Yu JW et al. 2020). Their binding was stable, hindering the interaction of the RBD of the S protein and ACE2, which is related to SARS-CoV-2 infection of host cells.

Inhibitors of SARS-CoV-2 replication and transcription

When the SARS-CoV-2 genome enters the cell, open reading frames are translated into nonstructural proteins (Nsps), forming a replicase complex. Among them, Nsp5, the main protease produced by SARS-CoV-2, also known as 3CLpro or Mpro, participates in the cleavage of polyproteins 1a and 1ab and is currently used as a target in drug development to inhibit viral replication (Jin Z et al. 2020). Mpro of SARS-CoV-2 is active in viruses and important for replication. A covalent bond was formed by cysteine-targeting covalent inhibitors, and binding to Cys145 in Mpro potentially inhibits virus replication (Paul et al. 2022). Therefore, a cysteine-targeting ligand facilitates the design of an effective lead drug for COVID-19 treatment. The three distinct substrates of PLpro, namely the viral polyprotein, degradative Lys48-polyubiquitin, and antiviral ISG15 signals, all of which are crucial for inhibiting the virus and regulating the innate immune system. It was encouraging that high-throughput analyses uncovered that rac5c specifically inhibited SARS2 PLpro activity with an IC_{50} of 0.81 μM, suggesting that a PLpro inhibitor can target viral replication directly and efficiently (Klemm et al. 2020). Additionally, it has been found that tanshinones, which were isolated from *Salvia miltiorrhiza*, are specific and selective inhibitors for the SARS-CoV 3CLpro and PLpro (Park JY et al. 2012). Nsp12, which contains RdRp is a crucial protease for coronavirus replication and transcription and an important antiviral drug target (Wang MY et al. 2020) (Table 2).

3CLpro inhibitors

Polyphenols

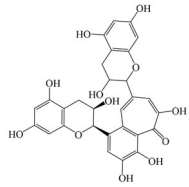
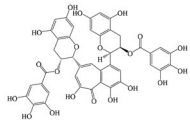
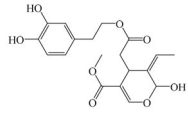
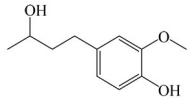
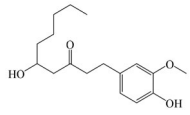
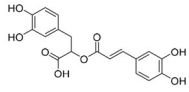
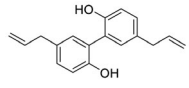
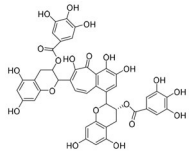
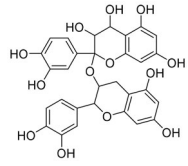
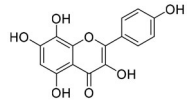
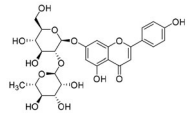
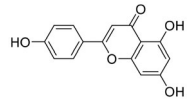
Jang et al. (2020) showed that EGCG and theaflavin significantly inhibit the protease activity of 3CLpro *in vitro* in a dose-dependent manner without significant cytotoxicity, with IC_{50} values of 7.58 μg/mL and 8.44 μg/mL, respectively. The inhibitory effect of EGCG was better than that of theaflavin. In addition, EGCE significantly reduced the level of viral RNA in coronavirus-infected cells and inhibited the replication of SARS-CoV-2 (Jang et al. 2021). According to the results of MD simulations, demethoxycurcumin, oleuropein, zingerol, and gingerol are potential inhibitors of 3CLpro, all of which form hydrogen bonds with the catalytic residues of 3CLpro (Bilginer et al. 2022). In addition, as predicted by the MD study, oleuropein inhibits SARS-CoV-2 Nsp15, reduces the virulence of SARS-CoV-2 Nsp15, and improves the immunity of the host (Khaerunnisa et al. 2020). Wu C et al. (2020). found that theaflavin 3,3'–di-*O*-gallate exhibits a high affinity for 3CLpro, which may affect the infection and replication of SARS-CoV-2, thus influencing the life cycle of the virus. In addition, anthocyanin derivatives might represent effective inhibitors of 3CLpro from SARS-CoV-2 (Fakhar et al. 2021).

Flavonoids

Flavonoids, found in a wide range of plants as secondary metabolites, have polyphenol structures. According to recent studies, many flavonoids resist COVID-19 and inhibit the proteolytic activity of SARS-CoV-2 3CLpro. Through virtual screening, Wu C et al. (2020) found that chrysin-7-*O*-glucuronide, hesperidin, cosmosiin and biorobin show high binding affinities for 3CLpro.

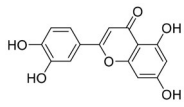
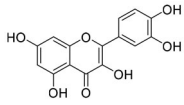
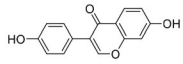
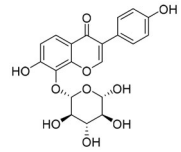
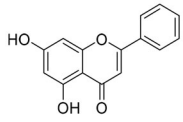
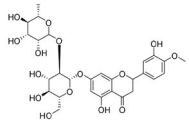
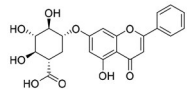
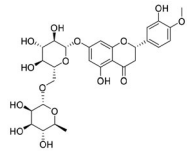
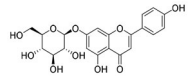
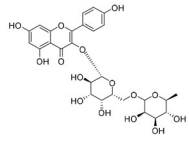
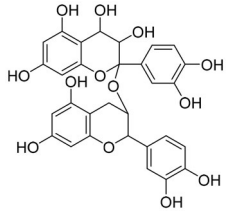
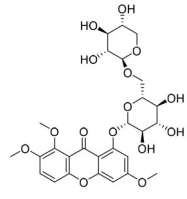
Researchers have reported that herbacetin, rhoifolin, apigenin, luteolin, quercetin, daidzein, puerarin, and kaempferol inhibit the proteolytic activity of SARS-CoV 3CLpro (Jo et al. 2020; Bilginer et al. 2022). Quercetin, a plant flavonoid, is widely

Table 2. SARS-CoV-2 inhibitors targeting viral transcription and replication.

