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The Potential of Anti-coronavirus Plant Secondary Metabolites in COVID-19 Drug Discovery as an Alternative to Repurposed Drugs: A Review

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Key words
SARS-CoV-2, antivirals, phytochemicals, natural products, medicinal plants, alternative medicine

received March 5, 2023
accepted after revision November 10, 2023
published online December 7, 2023

Bibliography
Planta Med 2024; 90: 172–203
DOI 10.1055/a-2209-6357
ISSN 0032-0943

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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ABSTRACT

In early 2020, a global pandemic was announced due to the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known to cause COVID-19. Despite worldwide efforts, there are only limited options regarding antiviral drug treatments for COVID-19. Although vaccines are now available, issues such as declining efficacy against different SARS-CoV-2 variants and the aging of vaccine-induced immunity highlight the importance of finding more antiviral drugs as a second line of defense against the disease. Drug repurposing has been used to rapidly find COVID-19 therapeutic options. Due to the lack of clinical evidence for the therapeutic benefits and certain serious side effects of repurposed antivirals, the search for an antiviral drug against SARS-CoV-2 with fewer side effects continues. In recent years, numerous studies have included antiviral chemicals from a variety of plant species. A better knowledge of the possible antiviral natural products and their mechanism against SARS-CoV-2 will help to develop stronger and more targeted direct-acting antiviral agents. The aim of the present study was to compile the current data on potential plant metabolites that can be investigated in COVID-19 drug discovery and development. This review represents a collection of plant secondary metabolites and their mode of action against SARS-CoV and SARS-CoV-2.

Introduction

The first COVID-19 case was identified in December 2019 in Wuhan, China. This was the beginning of one of the greatest pandemics facing humanity in modern times. This virus, later named SARS-CoV-2, is responsible for more than 6 million fatalities worldwide to date (March 1, 2023) [1].

SARS-CoV-2 with crown-shaped glycoproteins on its surface has a single-stranded RNA of 26.4–31.7 kb, which shares 80% of its genome with the SARS-CoV virus [2–9].

Given the vast dispersion and high fatality rate of the virus, scientists and research institutes all over the world have been searching for an effective treatment to manage the disease [10–12].

While antiviral drug development has grown and vaccines have become accessible, there remains a demand for cost-effective and easily applicable treatment approaches to combat COVID-19 [13]. The creation of broad-spectrum coronavirus inhibitors, which can be administered orally or via inhalation, may play a crucial role in dealing with emerging SARS-CoV-2 variants [13]. Such treatments would be greatly beneficial in the readiness for future outbreaks of pathogenic coronaviruses [13].

In response to the COVID-19 pandemic, much research has been conducted on the structural properties of SARS-CoV-2 proteins and viral-cellular protein complexes to find potential targets for therapeutic interventions [14]. The spike (S) protein, main protease (Mpro), papainlike protease (PLpro), and RNA-dependent RNA polymerase (RdRp) are the most intensively researched pharmacological targets [14]. In general, antiviral drugs against

ABBREVIATIONS

(h)ACE2	(human) angiotensin converting enzyme 2
3CLpro	3-chymotrypsin-like protease
COVID-19	coronavirus disease 2019
CQ	chloroquine
E	envelope
EC_{50}	half maximal effective concentration
ECG	(−)-epicatechingallate
EGC	(−)-epigallocatechin
EGCG	(−)-epigallocatechin-3-gallate
FMF	familial Mediterranean fever
HCQ	hydroxychloroquine
IC_{50}	half maximal inhibitory concentration
M	membrane
MD	molecular dynamics
MERS-CoV	Middle East respiratory syndrome coronavirus
Mpro	main protease
N	nucleocapsid
NRBD	N-terminal RNA binding domain
PLpro	papainlike protease
RBD	receptor-binding domain
RdRp	RNA-dependent RNA polymerase
S	spike
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SM(s)	secondary metabolite(s)
TMPRSS2	transmembrane serine protease 2

SARS-CoV-2 employ a number of different tactics to prevent viral replication. For example, the SARS-CoV-2 S protein is targeted by potential inhibitors of viral attachment to host cells and human angiotensin converting enzyme 2 (ACE2) receptor interaction-mediated viral entry [15–17]. Inhibiting viral proteases, Mpro [18], also known as 3-chymotrypsin-like cysteine protease (3CLpro), and PLpro [19, 20], is a different tactic. Moreover, RdRp, an enzyme that facilitates the synthesis of RNA using an RNA template, has been identified as a target for the development of anti-SARS-CoV-2 therapeutics [21]. Therefore, researchers are seeking substances with the aforementioned qualities in order to identify potential antiviral secondary metabolites to combat SARS-CoV-2.

Because there has been limited success in designing, developing, or discovering COVID-19 treatments, clinical and laboratory research is ongoing, most of which is still in an early stage of research [22].

The repurposed antiviral drugs used to treat COVID-19 may provide protection against infection or speed up recovery, but all COVID-19 antiviral drugs currently on the market have drawbacks that may prevent their use by the general public [23–37]. For example, remdesivir administration led to mild to moderate undesirable outcomes, including but not restricted to liver toxicity, queasiness, anemia, kidney impairment, low blood pressure, respiratory collapse, and constipation, among other things [38–42]. These shortcomings have highlighted the need for new and more targeted medications [43].

Plant-derived compounds have been shown to be efficient against viruses. For example, in 1952, the Boots pharmaceutical company in England tested 288 plants for the first time for their antiviral properties against influenza A [44]. According to the results of this study, 12 of the examined plants showed antiviral activity [44]. To date, hundreds of plants with antiviral properties have been identified and used for direct antiviral effects or to alleviate symptoms of viral diseases [45–47]. More recently, Guerra et al. conducted a comprehensive review of reports focusing on plant-derived compounds as potential inhibitors of the SARS-CoV-2 proteases [48]. Their findings indicated that flavonoids constitute a significant portion of these compounds, with quercetin emerging as the molecule with the highest number of reports, followed by kaempferol [48].

In response to the COVID-19 pandemic, Thailand's Ministry of Health has authorized the utilization of *Andrographis paniculata*, also known as green chiretta, as a pilot program to address the initial phases of COVID-19 [49]. This initiative was implemented during a surge in the coronavirus outbreak in the Southeast Asian nations, with the aim of providing an alternative treatment option to alleviate the severity of the outbreak and decrease treatment expenses [49].

To defend themselves against biotic and abiotic stresses including pests, microorganisms, and environmental conditions, plants produce structurally diverse low-molecular-weight compounds called secondary metabolites or specialized metabolites (SMs) [50, 51]. Based on their chemical structure, SMs are classified as phenolic compounds (e.g., flavonoids), terpenoids, sulfur-containing compounds (e.g., glucosinolates), and nitrogen-containing compounds (e.g., alkaloids) [52]. In this review, we have compiled the latest data on the potential antiviral properties of plant SMs and their mode of action against SARS-CoV-2. We conducted a search of the Google Scholar, PubMed, and Science Direct databases using terms such as phytochemical, plant-derived compounds, plant compounds, and secondary metabolites, in conjunction with antiviral, SARS-CoV-2, and coronavirus. Our search focused on original papers reporting *in vitro, in vivo*, and *in silico* studies from the emergence of SARS-CoV-2 in December 2019. To retrieve a comprehensive list of phytochemicals that have demonstrated inhibitory properties against drug targets with high similarity between SARS-CoV-2 and related viruses, we conducted additional searches using terms such as SARS-CoV and MERS-CoV. This approach enabled us to identify potential candidates for further investigation and development as antiviral agents against SARS-CoV-2. Additionally, we incorporated the terms classification and structure to explore the structural properties and classification of these compounds. The presented data may provide a new approach for designing and developing future antiviral drugs.

Classification of SARS-CoV-2

On January 12, 2020, China disclosed the genetic sequence of SARS-CoV-2 for use in diagnostic kits in other countries [53]. Researchers classified this virus by using a viral classification system after evaluating its sequence [54]. Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 belongs to the genus betacoronavirus, subfam-

▶ **Table 1** List of FDA-approved synthetic drugs against COVID-19, their mechanism of action, and probable side effects.

Name of Drug	Mechanism of Function	Side Effects	Reference/s
Remdesivir (Veklury)	Inhibition of viral replication	Headache, nausea, affecting blood tests	[23–26]
Tocilizumab (Actemra) and Infliximab/Tocilizumab	Tocilizumab as an antagonist for interleukin-6 (IL-6) receptor acts as an anti-inflammatory agent in patients with cytokine storm	No side effect in initial studies, enhancement of liver enzymes in the case of infliximab/tocilizumab	[27–23]
Baricitinib (Olumiant)	Inhibition of virus infection and acting as an anti-inflammatory agent	Vein thrombosis	[30–31]
Paxlovid (Nirmatrelvir-Ritonavir)	Inhibition of viral replication	Headache, diarrhea, vomiting dysgeusia	[32]
Molnupiravir (Lagevrio)	Inhibition of virus multiplying	Dizziness, rash, diarrhea, nausea	[33–34]
Kineret (anakinra)	Inhibition of interleukin-1 (IL-1) receptor	Reaction in injection site, enhancement of liver enzymes, hypertension	[35–36]
Gohibic (Vilobelimab)	Vilobelimab as an antagonist od complement component 5a (C5-a) receptor, acts as anti-inflammatory agent	Hypertension, pneumonia, pulmonary embolism, delirium, and sepsis	[37]

ily *Orthocoronavirinae*, and family *Coronaviridae*. The subfamily *Coronavirinae* is divided into the genera alphacoronavirus, betacoronavirus, gammacoronavirus, and deltacoronavirus based on genomic sequence, with betacoronaviruses and alphacoronaviruses being human-pathogenic [55].