Natural products	Category	Structure	References
Epigallocatechin gallate (EGCG)	Polyphenols	Table 1	Jang et al. 2020; Jang et al. 2021; Mhatre et al. 2021
Theaflavin	Polyphenols		Jang et al. 2020
Theaflavin digallate	Polyphenols		Mhatre et al. 2021
Oleuropein	Polyphenols		Bilginer et al. 2022; Khaerunnisa et al. 2020
Zingerol	Polyphenols		Bilginer et al. 2022
Gingerol	Polyphenols		Bilginer et al. 2022; Khaerunnisa et al. 2020; Rahman F et al. 2021
Rosmarinic acid	Polyphenols		Wu C et al. 2020
Magnolol	Polyphenols		Wu C et al. 2020
Theaflavin 3,3′-di-*O*-gallate	Polyphenols		Wu C et al. 2020
2-(3,4-dihydroxyphenyl)-2-[[2-(3,4-dihydroxyphenyl)-3,4-dihydro-5,7-dihydroxy-2H-1-benzopyran-3-yl]oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol	Polyphenols		Fakhar et al. 2021
Herbacetin	Flavonoids		Jo et al. 2020
Rhoifolin	Flavonoids		Jo et al. 2020
Apigenin	Flavonoids		Jo et al. 2020

(*continued*)

Table 2. Continued.

Natural products	Category	Structure	References
Luteolin	Flavonoids		Jo et al. 2020
Quercetin	Flavonoids		Abian et al. 2020; Bilginer et al. 2022; Khaerunnisa et al. 2020; Pandey et al. 2021; Zhang et al. 2020
Daidzein	Flavonoids		Jo et al. 2020
Puerarin	Flavonoids		Jo et al. 2020
Kaempferol	Flavonoids	Table 1	Bilginer et al. 2022; Jo et al. 2020
Chrysin	Flavonoids		Wu C et al. 2020
Neohesperidin	Flavonoids		Wu C et al. 2020
Chrysin-7-*O*-β-glucuronide	Flavonoids		Wu C et al. 2020
Hesperidin	Flavonoids		Wu C et al. 2020
Cosmosiin	Flavonoids		Wu C et al. 2020
Biorobin	Flavonoids		Wu C et al. 2020
2-(3,4-dihydroxyphenyl)-2-[[2-(3,4-dihydroxyphenyl)-3,4-dihydro-5,7-dihydroxy-2H-1-benzopyran-3-yl]oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol	Flavonoids		Wu C et al. 2020
1,2,6-trimethoxy-8-[(6-*O*-b-$_D$-xylopyranosyl-b-$_D$-glucopyranosyl)oxy]-9H-xanthen-9-one	Flavonoids		Wu C et al. 2020

(*continued*)

Table 2. Continued.

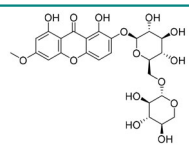
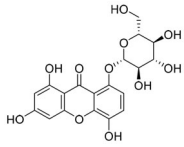
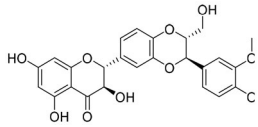
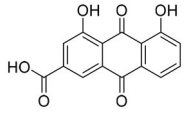
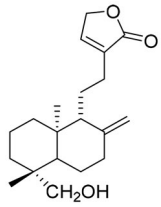
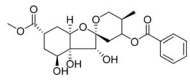
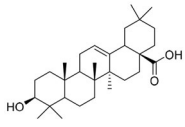
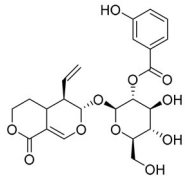
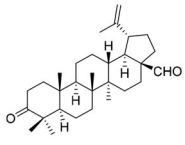
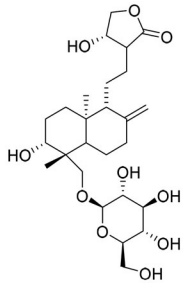
Natural products	Category	Structure	References
1,8-dihydroxy-6-methoxy-2-[(6-*O*-β-$_D$-xylopyranosyl-β-$_D$-glucopyranosyl)oxy]-9H-xanthen-9-one	Flavonoids		Wu C et al. 2020
8-(β-$_D$-glucopyranosyloxy)-1,3,5-trihydroxy-9H-xanthen-9-one (bellidin 8-*O*-β-glucopyranoside)	Flavonoids		Wu C et al. 2020
Silybin	Flavonoids		Bosch-Barrera et al. 2020
Hypericin	Anthraquinones	Table 1	Islam et al. 2021; Pitsillou et al. 2020
Rhein	Anthraquinones		Narkhede et al. 2020
Andrograpanin	Terpenoids		Wu C et al. 2020
Glycyrrhizin	Terpenoids	Table 1	Gowda et al. 2021; Yu S et al. 2021
Andrographolide	Terpenoids	Table 1	Enmozhi et al. 2021; Maurya et al. 2020; Sa-Ngiamsuntorn et al. 2021
Phyllaemblinol	Terpenoids		Wu C et al. 2020
Oleanolic acid	Terpenoids		Wu C et al. 2020
Deacetylcentapicrin	Terpenoids		Wu C et al. 2020
Betulonal	Terpenoids		Wu C et al. 2020
Andrographiside	Terpenoids		Wu C et al. 2020

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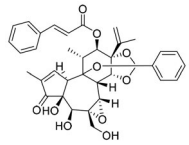
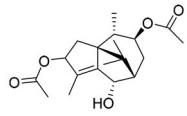
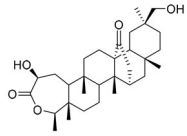
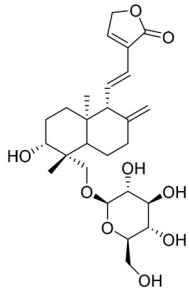
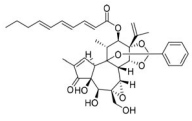
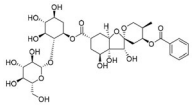
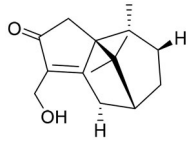
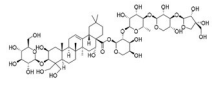
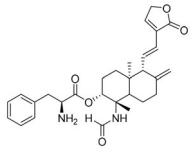
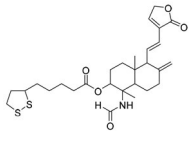
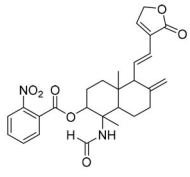
Table 2. Continued.