SARS-CoV-2 is classified as lineage B based on its greater similarity to SARS-CoV (79.5% sequence homology) compared to other betacoronaviruses such as MERS-CoV (50% sequence homology) [56]. Another finding supporting this classification is that the seven ORF1ab domains of SARS-CoV-2 have a 94.6% similarity to those of SARS-CoV, compared to less than 90% for other betacoronaviruses [57]. The reproductive number (R, which determines how infectious the agent is) is significantly higher for SARS-CoV-2 (2.9) compared to SARS-CoV R (1.77) [58, 59].

The coronaviridae study group (CSG) first classified these three viruses, SARS-CoV-2, SARS-CoV, and MERS-CoV, as distinct species within a new, informal subclass of the genus betacoronavirus [60, 61]. When subgenus rank was established in virus classification, these three informal subgroups were introduced as the three subgenera Sarbecovirus, Embecovirus, and Merbecovirus, respectively, and unique names were defined for these viruses and their species according to virus classification practice [62]. To date, five concerning SARS-CoV-2 variants have been identified: alpha, beta, gamma, delta, and omicron [63, 64].

SARS-CoV-2 Structure and COVID-19 Drug Targets

The genome of SARS-CoV-2 is a 30 kb single-stranded positive-sense RNA [56]. This virus shares less than 79% nucleotide sequence homology with SARS-CoV [56]. The novel coronavirus, SARS-CoV-2, is distinguished from other betacoronaviruses by its distinct polybasic cleavage sites, which result in increased transmission intensity and pathogenicity [65].

From 5′ to 3′, this virus has six major open reading frames (ORFs) and additional supplementary genes that are translated into replicase (ORF1a/ORF1b), S, envelope (E), membrane (M), and nucleocapsid (N) proteins [66]. In addition, the viral genome has seven sub-ORFs encoding accessory proteins distributed among structural genes [56, 57, 67].

There are 16 nonstructural proteins, 9 accessory proteins, and 4 structural proteins in the SARS-CoV-2 virus [68]. Most of them are of the same length as their SARS-CoV counterparts [56, 57]. The structural and nonstructural proteins of these two viruses exhibit 90% and 85% similarity, respectively [69].

SARS-CoV-2′s major therapeutic targets are S, 3CLpro or Mpro, and RdRp [70]. E proteins, M proteins, N proteins, helicase proteins, and PLpro are other potential therapeutic targets for developing or repurposing drugs to treat the COVID-19 disease [70].

It is worth noting that several host proteins can be utilized as therapeutic targets due to their roles in processes such as virus binding to host cells or viral protein activation. Angiotensin-converting enzyme 2 (ACE2) [71, 72], transmembrane serine protease 2 (TMPRSS2) [73–76], cathepsin L [77], and furin [78] are among the host proteins that can be used as COVID-19 drug targets.

Current Treatments for COVID-19 Disease

To date, numerous studies have been conducted on the application of repurposed medicines that can be effective for the treatment of COVID-19. Among the various drugs introduced as a remedy, only a few have been approved by the US Food and Drug Administration (FDA) based on their safety and efficacy (https://www.fda.gov/drugs/emergency-preparedness-drugs/coronavirus-covid-19-drugs). The complete list of approved drugs is provided in ▶ **Table 1**.

Prioritizing Potential Candidates for Anti-SARS-CoV-2 Drug Development and Discovery from Phytochemicals and Plant Secondary Metabolites

Numerous research studies have looked into the potential of phytochemicals as anti-COVID-19 drug candidates. However, with the plethora of compounds available, it is crucial to establish a rational approach to prioritize the most promising candidates for further investigation. This section aims to provide guidelines for prioritizing the compounds with the highest likelihood of exhibiting potent antiviral effects against SARS-CoV-2.

In silico screening and molecular docking studies

Drug design and discovery is a time-consuming and resource-intensive process. Traditional methods often fall short, leading to the introduction of modern computer-aided drug design (CADD) approaches aimed at reducing time and cost [79].

Molecular docking and molecular dynamics (MD) simulations are commonly employed methods in CADD for identifying and repurposing potential drugs against various life-threatening diseases [80, 81]. These techniques enable researchers to study the behavior of small chemical entities in the active sites of target proteins and determine their activity [82].

Molecular docking calculations focus on identifying the active site regions of receptors to determine ligand–receptor interactions and find the optimal binding modes. As discussed, in the case of COVID-19, the main drug targets for molecular docking are Mpro, PLpro, and RdRp, crucial proteins involved in viral replication and transcription.

Despite its merits, there are several limitations to the application of molecular docking in drug discovery. Scoring functions struggle to accurately predict binding energies due to challenges with certain intermolecular interaction terms [83]. Significant interactions like halogen bonding and guanidine–arginine interactions are often ignored [84, 85]. Handling water molecules in binding pockets is problematic due to a lack of hydrogen coordinates and theoretical approaches [86]. Additionally, failing to account for protein conformational changes due to a rigid receptor could lead to inaccurate negative findings [87]. Furthermore, assessing off-target activity is a challenge typically addressed through animal and human trials [82, 86]. These limitations highlight the need for ongoing research and improvement in molecular docking.

MD simulations, as an *in silico* computational approach, enable the prospective estimation of temporal system evolution and, consequently, anticipate the MD within the system [88]. This technique provides insights into the dynamic interactions between molecules and their target proteins.

Using MD simulations can be a useful tool in discovering drugs for COVID-19, but their limitations may impact their dependability and precision. These limitations arise from the current inadequacies of the force fields used in simulations [89, 90]. The force fields often overlook critical factors such as polarization effects, charge transfer, electronic-based interactions, including π–π and cation–π interactions, and halogen bonds [91]. To improve the accuracy of free-energy predictions, future developments will likely incorporate polarizable force fields and quantum mechanical calculations [91]. Furthermore, prolonging the duration of simulations to micro- and millisecond intervals can produce more reliable outcomes that correspond with real-life experimental situations [92].

Moreover, the accuracy of these simulations' application to complex target families like metalloproteins is limited [91]. Additionally, when utilizing MD simulations, there can be difficulties due to the lack of standardized protocols, inadequate analytical resources, and the management of extensive trajectory data [93].

A study conducted by Kumar et al. serves as an illustrative instance wherein a combination of methodologies, including molecular docking and MD simulations, were employed to identify potential inhibitors targeting the main Mpro of SARS-CoV-2 [94]. Notably, the study successfully identified three novel natural metabolites, namely ursolic acid, carvacrol, and oleanolic acid, which exhibited stable and high binding energies with the Mpro protein [94]. Furthermore, the compounds were found to comply with the principles of absorption, distribution, metabolism, and excretion (ADME), as well as Lipinski's rule of five, ensuring their pharmacological viability [94].

Despite the extensive computational exploration of various drugs for COVID-19, experimental methods remain irreplaceable in the identification of promising drug candidates [95]. *In vitro* experiments are needed to validate results of *in silico* studies, including assessing antiviral effects in infected human lung cells. *In vivo* studies using SARS-CoV-2 animal models are necessary for confirming inhibitory potential. However, only a few compounds have been tested in both *in vitro* and *in vivo* settings.

Nevertheless, by using meticulously curated prior experimental data and employing rigorous computational tools, it is possible to facilitate the successful discovery of viable drug candidates through experimental means.

Experimental validation and *in vitro* studies

Antiviral compounds are evaluated by monitoring their cytopathic effects in different cell lines [96]. *In vitro* antiviral studies against SARS-CoV-2 involve using cells and organoids. Cell lines such as Vero E6, HEK293T, Calu-3, Huh7, and Caco-2 are used to replicate and isolate the virus and conduct infection experiments. These cell lines provide valuable information about virus replication and infection, although they have limitations in accurately mimicking human physiological conditions.

SARS-CoV-2 mainly invades ciliated and type 2 pneumocyte cells in the human lung [97]. Hence, differentiated primary airway epithelial cells serve as a suitable model, but their restricted lifespan in cell culture needs improvement [98].

Moreover, Vero E6, a kidney cell line derived from African green monkeys, is commonly used due to its high susceptibility to SARS-CoV-2 and expression of key entry receptors [96]. However, cell lines derived from animals are insufficient, particularly for evaluating antiviral prodrugs like nucleos(t)ide inhibitors that necessitate metabolic stimulation in human cells [99, 100].

Organoids consist of various types of cells and replicate the physiological characteristics of human organs [101]. Due to their capacity for self-replication, organoids are well suited for exten-

▶ **Table 2** Plant SMs with potential inhibitory effects against SARS-CoV-2 and SARS-CoV.

Chemical superclass	Chemical class	Metabolite(s)	Plant	Virus	Study	Function	Ref.
Alkaloids	Amaryllidaceae alkaloid	Lycorine	*Lycoris radiata*	SARS-CoV SARS-CoV-2	*In vitro*	Anti-SARS-CoV activity (EC_{50}: 15.7 nM); Anti-SARS-CoV-2 activity due to reduction of viral RNA levels (EC_{50}: 0.31 µM) and cytopathic effects; Reduction of N protein production.	[188, 226]
	Benzylisoquinoline alkaloid	Tetrandrine	*Stephania tetrandra*	SARS-CoV-2	*In vitro*	Calcium channel blocker; Dose-dependent prevention of the SARS-CoV-2 pseudotyped virus entry.	[4]
	Benzylisoquinoline alkaloid	Cepharanthine	*Stephania* spp.	SARS-CoV-2	*In vitro*	Inhibition of ACE (0.98 mmol/L); Limiting the SARS-CoV-2 pseudotyped virus entry (IC_{50}: 2.8 µM); Reduction of the viral RNA quantity ensuing authentic virus infection.	[227–229]
	Benzylisoquinoline alkaloid	Berberine	*Berberis petiolaris*, *Berberis vulgaris*	SARS-CoV-2	*In vitro*	Reduction of viral production (EC_{50}: 10.6 µM); Reduction of viral production (EC_{50}: 2.1 µM).	[230, 231]
	Bisbenzylisoquinoline alkaloid	Berbamine	*Berbaris amurensis*	SARS-CoV-2	*In vitro*	Interference with the activity of 2-E protein channels (IC_{50}: 111.5 µM); Cellular defense against cytopathic effects (IC_{50}: 34.34 µM), Reduction of virus replication (EC_{50}: 14.5 µM), Reduction of titers and levels of viral RNA (EC_{50}: 2.4 µM); Preventing the introduction of the SARS-CoV-2 pseudotyped virus.	[232, 233]
	Bisbenzylisoquinoline alkaloid	Liensinine	*Nelumbo nucifera*	SARS-CoV-2	*In vitro*	Preventing the entry of the SARS-CoV-2 pseudotyped virus (EC_{50}: 11.52 µM).	[234]
	Bisbenzylisoquinoline alkaloid	Neferine	*Nelumbo nucifera*	SARS-CoV-2	*In vitro*	Reduction of the viral RNA quantity ensuing authentic virus infection; Preventing the entry of the SARS-CoV-2 S pseudotyped virus (EC_{50}: 0.36 µM); Inhibition of Ca^{2+}-dependent membrane fusion of pseudotyped virus with cells.	[234]
	Bisbenzylisoquinoline alkaloid	Hernandezine	*Thalictrum hernandezii*, *Thalictrum fendleri*	SARS-CoV-2	*In vitro*	Blocking the host calcium channels, followed by inhibiting Ca^{2+}-membrane fusion and suppressing virus entry; Limiting the SARS-CoV-2 pseudotyped virus entry (EC_{50}: 0.111 µM).	[227]
	Bisindole alkaloid	Strychnopentamine	*Strychnos usambarensis*	SARS-CoV-2 MERS-CoV	*In silico* *In vitro*	High binding affinity exhibition toward the RdRp enzyme (− 9.4 kcal/mol).	[235]
	Bisindole alkaloid	10′–Hydroxy-usambarensine	*Strychnos usambarensis*	SARS-CoV-2	*In silico*	High binding affinity exhibition toward the RdRp enzyme (− 10.1 ± 0.38 kcal/mol).	[235]
	Cephalotaxus alkaloid	Homoharringtonine	*Cephalotaxus harringtonia*	SARS-CoV-2	*In vitro*	Reduction of viral copy number (EC_{50}: 2.14 µM); Reduction of cytopathic effects (EC_{50}: 3.125 µM); Reduction of infectious virus (EC_{50}: 2.55 µM).	[236]
	Indole alkaloid	Cryptospirolepine	*Cryptolepis sanguinolenta*	SARS-CoV-2 SARS-CoV MERS-CoV	*In silico* *In vitro* *Clinical trial*	Favorable binding affinity exhibition toward the RdRp enzyme (− 10.5–0.57 kcal/mol); Favorable binding affinity exhibition toward the Mpro of SARS-CoV and MERS-CoV.	[190, 235]
	Indole alkaloid	Reserpine	*Rauvolfia serpentine*	SARS-CoV-2	*In vitro*	Reduction of viral double-stranded RNA production (EC_{50}: 29.2 µM).	[237]

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sive drug discovery and disease research screenings [101]. They offer insights into SARS-CoV-2 infection on human tissues and aid in evaluating antiviral effects of compounds [102].

In vivo and clinical studies

As noted in the preceding parts and ▶ **Table 2**, numerous *in silico* and *in vitro* studies have assessed the effectiveness of plant SMs against SARS-CoV-2. However, there remains a shortage of adequate *in vivo* and clinical research to establish the efficacy of plant SMs in preventing viral infections or reducing symptoms associated with viral infections [103]. In reality, several compounds that exhibit strong antiviral activity in laboratory settings may prove to be ineffective in pre-clinical or clinical trials [104].

Until now, the evaluation of the *in vivo* antiviral effects of plants in animal models infected with SARS-CoV-2 has primarily relied on crude extracts. Deng et al. conducted a study to evaluate the ef-

▶ **Table 2** Plant SMs with potential inhibitory effects against SARS-CoV-2 and SARS-CoV. *continued*

Chemical superclass	Chemical class	Metabolite(s)	Plant	Virus	Study	Function	Ref.
Alkaloids	Indole alkaloid	Indigodole B	*Strobilanthes cusia*	HCoV-NL63	*In vitro*	Reduction of viral yield (IC_{50}: 2.60 µM); Virucidal activity (IC_{50}: 2.09 µM).	[238]
	Isoquinoline alkaloid	Isoliensinine	*Nelumbo nucifera*	SARS-CoV-2	*In vitro*	Preventing the entry of the SARS-CoV-2 pseudotyped virus (EC_{50}: 3.31 µM (CC).	[234]
	Isoquinoline alkaloid	Emetine	*Psychotria ipecacuanha*	SARS-CoV-2	*In vitro* *Clinical trial*	Increase in oxygen levels; Reduction of viral RNA quantity (EC_{50}: 0.147 nM); Reduction in cytopathic effects (EC_{50}:1.56 µM); Reduction of viral titer (EC_{50}: 0.46 µM), and viral RNA levels (EC_{50}: 0.5 µM); Significant inhibition of viral replication (EC_{50}: 0.007 M) observed in pre-virus Vero cells; Inhibition of viral entry in Vero cells; Pre-drug therapy prevents viral entry (EC_{50}: 0.019 M) (pragmatic randomized clinical trial).	[228, 236, 239–241]
	Isoquinoline alkaloid	Somniferine	*Withania somnifera*	SARS-CoV-2	*In silico*	High binding affinity exhibition toward Mpro (IC_{50}: 9.62 kcal/mol).	[242]
	Methylxanthine alkaloid	Caffeine	*Paullinia cupana, Coffea canephora, Coffea arabica*	SARS-CoV-2	*In silico*	Prevention of viral entry by inhibiting the synthesis of RBD and the ACE-2 complex; Possible inhibition of Mpro activity to potentially reduce viral replication (− 5.6 ± 0.30 kcal/mol).	[243, 244]
	Phenanthraindolizidine alkaloid	Tylophorine and tylophorine analogs	*Tylophora indica*	SARS-CoV, MERS-CoV	*In vitro*	Virucidal activity (Prevention of coronavirus replication; Blocking the cytopathic impact that a virus causes in cells *in vitro* by inducing apoptosis; EC_{50} values for natural and synthesized tylophorine analogs were 8–1468 nM and 5–340 nM respectively; Attacking viral RNA.	[245, 246]
	Quinazoline alkaloid	Tryptanthrin	*Strobilanthes cusia*	HCoV-NL63	*In vitro*	Reduction of viral yield (IC_{50}:1.52 µM). Virucidal activity (IC_{50}: 0.06 µM); Inhibition of PLpro activity and viral RNA replication.	[238]
	Indole alkaloid	Indigo	*Baptisia tinctoria*	SARS-CoV	*In vitro*	Inhibition of Mpro in the peptide cleavage assay IC_{50}: 300 µM (cell-free assays), 752 µM (cell-based assays).	[247]
	Quinoline alkaloid	Quinidine	*Cinchona officinalis*	SARS-CoV-2	*In vitro*	Reduction of viral double-stranded RNA production (EC_{50}: 13.3 µM).	[237]
	Quinoline alkaloid	Quinine	*Cinchona officinalis*	SARS-CoV-2	*In silico* *In vitro*	Dose-dependent suppression of SARS-CoV-2 infection displayed in various A549-ACE2/TMPRSS2 structures (EC_{50}: 5.58–55.82 µM).	[248]
	Quinolizidine alkaloid	Oxysophoridine	*Sophora alopecuroides*	SARS-CoV-2	*In vitro*	Decreasing viral RNA quantity and cytopathic effects (EC_{50}: 0.18 µM) (CC_{50} > 40 µM)	[226]
	Tetrahydroxyindolizidine alkaloid	Castanospermine	*Castanospermum australe*	SARS-CoV-2	*In vitro*	Reduction of cytopathic effects dose-dependently; Reduction of viral RNA level.	[249]
	Tropane alkaloid	Schizanthine Z	*Schizanthus porrigens*	SARS-CoV-2	*In silico*	High binding affinity toward PLpro.	[189]

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fectiveness of Pudilan Xiaoyan Oral Liquid (PDL), a traditional Chinese medicine containing *Isatis indigotica, Corydalis bungeana, Taraxacum mongolicum*, and *Scutellaria baicalensis* [105]. The researchers examined the potential of PDL against SARS-CoV-2 through *in vitro* and *in vivo* studies [105]. Their findings, combined with bioinformatics and network pharmacology analyses, demonstrated that PDL exhibited strong antiviral activity against SARS-CoV-2 and showed promising results both *in vitro* and *in vivo* [105]. These results suggest that PDL could be considered for clinical use as a treatment for pneumonia caused by SARS-CoV-2 infection, either alone or in combination with other effective antiviral medications [105].