Natural products	Category	Structure	References
Gnidicin	Terpenoids		Wu C et al. 2020
Sugetriol-3,9-diacetate	Terpenoids		Wu C et al. 2020
2β,30β-dihydroxy-3,4-seco-friedelolactone-27-lactone	Terpenoids		Wu C et al. 2020
14-deoxy-11,12-didehydroandrographolide	Terpenoids		Wu C et al. 2020
Gniditrin	Terpenoids		Wu C et al. 2020
Phyllaemblicin B	Terpenoids		Wu C et al. 2020
14-Hydroxycyperotundone	Terpenoids		Wu C et al. 2020
Platycodin D	Terpenoids		Wu C et al. 2020
(S)-(1S,2R,4aS,5R,8aS)-1-formamido-1,4a-dimethyl-6-methylene-5-([E]-2-[2-oxo-2,5-dihydrofuran3yl]ethenyl)decahydronaphthalene-2-yl-2-amino-3-phenylpropanoate	Terpenoids		Wu C et al. 2020
(1S,2R,4aS,5R,8aS)-1-formamido-1,4a-dimethyl-6-methylene-5-([E]-2-[2-oxo-2,5-dihydrofuran-3-yl]ethenyl)decahydronaphthalen-2-yl 5-([R]-1,2-dithiolan-3-yl)pentanoate	Terpenoids		Wu C et al. 2020
(1S,2R,4aS,5R,8aS)-1-formamido-1,4a-dimethyl-6-methylene-5-([E]-2-[2-oxo-2,5-dihydrofuran-3-yl]ethenyl)decahydronaphthalen-2-yl 2-nitrobenzoate	Terpenoids		Wu C et al. 2020

(*continued*)

Table 2. Continued.

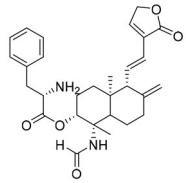
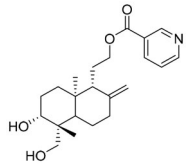
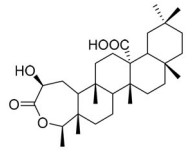
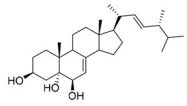
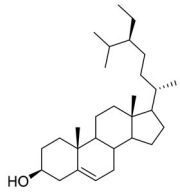
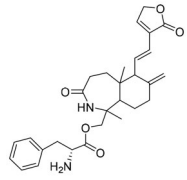
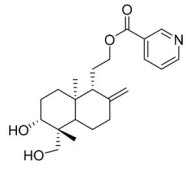
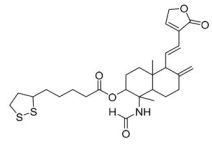
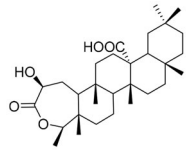
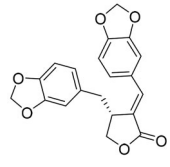
Natural products	Category	Structure	References
(S)-(1S,2R,4aS,5R,8aS)-1-formamido-1,4a-dimethyl-6-methylene-5-([E]-2-[2-oxo-2,5-dihydrofuran-3-yl]ethenyl) decahydronaphthalen-2-yl-2-amino-3-phenylpropanoate	Terpenoids		Wu C et al. 2020
2-([1R,5R,6R,8As]-6-hydroxy-5-[hydroxymethyl]-5,8a-dimethyl-2-methylenedecahydronaphthalen-1-yl)ethyl benzoate	Terpenoids		Wu C et al. 2020
2b-Hydroxy-3,4-seco-friedelolactone-27-oic acid	Terpenoids		Wu C et al. 2020
Cerevisterol	Terpenoids		Wu C et al. 2020
Stigmast-5-en-3-ol (sitosterol)	Terpenoids		Wu C et al. 2020
(R)-([1R,5aS,6R,9aS]-1,5a-dimethyl-7-methylene-3-oxo-6-([E]-2-[2-oxo-2,5-dihydrofuran-3-yl]ethenyl)decahydro-1H-benzo[c]azepin-1-yl)methyl 2-amino-3-phenylpropanoate	Terpenoids		Wu C et al. 2020
2-([1R,5R,6R,8aS]-6-hydroxy-5-[hydroxymethyl]-5,8a-dimethyl-2-methylenedecahydronaphthalen-1-yl)ethyl benzoate	Terpenoids		Wu C et al. 2020
(1S,2R,4aS,5R,8aS)-1-formamido-1,4a-dimethyl-6-methylene-5-([E]-2-[2-oxo-2,5-dihydrofuran-3-yl]ethenyl)decahydronaphthalen-2-yl 5-([R]-1,2-dithiolan-3-yl)pentanoate	Terpenoids		Wu C et al. 2020
2β,-hydroxy-3,4-seco-friedelolactone-27-oic acid	Terpenoids		Wu C et al. 2020
Savinin	Lignans		Sureja et al. 2022; Wu C et al. 2020

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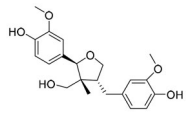
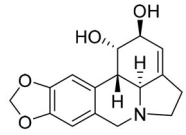
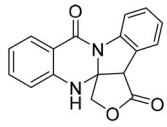
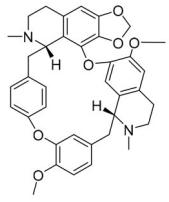
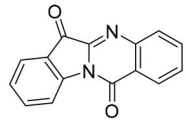
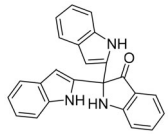
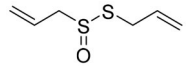
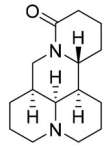
Table 2. Continued.

Natural products	Category	Structure	References
Berchemol	Lignans		Wu C et al. 2020
Lycorine	Alkaloids		Jin YH et al. 2021; Ngwa et al. 2020
Phaitanthrin D	Alkaloids		Wu C et al. 2020
Cepharanthine	Alkaloids		Hijikata et al. 2022; Liu et al. 2022a; Zhang S et al. 2022
Tryptanthrine	Alkaloids		Pitsillou et al. 2020
2,2-di(3-indolyl)-3-indolone	Alkaloids		Wu C et al. 2020
Allicin	Sulfur-containing natural products		Khaerunnisa et al. 2020
Matrine	Alkaloid		Hu et al. 2022a; Peng W et al. 2023; Yang MW et al. 2020

distributed in vegetables, seeds, leaves, and other plant tissues. Quercetin may be an effective inhibitor of SARS-CoV-2 3CLpro based on MD study (Khaerunnisa et al. 2020). Abian et al. (2020) confirmed quercetin as a stronger SARS-CoV-2 3CLpro inhibitor and assumed that quercetin was a competitive inhibitor for the same active site as 3CLpro. The experimental data showed that its Ki value is 7.4 μmol/L, which is similar to that of the first discovered SARS-CoV-2 3CLpro inhibitor. Based on the thermal shift assay, quercetin also dose-dependently alters the thermal stability of 3CLpro, rendering 3CLpro unstable. Moreover, the interaction of quercetin and 3CLpro reduces the activity of 3CLpro. Quercetin was identified as the top ligand of the S protein, and its molecular model binds to the host-receptor binding domain or interface of the S protein-hACE2 receptor. The complex of the S protein-hACE2 receptor has low binding energy (Pandey et al. 2021). Both of the abovementioned factors might restrict the virus from entering into host cells and/or interfere with host-virus interactions. Quercetin might serve as a suitable scaffold for designing new functional groups and developing new SARS-CoV-2 3CLpro inhibitors, and it might become an extremely promising antiviral small molecule.

Anthraquinones

Islam et al. (2021) reported that hypericin has a high binding affinity for SARS-CoV-2 3CLpro with a binding affinity of −10.7 kcal/mol, forming a strong noncovalent interaction with 3CLpro residues. Rhein is an anthraquinone compound with anti-influenza and antiviral activities. Narkhede et al. (2020) found that rhein binds tightly to SARS-CoV-2 3CLpro with a binding affinity of −8.9 kcal/mol. Rhein might treat COVID-19 by inhibiting virus replication.

Terpenoids

Gingerol, the main spicy component of ginger, can be used as a medicinal food derivative (Rahman F et al. 2021). It also contains

similar pharmacophores as nelfinavir and might bind to 3CLpro, based on MD (Khaerunnisa et al. 2020). By performing a virtual screen for phytochemicals, Wu C et al. (2020) proposed that in-house natural products might serve as potential 3CLpro inhibitors. For example, andrograpanin, phyllaemblinol, oleanolic acid, deacetylcentapicrin, betulonal, andrographiside, gnidicin, platycodin D, (S)-(1S,2R,4aS,5R,8aS)-1-formamido-(1S,2R,4aS,5R,8aS)-1-formamido-1,4a-dimethyl-6-methylene-5-([E]-2-[2-oxo-2,5-dihydrofuran-3-yl]ethenyl) decahydronaphthalen-2-yl 5-([R]-1,2-dithiolan-3-yl) pentanoate, (1S,2R,4aS,5R,8aS)-1-formamido-1,4a-dimethyl-6-methylene-5-([E]-2-[2-oxo-2,5-dihydrofuran-3-yl]ethenyl) decahydronaphthalen-2-yl 2-nitrobenzoate, (S)-(1S,2R,4aS,5R,8aS)-1-formamido-1,4a-dimethyl-6-methylene-5-([E]-2-[2-oxo-2,5-dihydrofuran-3-yl]ethenyl) decahydronaphthalen-2-yl-2-amino-3-phenylpropanoate, 2-([1R,5R,6R,8aS]-6-hydroxy-5-[hydroxymethyl]-5,8a-dimethyl-2-methylenedecahydronaphthalen-1-yl)ethyl benzoate, 2β-hydroxy-3,4-seco-friedelolactone-27-oic acid, cerevisterol, kouitchenside I, and stigmast-5-en-3-ol (sitosterol) might have high binding affinities for 3CLpro. These natural small-molecule compounds may be potential therapeutic candidates for SARS-CoV-2.

Lignans

Savinin, a lignan from *Pterocarpus santalinus* L. (Fabaceae), possesses potent antiviral activities against SARS-Cov-2 *via* inhibition of 3CLpro. By virtual screen of natural small molecules, it has been found berchemol from *Swertia bimaculata* (Siebold & Zucc.) Hook. & Thomson ex C.B.Clarke (Gentianaceae) exhibits high affinity for 3CLpro (Wu C et al. 2020).

Alkaloids

Tryptanthrine is an indole quinoline alkaloid with anti-inflammatory, antitumor, and antibacterial effects. In terms of the interaction mode of tryptanthrine, tryptanthrine formed hydrogen bonds with SARS-CoV-2 3CLpro (Pitsillou et al. 2020). Wu C et al. (2020) conducted a virtual screen of natural small molecules and found that a series of them have good binding affinities for 3CLpro, such as 2,2-di(3-indolyl)-3-indolon.

Sulfur-containing natural products

Some researchers screened small-molecule compounds from plants and found that many natural small-molecule compounds interact tightly with the key proteins of the virus and play an important role in blocking the invasion and replication of the virus.

Garlic or *Allium sativum* L. (Amaryllidaceae) is rich in several sulfur-containing phytoconstituents such as alliin, allicin, ajoenes, etc. It has been reported garlic extracts, containing phytochemicals such as ajoene and allicin, exhibited protective activity against influenza viruses in mice (Sawai et al. 2008). Moreover, it was predicted to inhibit SARS-CoV-2 6LU7 3CLpro by an MD study (Khaerunnisa et al. 2020).

PLpro inhibitors

Polyphenols

Wu C et al. (2020) conducted a virtual screen of natural small molecules and found that rosmarinic acid from *Salvia verticillata* L. (Lamiaceae), magnolol from *Magnolia officinalis* Rehder & E.H.Wilson (Magnoliaceae), 2-(3,4-dihydroxyphenyl)-2-[[2-(3,4-dihydroxyphenyl)-3,4-dihydro-5,7-dihydroxy-2H-1-benzopyran-3-yl]oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol and piceatannol from *Vitis vinifera* L. (Vitaceae) all show high binding affinities for PLpro.

Flavonoids

Computer-based research indicated that chrysin, savinin, and neohesperidin have high binding affinities for PLpro, in which the docking score of savinin is superior to that of remdesivir (Sureja et al. 2022; Wu C et al. 2020).

Anthraquinones

Pitsillou et al. (2020) found that hypericin forms a π-π interaction with Y268 of PLpro and inhibits the activity of the deubiquitinating enzyme. Therefore, hypericin might inhibit SARS-CoV-2 by inhibiting PLpro.

Terpenoids

Wu C et al. (2020) conducted a virtual screen of natural small molecules and found that a series of them display good binding affinities for PLpro, such as sugetriol-3,9-diacetate and 1,4a-dimethyl-6-methylene-5-([E]-2-[2-oxo-2,5-dihydrofuran3yl]ethenyl) decahydronaphthalene-2-yl-2-amino-3-phenylpropanoate.

Alkaloids

By performing MD, Wu C et al. (2020) found that phaitanthrin D, a 2,2-di(3-indolyl)-3-indolone, has a strong binding affinity for PLpro and thus may have potential inhibitory activity.

RdRp inhibitors

Polyphenols

In MD experiments, Mhatre et al. (2021) found that EGCG binds tightly to 3CLpro, PLpro, RdRp, spike RBD, and RBD-ACE2 of SARS-CoV-2. Compared with the RdRp inhibitors remdesivir and favipiravir, EGCG and theaflavin digallate have higher binding affinities for RdRp than remdesivir and favipiravir.