To advance phytochemicals into antiviral drugs for the treatment of COVID-19, more comprehensive experimental and preclinical investigations, including bioavailability, pharmacokinetics, pharmacodynamics, and toxicological studies, must be conducted in animal models. These essential steps are required before the compounds can be considered for human studies.

▶ **Table 2** Plant SMs with potential inhibitory effects against SARS-CoV-2 and SARS-CoV. *continued*

Chemical superclass	Chemical class	Metabolite(s)	Plant	Virus	Study	Function	Ref.
Phenolic compounds	Cannabinoid	Cannabidiol	*Cannabis sativa*	SARS-CoV-2	*In vitro*	Prevention of viral gene expression and reversing some of SARS-impacts CoV-2's on host gene transcription during viral infection in lung epithelial cells; Increasing the synthesis of interferon and turning on its antiviral signaling pathway.	[250, 251]
	Cannabinoid	Cannabigerolic acid	*Cannabis sativa*	SARS-CoV-2	*In silico* *In vitro*	Inhibition of live SARS-CoV-2 entry, as it effectively prevented the infection of human epithelial cells by a pseudovirus expressing the SARS-CoV-2 S protein.	[252]
	Cannabinoid	Δ9-Tetrahydro-cannabinol	*Cannabis sativa*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 10.25 μM).	[250]
	Cannabinoid	Cannabidiolic acid	*Cannabis sativa*	SARS-CoV-2	*In silico* *In vitro*	Inhibition of live SARS-CoV-2 entry, as it effectively prevented the infection of human epithelial cells by a pseudovirus expressing the SARS-CoV-2 S protein.	[252]
	Coumarin	Leptodactylone	*Boenninghausenia sessilicarpa*	SARS-CoV	*In vitro*	Demonstration of strong protective efficacy against SARS-CoV-infected cells, with a ratio of 60% at 100 mg/ml.	[253]
	Coumarin	Tomentin A	*Paulownia tomentosa*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 6.20 μM).	[254]
	Coumarin	Tomentin B	*Paulownia tomentosa*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 6.10 μM).	[254]
	Coumarin	Tomentin C	*Paulownia tomentosa*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 11.60 μM).	[254]
	Coumarin	Tomentin D	*Paulownia tomentosa*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 12.50 μM).	[254]
	Coumarin	Tomentin E	*Paulownia tomentosa*	SARS-CoV SARS-CoV-2	*In vitro*	Inhibition of PLpro (IC_{50}: 5.0 ± 0.06 μM) in a dose dependent manner.	[254]
	Coumarin	Psoralidin	*Psoralea corylifolia*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 4.2 ± 1.0 μM).	[255]
	Diarylheptanoid	Hirsutanonol	*Alnus japonica*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 105.60 μM); Inhibition of PLpro (IC_{50}: 7.80 μM).	[256]
	Diarylheptanoid	Hirsutenone	*Alnus japonica*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 36.20 μM); Inhibition of PLpro (IC_{50}: 4.10 μM).	[256]
	Diarylheptanoid	Oregonin	*Alnus japonica*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 129.50 μM); Inhibition of PLpro (IC_{50}: 20.10 μM).	[256]
	Diarylheptanoid	Rubranol	*Alnus japonica*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 1 44.60 μM); Inhibition of PLpro (IC_{50}: 12.30 μM).	[256]
	Diarylheptanoid	Rubranoside B	*Alnus japonica*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 105.3 μM); Inhibition of PLpro (IC_{50}: 8.00 μM).	[256]

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For instance, baicalein, a compound from *Scutellaria baicalensis*, was studied by Song et al. for its therapeutic effects on COVID-19 [106]. The research showed that baicalein protected cells from SARS-CoV-2 damage and improved their morphology [106]. Oral administration of baicalein reached effective concentrations, inhibiting virus replication and reducing lung tissue damage in infected mice [106]. In addition, baicalein improved respiratory function and decreased inflammation in mice with lung injury [106]. These findings suggest baicalein as a promising treatment for COVID-19.

The bioavailability and solubility challenges associated with utilizing plant secondary metabolites for antiviral administration in drug discovery and development can be overcome through the utilization of drug delivery systems. Encapsulating or linking these compounds with nanocarriers provides a promising solution to enhance their delivery, distribution, degradation, and availability [107]. Organic-based nanocarriers, such as micelles, liposomes, niosomes, bilosomes, solid lipid nanoparticles, and archaeosomes, are commonly employed for transporting hydrophobic drugs within the body [108]. Furthermore, various pharmaceuti-

▶ **Table 2** Plant SMs with potential inhibitory effects against SARS-CoV-2 and SARS-CoV. *continued*

Chemical superclass	Chemical class	Metabolite(s)	Plant	Virus	Study	Function	Ref.
Phenolic compounds	Diarylheptanoid	Curcumin	*Curcuma longa*	SARS-CoV-2	*In vitro* *Clinical trial*	Nano-curcumin decreased IL6 and IL1 expression and serum levels, with a 20% death rate in the curcumin group compared to a 40% mortality rate in the placebo group (randomized clinical trial); Higher capacity to maintain oxygen saturation, earlier symptomatic recovery, fewer deterioration, less red flag indicators, better clinical results, lessen the mortality rate and shorten the hospital stay for patients with mild to severe symptoms (randomized clinical trial); Pseudovirus dose-dependently inhibited by hACE2 on A549; Dose-dependent suppression of A549/hACE2 syncytia; A dose-dependent reduction in the activity of TMPRSS2 and ACE2 Reduction of SARS-CoV-2 RNA levels (EC_{50}: 7.9 µg/ml) in Vero E6 and human Calu-3 cells.	[257–260]
	Diarylheptanoid	Rubranoside A	*Alnus japonica*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 102.10 µM); Inhibition of PLpro (IC_{50}: 9.10 µM).	[256]
	Ellagitannin	Punicalagin	*Punica granatum*, *Terminalia catappa*	SARS-CoV-2	*In vitro*	Inhibition of RBD-hACE2 binding.	[261, 262]
	Ellagitannin	Chebulagic acid	*Terminalia chebula*	SARS-CoV-2	*In vitro*	Inhibition of S protein, ACE-2, Mpro.	[261]
	Gallotannin	Tannic acid	*Caesalpinia spinosa*, *Rhus* spp. *semialata*	SARS-CoV-2	*In vitro*	Inhibition of TMPRSS (IC_{50}: 22.31 µM) and Mpro (IC_{50}: 13.4 µM).	[225]
	Flavonoid (catechin)	Epigallocatechin gallate	*Camellia sinensis*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 73.00 µM).	[133]
	Flavonoid (catechin)	Gallocatechin gallate	*Camellia sinensis*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 47.00 µM).	[133]
	Flavonoid (catechin)	Catechin	*Camellia sinensis*	SARS-CoV-2	*In vitro*	Virus incubation with catechin, resulted in a dose-dependent decrease in viral titers.	[263]
	Flavonoid (catechin)	Epigallocatechin-3-gallate	*Camellia sinensis*	SARS-CoV-2	*In vitro*	Prevention of the SARS-CoV-2 pseudotyped virus entry; Blocking receptor-binding domain (RBD)/hACE2 binding; Early addition lowers viral RNA concentration; Inhibition of Mpro (IC_{50}: 7.58 µM); Non-structural protein 15 inhibition (IC_{50}: 1.62 M); Reduction of viral titers (EC_{50}: 0.20 M).	[161, 264–266]
	Flavonoid (catechin)	Theaflavin 3,3′-di-O-gallate	*Camellia sinensis*	SARS-CoV-2	*In vitro*	Reduction in ACE2/TMPRSS2 activity; Inhibition of Mpro (IC_{50} 8.44 g/ml); Reduction of SARS-CoV-2 RNA and titer levels; Inhibition of Cathepsin L. pseudovirus and viral entry.	[259, 265, 266]
	Flavonoid (chalcone)	4-Hydroxyderricin	*Angelica keiskei*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 26.00 µM); Inhibition of Mpro (IC_{50}: 81.40 µM).	[267]
	Flavonoid (chalcone)	Xanthoangelol E	*Angelica keiskei*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 1.2 ± 0.4 µM); Inhibition of Mpro activity (IC_{50}: 11.4 ± 1.4 µM)	[267]
	Flavonoid (chalcone)	Panduratin A	*Boesenbergia pandurata*	SARS-CoV-2	*In vitro*	Inhibition of SARS-CoV-2 (IC_{50} of 5.30 µM, CC_{50}: 43.47 µM); Inhibition of SARS-CoV-2 pathogenicity in Vero E6 cells with corresponding IC_{50} values of 3.62 µg/mL (CC_{50}: 28.06 µg/mL) and 0.81 M (CC_{50}: 14.71 µM).	[268]
	Flavonoid (chalcone)	4′-O-Methylbavachalcone	*Psoralea corylifolia*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 10.10 µM).	[255]

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▶ **Table 2** Plant SMs with potential inhibitory effects against SARS-CoV-2 and SARS-CoV. *continued*

Chemical superclass	Chemical class	Metabolite(s)	Plant	Virus	Study	Function	Ref.
Phenolic compounds	Flavonoid (chalcone)	Isobavachalcone	*Psoralea corylifolia*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 7.30 µM).	[255]
	Flavonoid (flavanone)	Hesperetin	*Aloe barbadensis, Rutaceae family*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 60.00 µM)	[247]
	Flavonoid (flavanone)	Naringenin	*Citrus* spp., *Lycopersicum esculentum*	SARS-CoV-2 SARS-CoV	*In vitro*	Targeting TPCs and the Akt/mTOR signaling pathway; Dose-dependent reduction in cytopathic effects; Inhibition of Mpro (IC50: 92 nM); Reduction of cytopathic effects (EC50: 28.35 µg/mL).	[269, 270]
	Flavonoid (flavanone)	6-Geranyl-4′,5,7-trihydroxy-3′,5′-dimethoxy-flavanone	*Paulownia tomentosa*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 13.90 µM).	[254]
	Flavonoid (flavanone)	3′-O-Methyl-diplacol	*Paulownia tomentosa*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 9.50 µM).	[254]
	Flavonoid (flavanone)	3′-O-Methyl-diplacone	*Paulownia tomentosa*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 13.20 µM).	[254]
	Flavonoid (flavanone)	4′-O-Methyl-diplacol	*Paulownia tomentosa*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 9.20 µM).	[254]
	Flavonoid (flavanone)	4′-O-Methyl-diplacone	*Paulownia tomentosa*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 12.70 µM).	[254]
	Flavonoid (flavanone)	Diplacone	*Paulownia tomentosa*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 10.40 µM).	[254]
	Flavonoid (flavanone)	Mimulone	*Paulownia tomentosa*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 14.40 µM).	[254]
	Flavonoid (flavanone)	Bavachinin	*Psoralea corylifolia, Rutaceae family*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 38.40 µM).	[255]
	Flavonoid (flavone glycoside)	Rhoifolin	*Rhus succedanea*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 27.45 µM).	[271]
	Flavonoid (flavone glycoside)	Baicalin	*Scutellaria baicalensis, Scutellaria lateriflora*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 6.41 µM); Reduction of viral RNA level (EC_{50}: 27.87 µM); Inhibition of Mpro (IC_{50}: 83.4); Inhibition of non-structural protein 15 RNAse activity (IC_{50}: 7.98 µM); Inhibition of Mpro (IC_{50}: 34.71 µM).	[170, 172, 173, 264]
	Flavonoid (flavone)	Pectolinarin	*Cirsium* spp., *Linaria* spp.	SARS-CoV SARS-CoV-2	*In vitro*	Inhibition of SARS-CoV-2 Mpro (IC_{50}: 51.64 mM); Inhibition of SARS-CoV Mpro (IC_{50}: 37.78 µM).	[133, 173]
	Flavonoid (flavone)	Corylifol A	*Psoralea corylifolia*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 32.20 µM)	[255]
	Flavonoid (flavone)	Baicalein	*Scutellaria baicalensis, Scutellaria lateriflora*	SARS-CoV-2	*In vitro* *In vivo*	Reduction of viral RNA concentration (EC_{50}: 2.94 M); Reduction of viral RNA levels (EC_{50}: 10 µM); Inhibition of Mpro (IC_{50}: 0.39 µM); Reduction of viral RNA concentration (EC_{50}: 2.92 µM); Reduction of cytopathic effects; Reduction of viral load, body weight loss, and cellular inflammation in the lungs in laboratory mice (0.1–50 µM); Inhibition of Mpro and RNA polymerization activity of SARS-CoV-2 Mpro (IC_{50}: 4.5 Mm).	[106, 169–172]

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▶ **Table 2** Plant SMs with potential inhibitory effects against SARS-CoV-2 and SARS-CoV. *continued*

Chemical superclass	Chemical class	Metabolite(s)	Plant	Virus	Study	Function	Ref.
Phenolic compounds	Flavonoid (flavone)	Quercetagetin	*Scutellaria baicalensis*, *Tagetes erecta*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 1.24 µM).	[170]
	Flavonoid (flavone)	Scutellarein	*Scutellaria* spp.	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 5.8 µM) through a protease assay.	[170]
	Flavonoid (flavonol glycoside)	Rutin	*Fagopyrum esculentum*, *Rheum* spp.	SARS-CoV-2	*In vitro*	Exhibition of stable binding affinity against S-ACE2 protein through a deubiquitinase inhibition assay.	[272]
	Flavonoid (flavonol)	Quercetin	*Allium cepa*, *Vaccinium* spp., *Torreya nucifera*	SARS-CoV SARS-CoV-2	*In silico* *In vitro*	Inhibition of SARS-CoV-2 Mpro (K_i ~ 7.00 µM); Inhibition of SARS-CoV Mpro (IC_{50}: 23.80 µM); Favorable binding affinity exhibition toward SARS-CoV S protein (− 8.5 kcal/Mol).	[273–275]
	Flavonoid (flavonol)	Kaempferol	*Capparis spinosa*, *Crocus sativus*	SARS-CoV-2 SARS-CoV	*In silico* *In vitro*	Reduction of cytopathic effects (EC_{50}: 34.46 µM); Inhibition of Mpro; Inhibition of 3a ion channel of coronavirus; Favorable binding affinity exhibition toward SARS-CoV-2 S protein (− 7.4 kcal/Mol).	[146, 157, 276]
	Flavonoid (flavonol)	Myricetin	*Ceratonia siliqua*, *Vaccinium* spp.	SARS-CoV-2 SARS-CoV	*In vitro* *Clinical trial*	Inhibition of Mpro (IC_{50}: 2.86 µM); Inhibition of nonstructural protein 13 by affecting the ATPase activity; Inhibition of the enzymatic activity of SARS-CoV-2 Mpro and interfere the replication of SARS-CoV-2 (IC_{50}: 0.63 µM) in Vero E6 cells.	[170, 277, 278]
	Flavonoid (flavanonol)	Dihydromyricetin	*Ampelopsis grossedentata*	SARS-CoV-2	*In vitro*	Significant inhibition of viral replication in Vero cells and inhibition of Mpro (IC_{50}: 1.20 µM).	[170]
	Flavonoid (flavonol)	Isorhamnetin	*Hippophae rhamnoides*, *Opuntia ficus-indica*	SARS-CoV-2 SARS-CoV	*In vitro*	Limiting the entry of the SARS-CoV-2 pseudotyped virus.	[279]
	Flavonoid (flavonol)	Herbacetin	*Linum usitatissimum*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 53.90 µM).	[173]
	Flavonoid (isoflavone)	Neobavaisoflavone	*Psoralea corylifolia*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 18.30 µM).	[255]
	Flavonoid (rotenoid)	12α-epi-Millettosin	*Millettia usaramensis*	SARS-CoV-2	*In silico*	Favorable binding affinity exhibition toward the RdRp enzyme (− 8.0 kcal/mol).	[280]
	Flavonoid (rotenoid)	Usararotenoid A	*Millettia usaramensis*	SARS-CoV-2	*In silico*	Favorable binding affinity exhibition toward the RdRp enzyme (− 8.4 kcal/mol).	[280]
	Flavonoid glycoside	Vicenin	*Ocimum sanctum*	SARS-CoV-2 SARS-CoV	*In silico* *In vitro*	Favorable binding affinity exhibition toward Inhibition of Mpro (IC_{50}: 8.97 kcal/mol).	[242]
	Flavonoid glycoside	Isorientin 4′-O-glucoside 2′ ′-O-p-hydroxybenzoate	*Ocimum sanctum*	SARS-CoV-2	*In silico*	Favorable binding affinity exhibition toward Mpro (8.55 kcal/mol).	[242]
	Homoisoflavonoid	Brazilin	*Paubrasilia echinata*, *Caesalpinia sappan*	SARS-CoV-2 SARS-CoV	*In vitro*	Inhibition of SARS-CoV-2 RBD/hACE2 dose-dependently; Limiting the SARS-CoV-2 pseudotyped virus entry dose-dependently.	[259]
	Biflavonoid	Amentoflavone	*Torreya nucifera*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 8.3 ± 1.2 µM) dose-dependently.	[275]
	Biflavonoid	Bilobetin	*Torreya nucifera*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 72.3 ± 4.5 µM) dose-dependently.	[275]

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▶ **Table 2** Plant SMs with potential inhibitory effects against SARS-CoV-2 and SARS-CoV. *continued*