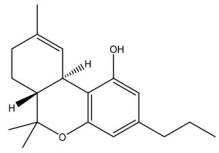
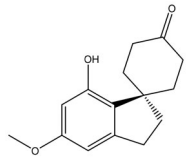
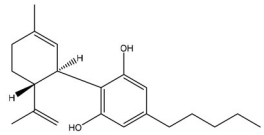
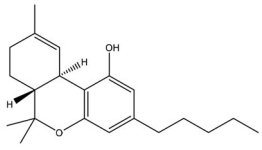
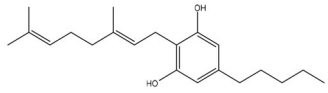
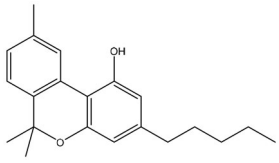
Flavonoids

Wu C et al. (2020) conducted a virtual screen of natural small molecules and found that a series of them have good binding affinity for RdRp. For example, 2-(3,4-dihydroxyphenyl)-2-[[2-(3,4-dihydroxyphenyl)-3,4-dihydro-5,7-dihydroxy-2*H*-1-benzopyran-3-yl]oxy]-3,4-dihydro-2*H*-1-benzopyran-3,4,5,7-tetrol from *Vitis vinifera* and 1,7-dihydroxy-3-methoxyxanthone (gentisin), 1,2,6-trimethoxy-8-[(6-*O*-b-D-xylopyranosyl-b-D-glucopyranosyl)oxy]-9H-xanthen-9-one, 1,8-dihydroxy-6-methoxy-2-[(6-*O*-β-D-xylopyranosyl-β-D-glucopyranosyl)oxy]-9H-xanthen-9-glucopyrone, and 8-(β-D-glucopyranosyloxy)-1,3,5-trihydroxy-9H-xanthen-9-one (bellidin 8-*O*-β-glucopyranoside) from *Swertia mussotii* Franch. (Gentianaceae) all exhibited high affinities for RdRp. SARS-CoV-2 RdRp assay data and *in silico* study showed that baicalein is a potent inhibitor of SARS-CoV-2 RdRp, making it a potential candidate against COVID-19 (Zandi et al. 2021).

Terpenoids

Wu C et al. (2020) found that betulonal, andrographiside, gnidicin, sugetriol-3,9-diacetate, 2β,30β-dihydroxy-3,4-seco-

Table 3. SARS-CoV-2 inhibitors targeting assembly and release.

Natural products	Category	Structure	References
Tetrahydrocannabivarin	Terpenoids		Erukainure et al. 2021
Cannabispiran			Erukainure et al. 2021
Cannabidiol			Erukainure et al. 2021
Tetrahydrocannabinol			Erukainure et al. 2021
Cannabigerol			Erukainure et al. 2021
Cannabinol			Erukainure et al. 2021

friedelolactone-27-lactone, gniditrin, phyllaemblicin B, 14-deoxy-11,12-didehydroandrographolide, 14-hydroxycyperotundone, (R)-([1R,5aS,6R,9aS]-1,5a-dimethyl-7-methylene-3-oxo-6-([E]-2-[2-oxo-2,5-dihydrofuran-3-yl]ethenyl) decahydro-1H-benzo[c]azepin-1-yl) methyl 2-amino-3-phenylpropanoate, 2-([1R,5R,6R,8As]-6-hydroxy-5-[hydroxymethyl]-5,8a-dimethyl-2-methylenedecahydronaphthalen-1-yl)ethyl benzoate, (1S,2R,4aS,5R,8aS)-1-formamido-1,4a-dimethyl-6-methylene-5-([E]-2-[2-oxo-2,5-dihydrofuran-3-yl]ethenyl) decahydronaphthalen-2-yl 5-([R]-1,2-dithiolan-3-yl) pentanoate, and 2β-hydroxy-3,4-seco-friedelolactone-27-oic acid may be potential RdRp inhibitors.

Alkaloids

Lycorine is an active alkaloid present in Amaryllidaceae plants and is considered to be a potential therapeutic agent for COVID-19. The MD and subsequent study *in vitro* both suggest that the anti-infection activity of lycorine is equivalent to that of remdesivir, and IC_{50} of lycorine in SARS-CoV-2-infected Vero cells was 0.878 ± 0.022 mM (Jin YH et al. 2021). Lycorine inhibits SARS-CoV-2 by inhibiting viral RdRp activity (Ngwa et al. 2020).

Assembly and release inhibitors against SARS-CoV-2

The N protein is an important and highly conserved component of SARS-COV-2 and plays critical roles in SARS-CoV-2 genome transcription and packaging, thus, N proteins may be designed to develop as inhibitors of SARS-CoV-2 (Peng Y et al. 2020). There have been reported some potential compounds targeting viral assembly and release. Erukainure et al. (2021) studied the phytochemical constituents of *Cannabis sativa* L. (Cannabaceae). Through MD, it was found that cannabinol, tetrahydrocannabivarin, tetrahydrocannabinol, cannabispiran, cannabidiol, and cannabigerol have binding affinities ranging from −40.78 to $-36.21\ kcal^{-1}$ for the nucleocapsid phosphoprotein translation initiation site and nucleocapsid phosphoprotein translation termination site. Despite this finding, limited reports are available on the N protein, emphasizing the need for researchers to update their understanding of it (Table 3).

Potential immunoregulators of SARS-CoV-2

The innate immune system is the first line of defence against viral infections (Diamond and Kanneganti 2022). Viruses activate innate immune cells by engaging any one of several intracellular pattern recognition receptors (PRRs). Following PRRs activation, molecular signaling cascades culminate in the activation of downstream transcription factors, such as interferon regulatory factors and nuclear factor-κB (NF-κB). These transcription factors trigger the initial cellular antiviral defenses by inducing the transcriptional activation of type I and III interferons and interferon-stimulated genes, as well as cytokines and chemokines