Chemical superclass	Chemical class	Metabolite(s)	Plant	Virus	Study	Function	Ref.
Phenolic compounds	Biflavonoid	Ginkgetin	*Torreya nucifera*	SARS-CoV		Inhibition of Mpro (IC_{50}: 32.0 ± 1.7 μM) dose-dependently.	[275]
	Biflavonoid	Sciadopitysin	*Torreya nucifera*	SARS-CoV		Inhibition of Mpro (IC_{50} 38.4 ± 0.2 μM) dose-dependently.	[275]
	Lignan	Nordihydroguaiaretic acid	*Larrea tridentata*	SARS-CoV-2	*In vitro*	Inhibition of PLpro (IC_{50}: 1.06 μM); Inhibition of nonstructural protein 3 (IC_{50}: 1.62 μM).	[281]
	Lignan	Savinin	*Chamaecyparis taiwanensis*	SARS-CoV SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 25.00 μM).	[282]
	Lignan glycoside	Phillyrin	*Forsythia suspensa*	SARS-CoV-2	*In vitro*	Inhibition of viral replication (IC_{50}: 63.90 μg/ml) in Vero E6 cells; Reduction of mRNA levels of TNF-α, IL-6, IL-1β, MCP-1, and IP-10, (markers of pro-inflammatory cytokine production).	[283]
	Arylnaphtalene lignan	Diphyllin	*Cleistanthus collinus*	SARS-CoV-2	*In vitro*	Reduction of SARS-CoV-2 viral titers in Vero cells.	[284]
	Arylnaphthalene lactone lignan glycoside	Cleistanthin B	*Cleistanthus collinus*	SARS-CoV-2	*In vitro*	Reduction of viral titers (EC_{50}: 6.51 μM).	[284]
	Phenolic acid	Ginkgolic acid	*Ginkgo biloba*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 1.79 ± 0.58 μM); Inhibition of PLpro (IC_{50}: 16.30 ± 0.64 μM).	[285]
	Phenolic acid	Anacardic acid	*Anacardium occidentale*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 2.07 ± 0.35 μM); Inhibition of PLpro (IC_{50}: 17.08 ± 1.30 μM).	[285]
	Phenolic acid	Chlorogenic acid	*Pimenta dioica*	SARS-CoV-2	*In vitro*	Promising antiviral activity against SARS-CoV-2 (IC_{50}: 360 μg/mL)	[286]
	Phenolic acid	Ellagic acid	*Rubus fruticosus*, *Fragaria ananassa*	SARS-CoV-2	*In vitro*	Inhibition of RBD-hACE2 binding (IC_{50}: 2.5 μg/mL).	[287]
	Phenylethanoid glycoside	Forsythoside A	*Forsythia suspensa*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 3.18 μM).	[172]
	Phenylethanoid glycoside	Forsythoside B	*Forsythia suspensa*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 2.88 μM).	[172]
	Phenylethanoid glycoside	Forsythoside E	*Forsythia suspensa*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 6.88 μM).	[172]
	Phenylethanoid glycoside	Forsythoside H	*Forsythia suspensa*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 10.17 μM).	[172]
	Phenylethanoid glycoside	Forsythoside I	*Forsythia suspensa*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 5.47 μM).	[172]
	Phenylethanoid glycoside	Isoforsythiaside	*Forsythia suspensa*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 5.85 μM).	[172]
	Phenylethanoid glycoside	Acteoside	*Scrophularia ningpoensis*, *Byblis liniflora*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 43 nM).	[269]
	Gingerols	6-Gingerol	*Zingiber officinale*	SARS-CoV-2	*In silico* *In vitro*	Favorable binding affinity with viral proteases (Mpro with − 15.7591 kJ/mol), RNA binding protein and S protein; Reduction of viral titers (EC_{50}: 1.38 μM).	[268, 288]

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▶ **Table 2** Plant SMs with potential inhibitory effects against SARS-CoV-2 and SARS-CoV. *continued*

Chemical superclass	Chemical class	Metabolite(s)	Plant	Virus	Study	Function	Ref.
Phenolic compounds	Stilbenoid	Kobophenol A	*Caragana chamlagu, Caragana sinica, Carex folliculata*	SARS CoV-2	*In vitro*	Inhibition of S protein (IC_{50}: 1.81 µM).	[289]
	Stilbenoid	Resveratrol	*Polygonum cuspidatum*	SARS-CoV-2	*In vitro*	Reduction of the expression of ACE2, the control of the renin-angiotensin system (RAS), the activation of the immune system, and the production of pro-inflammatory cytokines; Potential inhibitory activity against RdRp and PLpro of SARS-CoV-2; Interfering with the virus's infectious cycle of reproduction; Reduction of SARS-CoV-2 replication in Vero-E6 cells, as well as in a primary human bronchial epithelial cell type.	[290–292]
	Stilbenoid	Pterostilbene	*Vaccinium* spp., *Pterocarpus marsupium*	SARS-CoV-2	*In vitro*	Reduction of viral titers in Vero E6 (EC_{50}: 19 µM); Inhibition of infection in human primary bronchial epithelial cells.	[292]
	Anthraquinone	Aloe emodin	*Aloe barbadensis*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 132.00 µM).	[247]
	Dianthrone	Sennoside B	*Cassia fistula*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 104 nM).	[269]
	Naphthodianthrone	Hypericin	*Hypericum perforatum*	SARS-CoV-2	*In vitro*	Reduction of SARS-CoV-2 replication in Vero-E6 cells, as well as in a primary human bronchial epithelial cell type. Inhibition of Mpro (IC_{50}: 63.6 µM); Inhibition of PLpro deubiquitinase activity.	[272, 293]
Terpenoids	Monoterpenoid phenol	Carvacrol	*Thymus vulgaris*	SARS-CoV-2	*In silico*	Favorable binding affinity exhibition toward Mpro (− 4.0 kcal/Mol).	[94]
	Sesquiterpene glycoside	Tinocordiside	*Tinospora cordifolia*	SARS-CoV-2	*In silico* *In vitro*	Favorable binding affinity exhibition toward Mpro (8.10 kcal/mol).	[242]
	Sesquiterpene lactone	Arteannuin B	*Artemisia annua*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (EC_{50}: 10.28 ± 1.12 µM).	[294, 295]
	Sesquiterpene lactone	Artemisinin	*Artemisia annua*	SARS-CoV-2	*In silico* *In vitro*	Inhibition of Mpro (IC_{50}: 70 µM); Antiviral activity (EC_{50}: 64.45 ± 2.58 µM); Range of EC_{50} in different cell types: 151 to at least 208 µg/mL; The artemisinin-piperaquine group cleared SARS-CoV-2 faster in mild-to-moderate COVID-19 patients compared to the control group. Nonetheless, physicians should be cautious of QT interval changes when administering artemisinin-piperaquine (an open-label, non-randomized, and controlled trial).	[294–299]
	Sesquiterpene lactone	Artesunate	*Artemisia annua*	SARS-CoV-2	*In vitro*	Antiviral activity (EC_{50}: 12.98 ± 5.30 µM); Range of EC_{50} in different cell types: 7–12 µg/mL; Inhibition of Mpro.	[294, 295, 297]
	Sesquiterpene lactone	Artelinic acid	*Artemisia annua*	SARS-CoV-2	*In silico*	Favorable binding affinity exhibition toward S protein (− 7.1 kcal/mol) and Mpro.	[295, 299]
	Sesquiterpenoid	Ichangin	*Citrus cavaleriei, Citrus medica, Raputiarana heptaphylla*	SARS-CoV-2	*In silico*	Favorable binding affinity exhibition toward Mpro (− 8.40 kcal/Mol).	[216]
	Diterpenoid	Ferruginol	*Torreya nucifera*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 49.6 ± 1.5 µM) dose-dependently.	[275]
	Diterpenoid	Dihydrotanshinone I	*Salvia miltiorrhiza*	SARS-CoV-2 SARS-CoV	*In vitro* *In vivo*	Inhibition of SARS-CoV-2 PLpro (IC_{50}: 0.5861 µM); Inhibition of Mpro (EC_{50}: 14.40 µM) and PLpro (EC_{50}: 4.90 µM) of SARS-CoV.	[217, 300]

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▶ **Table 2** Plant SMs with potential inhibitory effects against SARS-CoV-2 and SARS-CoV. *continued*

Chemical superclass	Chemical class	Metabolite(s)	Plant	Virus	Study	Function	Ref.
Terpenoids	Diterpenoid	Rosmariquinone	*Salvia miltiorrhiza*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 21.10 µM); Inhibition of PLpro (IC_{50}: 30.00 µM).	[217]
	Diterpenoid	Tanshinone I	*Salvia miltiorrhiza*	SARS-CoV-2 SARS-CoV	*In vitro*	Reduction of viral titers (EC_{50}: 2.26 µM); Inhibition of SARS-CoV-2 PLpro (IC_{50}: 5.63 µM); Inhibition of Mpro (EC_{50}: 38.70 µM) and PLpro (EC_{50}: 8.80 µM) of SARS-CoV.	[217, 301]
	Diterpenoid	Tanshinone II	*Salvia miltiorrhiza*	SARS-CoV-2	*In vitro*	Inhibition of PLpro (IC_{50}: 1.571 µM).	[217]
	Diterpenoid	Andrographolide	*Andrographis paniculata*	SARS-CoV-2	*In vitro*	Reduction of viral titers in Calu-3 cell line and Vero E6 cells (EC_{50}: 0.034 µM and 0.28 µM resp.); Inhibition of Mpro (IC_{50}: 15.05 µM).	[302, 303]
	Triterpenoid	Ursolic acid	*Vaccinium* spp., *Ocimum sanctum*	SARS-CoV-2	*In silico* *In vitro*	Inhibition of Mpro (IC_{50}: 12.57 µM); Favorable binding affinity exhibition toward Mpro (8.52 kcal/mol); Favorable binding affinity exhibition toward Mpro (− 5.9 kcal/mol).	[94, 242, 304]
	Triterpenoid	Betulinic acid	*Betula pubescens*, *Ziziphus mauritiana*, *Breynia fruticosa*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 14.55 µM); Inhibition of SARS-CoV-2 S protein RBD binding to ACE2 of host cell (IC_{50}: 0.1 µM).	[210, 304]
	Triterpenoid	Oleanolic acid	*Betula pubescens*, *Ziziphus mauritiana*, *Breynia fruticosa*	SARS-CoV-2	*In silico* *In vitro*	Favorable binding affinity exhibition toward Mpro (− 6.0 kcal/mol); Inhibition of SARS-CoV-2 S protein RBD binding to ACE2 of host cell (IC_{50}: 1 µM).	[94, 210]
	Triterpenoid	Betulin	*Betula pubescens*, *Ziziphus mauritiana*	SARS-CoV-2	*In vitro*	Inhibition of Mpro (IC_{50}: 89.67 µM).	[304]
	Triterpenoid	Glycyrrhetinic acid	*Glycyrrhiza glabra*	SARS-CoV-2	*In vitro*	Inhibition of S protein-ACE2 binding between SARS-CoV-2 and host cell (IC_{50}: 10 µM).	[210]
	Triterpenoid	Maslinic acid	*Olea europaea*	SARS-CoV-2	*In vitro*	Inhibition of Mpro through a protease assay (IC_{50}: 3.22 µM).	[304]
	Triterpenoid	β-Amyrin	*Pisum sativum* *Brassica oleracea* *Celastrus hindsii*	SARS-CoV-2	*In silico*	Favorable binding affinity exhibition toward Mpro (− 8.79 kcal/Mol).	[216]
	Triterpenoid	Iguesterin	*Tripterygium regelii*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 2.6 ± 0.3 µM).	[305]
	Triterpenoid	Celastrol	*Tripterygium regelii*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 10.3 ± 0.2 µM).	[305]
	Triterpenoid	Pristimerin	*Tripterygium regelii*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 5.5 ± 0.7 µM).	[305]
	Triterpenoid	Tingenone	*Tripterygium regelii*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 9.9 µM).	[305]
	Triterpenoid (limonoid)	Deacetylnomilin	*Citrus spp.*	SARS-CoV-2	*In silico*	Favorable binding affinity exhibition toward Mpro (− 8.35 kcal/Mol).	[216]
	Triterpenoid (saponin)	Glycyrrhizin	*Glycyrrhiza glabra*	SARS-CoV-2	*In silico* *In vitro*	Reduction of viral titers (EC_{50}: 0.44 mg/ml); Dose-dependent inhibition of Mpro.	[306, 307]