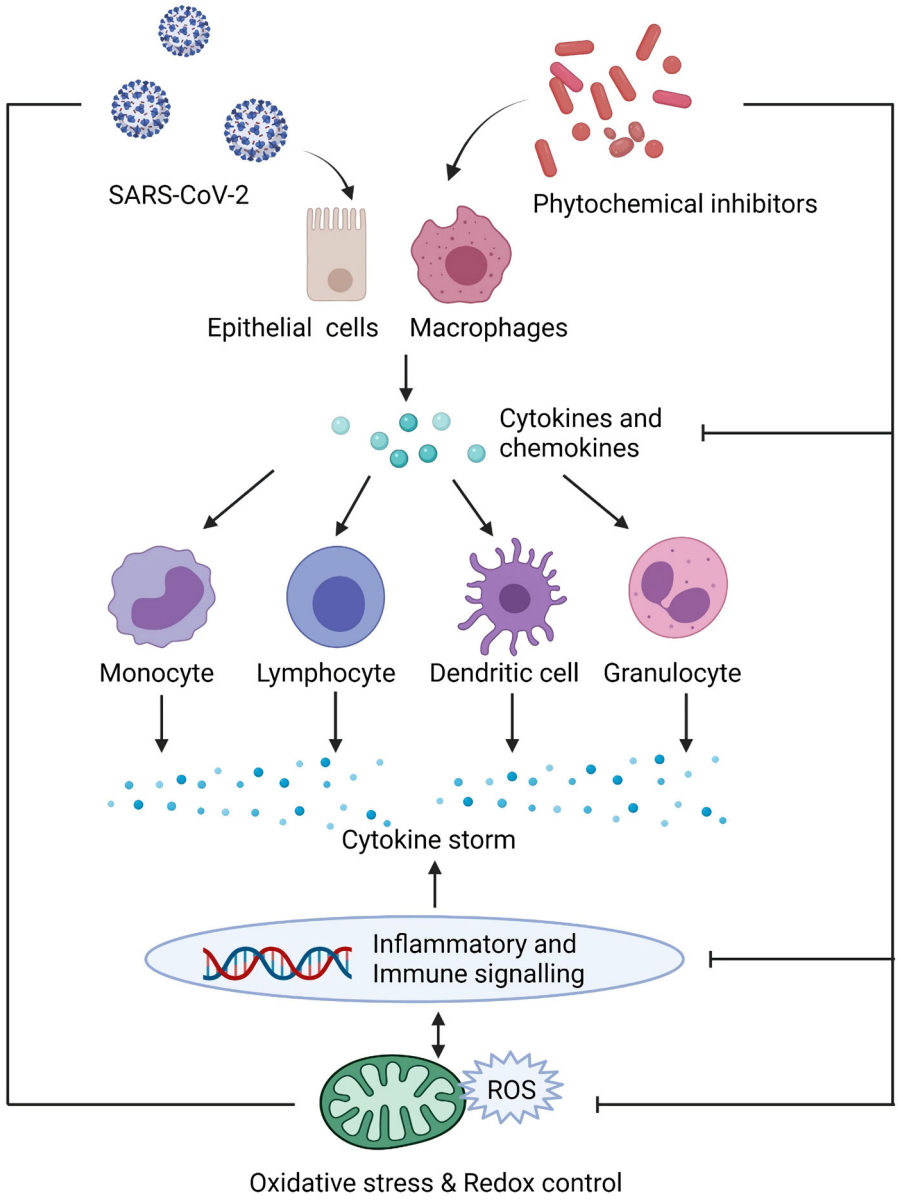


Figure 3. Schematic presentation of anti-SARS-CoV-2 mechanisms from plant natural products and TCMs *via* proinflammatory regulation (Bosch-Barrera et al. 2020).

(Wüst et al. 2021). Acute release of large amounts of cytokines, which is called a 'cytokine storm', has been observed in patients with COVID-19. Cytokine storm plays a pivotal role in the pathophysiology of severe 2019-nCoV-infected patients (Wright 2021). Plant-derived natural products and TCMs may act on the host immune system to generate a holistic effect, regulating the immune system, and suppressing inflammation (Figure 3). In this section, representative natural products with immunoregulatory effects are discussed, including silybin, matrine, curcumin, and phillyrin (Table 4). TCMs may play a regulatory role in the causes, processes, and other aspects of the cytokine storm by modulating the release of cytokines; the functions of macrophages, monocytes, and neutrophils; the permeability of pulmonary vessels, and the activities of T cells (Chen Q et al. 2019). TCMs formulations and their ingredients were also summarized, including 'Three Drugs Three Prescriptions' (Jinhua Qinggan granules, Lianhua Qingwen capsules, Xuebijing injection, Qingfei Paidu decoction, Huashi Baidu Tang, and Xuanfei Baidu decoction) and JingYinGuBiao formula (Table 5).

The flavonoid lignan silybin could directly inhibit transcription-3, which is the main checkpoint regulator of inflammatory cytokine signal transduction and the immune response. Silybin has the dual ability to target the host cytokine storm and virus replication mechanism and is expected to reduce the viral load and prevent the delayed interferon response (Bosch-Barrera et al. 2020).

Matrine, an alkaloid isolated from the root of *Sophora flavescens* Aiton (Fabaceae), is used to treat COVID-19 patients *via* intravenous infusion. For higher bioavailability, matrine could be developed into an oral drug with a sustained release by drug co-amorphization technology (Hu et al. 2022a). The result of MD suggests matrine has anti-inflammatory effects in COVID-19 by targeting the TNF-α, IL-6, and caspase-3 in the TNF signaling pathway (Peng W et al. 2023; Yang MW et al. 2020).

Some researchers found that nanocurcumin could regulate the inflammatory response to improve clinical performance and promote the self-repair ability of COVID-19 patients. It significantly

Table 4. Immunomodulators for SARS-CoV-2.

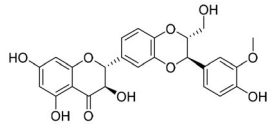
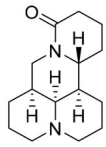
Natural Products	Category	Structure	References
Silybin	Flavonoids		Bosch-Barrera et al. 2020
Baicalein	Flavonoids	Table 1	Su et al. 2020
Matrine	Alkaloid		Hu et al. 2022a; Peng W et al. 2023; Yang MW et al. 2020
Phillyrin	Lignans	Table 1	Ding et al. 2017; Ma et al. 2020a
Nanocurcumin	Polyphenols	Table 1	Tahmasebi et al. 2021

Table 5. Composition of TCMs for the potential treatment of COVID-19.