continued next page

▶ **Table 2** Plant SMs with potential inhibitory effects against SARS-CoV-2 and SARS-CoV. *continued*

Chemical superclass	Chemical class	Metabolite(s)	Plant	Virus	Study	Function	Ref.
Terpenoids	Triterpenoid (saponin)	Saikosaponins U and V	*Bupleurum* spp., *Heteromorpha* spp., *Scrophularia scorodonia*	SARS-CoV-2	*In silico*	Favorable binding affinity exhibition toward S protein (− 7.272 and − 8.358 Kcal/Mol respectively).	[308]
	Triterpenoid (saponin)	Platycodin D	*Platycodon grandiflorus*	SARS-CoV-2	*In vitro*	Limiting the SARS-CoV-2 pseudotyped virus entrance into H1299/ACE2 (EC_{50}: 0.69 μM) and H1299/ACE2-TMPRSS2 cells (EC_{50}: 0.72 μM).	[309]
	Steroidal sapogenin	Sarsasapogenin	*Anemarrhena asphodeloides*	SARS-CoV-2	*In silico*	Favorable binding affinity exhibition toward non-structural protein 15 (− 8.5 kcal/Mol).	[310]
	Cardiac glycoside	Ouabain	*Acokanthera schimperi, Strophanthus Gratus, Breynia fruticosa*	SARS-CoV-2	*In vitro*	Reduction of viral RNA when added pre-infection and post-entry (IC_{50}: 0.024 μM).	[311]
	Cardiac glycoside	Digoxin	*Digitalis lanata*	SARS-CoV-2	*In vitro*	Reduction of viral RNA when added pre-infection and post-entry (EC_{50}: 0.043 μM).	[311]
	Withanolide glycoside	Withanoside V	*Withania somnifera*	SARS-CoV-2	*In silico*	Favorable binding affinity exhibition toward Mpro (IC_{50}: 10.32 kcal/mol).	[242]
Miscellaneous compounds	Cinnamic amide	Terrestriamide	*Tribulus terrestris, Ocimum sanctum*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 21.50 μM).	[312]
	Cinnamic amide	N-trans-caffeoyltyramine	*Tribulus terrestris*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 44.40 μM)	[312]
	Cinnamic amide	N-trans-coumaroyltyramine	*Tribulus terrestris*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 38.80 μM).	[312]
	Cinnamic amide	N-trans-feruloyloctopamine	*Tribulus terrestris*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 26.60 μM).	[312]
	Cinnamic amide	N-trans-feruloyltyramine	*Tribulus terrestris*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 70.10 μM).	[312]
	Cinnamic amide	Terrestrimine	*Tribulus terrestris*	SARS-CoV	*In vitro*	Inhibition of PLpro (IC_{50}: 15.80 μM).	[312]
	Glucosinolate	Sinigrin	*Isatis indigotica*	SARS-CoV	*In vitro*	Inhibition of Mpro (IC_{50}: 121.00 μM).	[247]
	Lectin	Griffithsin	*Griffithsia capitata*	SARS-CoV	*In vitro* *In vivo*	Antiviral activity (EC_{50}:48–94 nM); Inhibition of SARS-CoV S protein; Reduction of SARS-CoV infectivity *in vivo* (mouse-adapted SARS-CoV) and *in vitro* investigations; Recombinant griffithsin exhibited IC_{50} values of 34.0 and 5.4 nM against Delta and Omicron variants, respectively; Q-Griffithsin, when combined with carrageenan, exhibited a synergistic effect (EC_{50}: 0.2–3.8 μg/mL), and the combination index was less than 1, indicating a strong synergistic effect; Inhibition of SARS-CoV-2 pseudovirus infection (IC_{50}: 63 nmol/L); Inhibition of SARS-CoV-2 S-mediated cell to cell fusion (IC_{50}: 323 nmol/L).	[313–316]

cal formulations and delivery systems, including nanosuspensions, solid dispersions, microspheres, crystals, self-nanoemulsifying drug delivery systems (SNEDDS), and self-microemulsifying drug delivery systems (SMEDDS), have been developed and utilized to deliver natural products with antiviral properties [109]. These diverse technologies offer effective and reliable delivery of medicinal phytochemicals, addressing the challenges of bioavailability and solubility in antiviral drug administration.

A number of plant secondary metabolites have been subjected to clinical trials, with some trial outcomes still pending publication. These trials assess the efficacy of phytochemicals as standalone compounds, in combination with other natural bioactive compounds, drugs, or polyphenol-rich extracts and are specifically enumerated in ▶ **Table 3**. The list is sourced from ClinicalTrials.gov (accessed on June 20, 2023). As previously mentioned, numerous plant secondary metabolites have demonstrated favorable results in *in silico*, *in vitro*, and *in vivo* studies. Considering this, there is an optimistic outlook for the continuation of further clinical trials on these promising plant secondary metabolites.

Plant Metabolites and Their Effectiveness in Treatment of COVID-19

Plant compounds can be classified into primary and SMs [52]. Primary metabolites like proteins, lipids, and carbohydrates directly contribute to plant growth and development [52]. SMs, on the other hand, are versatile molecules that are often involved in environmental communication and plant defense [110]. They are also responsible for plant taste, odor, and color [52]. SMs are low-molecular-weight compounds and are biosynthetically derived from primary metabolites but are restricted to specific taxonomic groups or families in the plant kingdom [50, 110]. They are synthesized by specialized cell types at certain developmental stages [111]. SMs are found to have ecological functions, such as attracting pollinators, chemical adaptation to stress, or defense against predators or harmful microorganisms [111, 112].

Medicinal products from plants or herbs account for about 35% of the global medicine market (valued at USD1.1 trillion) [113]. As a source of antiviral chemicals, plant SMs offer a less expensive alternative to conventional medicines [114]. Metabolites of different medicinal plants and their mechanisms in dealing with SARS-CoV-2 and other coronaviruses are summarized in ▶ **Table 2**.

Flavonoids

Flavonoids are SM compounds found in many fruits, seeds, and leaves that act as a defensive mechanism against abiotic stressors [115–117]. The structure of flavonoids consists of a 15-carbon skeleton composed of two benzene rings joined by a pyran ring [118].

A large number of compounds belonging to this group show significant antiviral effects [119, 120]. Flavonoids have antiviral properties that hinder the virus's ability to attach and penetrate cells, impede its growth and transmission, stop the production of viral proteins and coatings formed by glycoprotein complexes [120]. Flavonoids also aid the communication process within the infected cell by activating transcription factors and releasing cytokines [121].

To date, a large number of flavonoids have been identified from various plant species. Based on their chemical structure, degree of oxidation, and substitution pattern of the C ring (heterocyclic pyran ring), they are divided into flavanones, flavonols, flavanols, flavones, isoflavonoids, chalcones, and anthocyanidins [119]. Considering that these compounds have shown potential antiviral properties against coronaviruses, they may also be effective in the treatment of COVID-19 [122].

Silymarin is obtained from the plant source *Silybum marianum*, native to Crete, Greece, Iran, and Afghanistan, and is a blend of flavonolignans (silybin, isosilybin, silychristin, and siliandrin) and a flavonol (taxifolin) [123]. It is widely recognized for its liver-protective properties [124]. Its anti-SARS-CoV-2 potential stems from its ability to decrease the expression of the host cell surface receptor TMPRSS2 [123]. Hanafy et al. produced bovine serum albumin nanoparticles loaded with silymarin and curcumin to build an inhalable delivery method for pneumonia treatment [125]. They discovered that silymarin has potential antiviral efficacy against SARS-CoV-2 *in vitro* at a dose of 25 g/mL [125]. According to the findings, silymarin's anti-inflammatory and antioxidant properties may protect the lungs during SARS-CoV-2 infection and inhibit the ACE2 receptor, preventing viral entry [125]. Currently, a phase III clinical study (NCT04394208) is recruiting participants to assess the clinical outcomes of silymarin in adults with COVID-19 pneumonia under standard care, with either a placebo or oral silymarin [126].