TCMs	Compositions	References
Lianhua qingwen capsule (LHQWC)	*Forsythia suspensa* (Thunb.) Vahl, *Lonicera japonica* Thunb., roasted *Ephedra sinica* Stapf, roasted *Armeniacae amarum* Semen, Gypsum fibrosum, *Isatis tinctoria* L., *Dryopteris crassirhizoma* Nakai, *Houttuynia cordata* (Thunb.), *Pogostemon cablin* (Blanco) Benth., *Rhodiola rosea* L., *Mentha haplocalyx* Briq., *Glycyrrhiza uralensis* Fisch.	Appelberg et al. 2020; Ding et al. 2017; Hu et al. 2020
Jinhua Qinggan granule (JHQG)	*Lonicera japonica* L., *Ephedra sinica* Stapf, Gypsum fibrosum, *Armeniacae amarum* Semen, *Scutellaria baicalensis* Georgi, *Forsythia suspensa* (Thunb.) Vahl, *Fritillariae Thunbergii Bulbus*, *Anemarrhenae Rhizoma*, *Arctii* Fructus, *Artemisia annua* L., *Mentha canadensis* L., *Glycyrrhiza glabra*	Shah et al. 2022; Zhu et al. 2023
Xuebijing injection (XBJ)	*Carthami* Flos L., *Angelica sinensis* (Oliv.) Diels, *Salvia miltiorrhiza* Bunge, *Paeonia lactiflora* Pall, *Conioselinum anthriscoides* (H.Boissieu) Pimenov & Kljuykov	Zheng et al. 2020; Luo et al. 2021; Ma, et al. 2020
Qingfei Paidu decoction(QFPDD)	*Ephedra sinica* Stapf, *Glycyrrhiza glabra*, *Armeniacae amarum* Semen, *raw* Gypsum fibrosum, *Cinnamomi ramulus*, *Alisma plantago-aquatica* Linn., *Polyporus Umbellatus* (Pers.) Fries, *Atractylodes macrocephala* Koidz, *Wolfiporia extensa* (Peck) Ginns, *Bupleurum falcatum* L., *Scutellaria baicalensis* Georgi, *Pinellia ternata* (Thunb.) Breit., *Zingiber officinale* Rosc., *Rhizoma Aster tataricus* L.f., *Tussilago farfara* L., *Iris domestica* (L.) Goldblatt & Mabb., *Asarum heterotropoides* F.Schmidt, *Rhizoma Dioscoreae*, *Fructus aurantii immaturus*, *Citri Reticulatae Pericarpium*, *Pogostemon cablin* (Blanco) Benth	Yang R et al. 2020; Li Y et al. 2022; Zong et al. 2022
Liushen capsule (LSC)	*Calculus bovis*, *Abelmoschus moschatus* Medik, *Borneolum syntheticum*, *Bufonis venenum*, peal, realgar	Ma et al. 2020; Ma et al. 2022
Shufeng Jiedu capsule (SFJDC)	*Reynoutria japonica* Houtt., *Forsythia suspensa* (Thunb.) Vahl, *Isatis tinctoria* L., *Bupleurum falcatum* L., *Thlaspi arvense* L., *Verbena officinalis* L., *Phragmitis Rhizoma*, *Glycyrrhiza glabra*	Bao et al. 2016; Xia et al. 2021
Shuanghuanglian liquid (SHL)	*Lonicera japonica*, *Scutellaria baicalensis* Georgi, *Forsythia suspensa*	Han et al. 2018; Su et al. 2020

reduces the number of T helper (Th) 17 cells and expression of related inflammatory factors and alleviates the cytokine storm (Tahmasebi et al. 2021).

Phillyrin, an active lignan compound extracted from *Forsythia suspensa* (Thunb.) Vahl (Oleaceae), has antioxidant, antiviral, and anti-inflammatory activities. Phillyrin has a certain level of anti-inflammatory activity against SARS-CoV-2-induced inflammation by suppressing the NF-κB signaling pathway, significantly inhibiting SARS-CoV-2 replication, and reducing the mRNA expression of the proinflammatory cytokines TNF-α, IL-6, IL-1β, IP-10, and monocyte chemoattractant protein-1 (MCP-1/CCL2) (Ding et al. 2017; Ma et al. 2020a).

Lianhua Qingwen capsule (LHQWC) has broad-spectrum antiviral and immunoregulatory effects and contains 13 herbs, including *Forsythia suspensa*, *Lonicera japonica*, and other herbs (Table 1) (Ding et al. 2017). The active compounds of LHQWC have good binding affinity for 3CLpro on the surface of the virus, hACE2 receptors as well as Akt1 (a core target associated

with immune cell modulation) through network pharmacology (Appelberg et al. 2020). LHQWC significantly inhibited the expression of TNF-α, IL-6, CCL-2/MCP-1, and CXCL-10/IP-10 induced by H1N1 *in vitro* (Ding et al. 2017). Therefore, LHQWC may have the potential to inhibit the cytokine storm. Despite the potential mechanisms and targets of LHQWC in COVID-19 that have been investigated, the in-depth mechanism of these active compounds still requires further elucidation.

Jinhua Qinggan granule (JHQG), an effective Chinese medicine formula with the effects of dispersing wind, promoting lungs, clearing heat, and detoxifying, was proposed as a therapeutic formulation for COVID-19 by the NHC. It is composed of *Lonicera japonica*, *Ephedra sinica* Stapf (Ephedraceae), Gypsum fibrosum, and other components (Table 2). In the clinic, JHQG effectively eased the COVID-19 patients' symptoms (Shah et al. 2022). In the model of LPS-induced mice, JHQG significantly reduced the levels of TNF-α, IL-1β, and IL-6, and inhibited the TLR4/MyD88/NF-κB pathway, which helps to further reveal the underlying mechanism of JHQG (Zhu et al. 2023).

XueBiJing injection (XBJ injection) is an injection composed of five Chinese herbal extracts: *Carthami Flos* L. (Compositae), *Angelica sinensis* (Oliv.) Diels (Apiaceae), *Salvia miltiorrhiza*, *Paeonia lactiflora* Pall (Paeoniaceae), and *Conioselinum anthriscoides* (H.Boissieu) Pimenov & Kljuykov (Apiaceae) (Chuanxiong in Chinese). Based on network pharmacology, XBJ might alleviate lung inflammation during COVID-19 by different genes and pathways, including inhibiting NF-κB activation and downregulating TNF-α, IL-6, and IL-1β (Zheng et al. 2020). A randomized double-blind trial showed that XBJ might prevent the occurrence of cytokine storms in patients with severe pneumonia by regulating the secretion of the proinflammatory factors IL-6, IL-8, and TNF-α (Luo et al. 2021). Ma et al. (2020c) reported that XBJ ameliorated lung injury in severely or critically ill patients. The anti-SARS-CoV-2 mechanism of action may be related to blocking virus proliferation and inhibiting virus-induced expression of proinflammatory factors. It protects cells from virus-induced cell death and reduces inflammation in patients with COVID-19. Additionally, the authors performed a clinical safety evaluation of XBJ injection in 93 medical institutions. The results indicated no other severe adverse reactions other than those already noted in the specification. Therefore, XBJ injection may have satisfactory safety within a reasonable scope of use.

The prescription of Qingfei Paidu decoction (QFPDD) is suitable for all types and stages of patients with COVID-19. As a key recommended drug for COVID-19, QFPDD is composed of *Ephedra sinica* Stapf, *Glycyrrhiza glabra*, *Aconiti Lateralis Radix Praeparata* (Ranunculaceae), *Armeniacae amarum* Semen (Rosaceae), and other herbs (Table 2) (NHC 2020; Zong et al. 2022). Using network pharmacology and molecular network methods, Yang R et al. (2020) determined that COVID-19 treatment is related to the Toll-like signalling pathway, which directly interferes with TLR4, regulates downstream signalling pathways, and inhibits the release of proinflammatory cytokines. Oroxylin A, hesperetin, and scutellarin are three key components in QFPDD. Recent research by Li Y et al. (2022) has shown that these components exhibit significant inhibitory effects on the release of IL-6, IL-1β, and CXCL-10, which are induced by the SARS-CoV-2 S protein.

Liushen capsule (LSC) contains several natural ingredients, including *Calculus bovis* (Bovidae), *Abelmoschus moschatus* Medik (Malvaceae), *Borneolum syntheticum* (Dipterocarpaceae), *Bufonis venenum* (Bufonidae), pearl and realgar. LSC could inhibit SARS-CoV-2 virus infection *via* suppressing NF-κB signaling pathway and the levels of pro-inflammatory cytokines *in vitro* (Ma et al. 2020b). Interestingly, LSC remains antiviral effects against two SARS-CoV-2 variants. Its therapeutic effect on COVID-19 is further proved in the hACE2 mouse model (Ma et al. 2022).

Shufeng Jiedu capsule (SFJDC) is composed of *Reynoutria japonica* Houtt. (Polygonaceae), *Forsythia suspensa*, *Isatis tinctoria*, and other components (Table 2) (Bao et al. 2016). It is one of the Chinese prescriptions summarized in clinical observations and recommended in the early stage for COVID-19 in the 7th edition of the 'New Coronavirus Pneumonia Diagnosis and Treatment Protocol (Trial)' (NHC 2020). Xia et al. (2021) identified that three biologically active compounds in SFJDC, including polydatin, quercetin, and wogonin, directly inhibit 3CLpro and virus replication by MD. Subsequently, they found that SFJDC reduces the expression of proinflammatory factors in mice and may exhibit anti-inflammatory effects.

Shuanghuanglian (SHL) preparation is simplified from the 'Yinqiao San' prescription recorded in the 'Wenbing Tiaobian' in the Qing Dynasty. It is composed of *Lonicera japonica*, *Forsythia suspensa*, and *Scutellaria baicalensis*. Modern medical research suggests that SHL oral liquid has broad-spectrum antiviral and immune-enhancing properties, thus it could be used as an effective broad-spectrum antiviral drug (Han et al. 2018). Baicalin and baicalein in SHL might be the 3CLpro inhibitors by affecting the replication of SARS-CoV-2 (Su et al. 2020).

Conclusions

TCMs play an important role in the treatment of COVID-19. Clinical studies suggested that TCMs are linked to better patient outcomes and lower levels of inflammation. In this work, we summarized pre-clinical data available from recent research investigating potential SARS-CoV-2 inhibitors derived from clinical Chinese medicine preparations or plants. The effective compounds are identified and classified into 7 categories, including flavonoids, polyphenols, terpenoids, alkaloids, lignans, anthraquinones, and sulfur-containing compounds. Numerous results revealed that natural compounds show anti-SARS-CoV-2 characteristics due to their molecular structure and receptors binding sites. It is hoped that the scientific community will continue to conduct many more *in vivo* studies and clinical investigations to select safe and effective anti-SARS-CoV-2 therapeutic agents from naturally derived compounds.

Future studies are warranted to uncover the in-depth mechanisms of TCMs against COVID-19. For prescription preparations that have been proven effective, studies of pharmacokinetic characteristics and their mechanisms of action after administration might provide sufficient evidence to apply further. At the same time, the development of these formulas as therapeutics is becoming more feasible because of the advances in the identification of TCMs standardization, such as the analytical technology and NMR-metabolomics discussed above. Considered collectively, further research on their mechanisms of action, safety, and effectiveness is necessary to promote the treatment of COVID-19 with TCMs as a priority strategy.

In the face of the urgent need for controlling this epidemic, the combination of pharmaceutical analysis, molecular biology, bioinformatics, and artificial intelligence can allow us to identify potential inhibitors in a rapid and therefore constantly updated way. Priority should be given to natural products that demonstrate potential inhibitory effects against SARS-CoV-2 for further drug research. Additionally, it is crucial to consider the crystal

forms and chemical properties of candidate small molecules. Small molecules with different crystal forms can impact the physical, chemical, and pharmacokinetic properties of the drug (Song et al. 2021). For example, the absorption of the β crystal form of baicalin in rats is significantly better than that of the α crystal form of baicalin (α crystal form: β crystal form = 47.40:7.31) (Chen and Du 2020).

It's worth noting that apart from the plant-derived products above, the plant is utilized for the development of a vaccine against SARS-CoV-2 as well, in which CoVLP + AS03 is the first plant-based vaccine that has been approved for humans (Hager et al. 2022). This is a new technology platform for the development of vaccines. Using multi-omics and systems pharmacological strategy is becoming the development trend for unravelling the multi-targeted curative potential of bioactive molecules, not just for screening anti-COVID-19 drugs but also for other diseases, such as cervical cancer (Aarthy et al. 2022). Fully exploring the various modes of action of phytoconstituents, both compound preparations and single compounds, would lead to maximizing the practical value of the natural resources of plants and herbs for combating this pandemic effectively.

Author contributions

Zhouman He, Jia Yuan and Yuanwen Zhang contributed to the drafting and revision of the manuscript. Zhouman He, Jia Yuan, Yuanwen Zhang, Runfeng Li, Meilan Mo, Yutao Wang and Huihui Ti contributed to data curation, formal analysis, and writing of the original draft. Yutao Wang and Huihui Ti contributed constructive suggestions to the manuscript. All authors contributed toward drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by grants from the National Natural Science Foundation of China (NO. 81873071), Natural Science Foundation of Guangdong Province (NO. 2021A1515011512), Supporting talent development plan of Guangdong Pharmaceutical University and Project funding of Yangtze River Pharmaceutical Group Jiangsu Pharmaceutical Co., Ltd.

Data availability statement

Data sharing does not apply to this article as no new data were created or analyzed in this study.

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