One of the main concerns with the administration of flavonoids is that they have limited absorption and bioavailability when taken orally due to their hydrophilic nature as glycosides [127, 128]. Flavonoids are extensively metabolized in the intestine and liver, resulting in the formation of conjugated forms that facilitate their elimination [127]. Consequently, the low bioavailability of flavonoids poses a challenge for oral administration [127]. To address this issue, various strategies have been employed, such as using nano-formulations to improve intestinal absorption, employing microemulsions or complexing with β-cyclodextrin to enhance bioavailability [127]. Inhalation of flavonoids encapsulated in smart nanoparticles targeting ACE2 receptors has been shown to increase bioavailability and efficacy in mice [122]. Additionally, nano-emulsion and nano-liposomal formulations have been found to improve oral bioavailability, therapeutic efficacy, and stability of flavonoids like naringenin and fisetin, with the latter exhibiting a 47-fold increase in bioavailability compared to the free form [129, 130].

Here, we focus on the flavonoids quercetin, baicalin, baicalein, kaempferol, luteolin, and a group of flavan-3-ols known as catechins, which have shown promise in COVID-19 drug discovery and development. These compounds have been the subject of numerous studies due to their potential antiviral effects against SARS-CoV-2.

▶ **Table 3** List of promising SMs undergoing clinical trials as of June 20, 2023. Retrieved from www.clinicaltrials.gov.

SM	Official title of the clinical trial	Intervention/treatment	Results	ClinicalTrials.gov identifier	References
Q-Griffithsin	A phase 1a safety, acceptability and pharmacokinetics study of Q-griffithsin intranasal spray for broad-spectrum coronavirus pre-exposure prophylaxis: a study of the prevent-COVID-19 program	Drug: Q-Griffithsin intranasal spray administered as a single dose	Not posted yet	NCT05122260	–
Ferulic acid	Retrospective observational study to describe the evolution of SARS-CoV-2 disease and the profile of patients treated or not with Imuno TF and a combination of nutraceuticals and who have tested positive for COVID-19	Dietary supplement: ImmunoFormulation (ImmunoFormulation contains Imuno TF, selenium, zinc, ascorbic acid, vitamin D, Miodesin, resveratrol, Spirulina, ferulic acid, glucosamine, N-acetylcysteine, and SiliciuMax.)	Not posted yet	NCT04666753	–
Luteolin	Effects of palmitoylethanolamide co- ultramicronized with luteoline (Pea-lut) on frontal lobe functions and GABAergic transmission in long COVID patients. An 8-week randomized controlled trial	Dietary supplement: palmitoylethanolamide co-ultramicronized with antioxidant flavonoid luteolin (PEA-LUT)	Not posted yet	NCT05311852	–
	Olfactory dysfunction after COVID-19: conventional therapy versus intervention treatment with co-ultraPEALut	Combination product: co-ultraPEALut	Not posted yet	NCT04853836	–
Quercetin	A prospective, randomized, open-labelled, controlled trial to study the adjuvant benefits of Quercetin Phytosome in patients with diagnosis of COVID-19	Drug: Standard COVID-19 care Dietary supplement: Quercetin Phytosome	The supplementation demonstrated notable reductions in the hospitalization rate (9.2% vs. 28.9%), length of hospital stay (1.6 vs. 6.8 days), need for oxygen therapy (1.3 vs. 19.7%), and symptom severity when compared to the control group.	NCT04578158	[317]
	Study to investigate the benefits of dietary supplement quercetin for early symptoms of COVID-19	Drug: standard of care for COVID-19 as per the hospital guidelines Dietary supplement: Quercetin Phytosome (QP)	The results indicated that quercetin not only expedited the conversion of positive molecular test results to negative but also alleviated the severity of COVID-19 symptoms. The number of patients hospitalized was lower than in the control group.	NCT04861298	[318, 319]
	The study of quadruple therapy zinc, quercetin, bromelain and vitamin C on the clinical outcomes of patients infected with COVID-19	Drug: quercetin Dietary supplement: bromelain Drug: Zinc Drug: vitamin C	Not posted yet	NCT04468139	–
	Treatment benefits of flavonoids quercetin and curcumin supplements for mild symptoms of COVID-19	Drug: standard of care Dietary supplement: investigational treatment	Not posted yet	NCT05130671	–
	Randomized, placebo-controlled clinical trial to evaluate the efficacy of an oral nutritional supplement based on quercetin in the prevention of COVID-19 infection for a duration of 3 months	Dietary supplement: quercetin	Not posted yet	NCT05037240	–
	Complementary therapy of dietary supplements curcumin, quercetin and vitamin D3 for mild to moderate symptoms of COVID-19	Dietary supplement: complementary therapy Drug: standard of care	Not posted yet	NCT04603690	–

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▶ **Table 3** List of promising SMs undergoing clinical trials as of June 20, 2023. Retrieved from www.clinicaltrials.gov. *continued*

SM	Official title of the clinical trial	Intervention/treatment	Results	ClinicalTrials.gov identifier	References
Quercetin	The effectiveness of phytotherapy in the treatment of SARS-COV2 (COVID-19)	Drug: quercetin	Not posted yet	NCT04851821	–
	Efficacy of Psidii guava's extract for mild and symptomless coronavirus disease-19 (COVID-19)	Drug: extract Psidii guava Combination product: standard therapy for COVID-19 patient	Not posted yet	NCT04810728	–
	Safety and efficacy of hydroxychloroquine for the treatment & prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Drug: hydroxychloroquine Dietary supplement: vitamins and minerals Drug: azithromycin	Not posted yet	NCT04590274	–
	A comparative randomized clinical study on COVID-19 positive hospitalized patients supplemented with NASAFYTOL	Dietary supplement: NASAFYTOL (NASAFYTOL is a dietary supplement that contains a mixture of curcumin, quercetin, and vitamin D.) Dietary supplement: FULTIUM-D3 800 Drug: standard of care treatment	Not posted yet	NCT04844658	–
Epigallocatechin-3-gallate (EGCG)	A multicenter, double-blind, randomized, placebo-controlled clinical trial to protect health workers against COVID-19 by Using Previfenon as chemoprophylaxis during a SARS-CoV-2 outbreak. The HERD study	Drug: Previfenon (EGCG)	Not posted yet	NCT04446065	–
Curcumin	The effect of a mixture of micellized curcumin/*Boswellia serrata*/ascorbic acid on health-related quality of life in patients with post-acute COVID-19 syndrome	Dietary supplement: curcumin/*Boswellia serrata*/ascorbic acid mixture	Not posted yet	NCT05150782	–
	Treatment benefits of flavonoids quercetin and curcumin supplements for mild symptoms of COVID-19	Drug: standard of care Dietary supplement: investigational treatment	Not posted yet	NCT05130671	–
	Complementary therapy of dietary supplements curcumin, quercetin and vitamin D3 for mild to moderate symptoms of COVID-19	Dietary supplement: complementary therapy Drug: standard of care	Not posted yet	NCT04603690	–
	A phase III, double-blind, controlled clinical study designed to evaluate the effect of CimetrA in patients diagnosed with COVID-19	Drug: CimetrA-1 (CimetrA-1 contains a combination of curcumin (40 mg), frankincense extract (30 mg), and ascorbic acid (120 mg).) Drug: CimetrA-2 (CimetrA-2 contains a combination of curcumin (28 mg), frankincense extract (21 mg), and ascorbic acid (84 mg).)	Not posted yet	NCT04802382	–
	A phase II, controlled clinical study designed to evaluate the effect of ArtemiC in patients diagnosed with COVID-19	Drug: ArtemiC (ArtemiC contains a combination of artemisinin (12 mg), curcumin (40 mg), frankincense extract (30 mg) and ascorbic acid (120 mg).	Not posted yet	NCT04382040	–
	A Phase II b, double blind, placebo-controlled clinical study designed to evaluate the effect of CimetrA in patients diagnosed with COVID-19	Drug: treatment administration (twice a day)	Not posted yet	NCT05037162	–
	Oral nutritional supplements in treatment of elderly mild-to- moderate COVID-19 (ONSITEMC)	Dietary supplement: oral nutritional supplements	Not posted yet	NCT05629975	–

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▶ **Table 3** List of promising SMs undergoing clinical trials as of June 20, 2023. Retrieved from www.clinicaltrials.gov. *continued*

SM	Official title of the clinical trial	Intervention/treatment	Results	ClinicalTrials.gov identifier	References
Curcumin	A comparative randomized clinical study on COVID-19 positive hospitalized patients supplemented with NASAFYTOL	Dietary supplement: NASAFYTOL (NASAFYTOL is a dietary supplement that contains a mixture of curcumin, quercetin, and vitamin D.) Dietary supplement: FULTIUM -D3 800 Drug: standard of care treatment	Not posted yet	NCT04844658	–
Resveratrol	Randomized double-blind placebo-controlled proof-of- concept trial of resveratrol, a plant polyphenol, for the outpatient treatment of mild coronavirus disease (COVID- 19)	Drug: resveratrol Dietary supplement: vitamin D3	The resveratrol group exhibited a lower incidence of hospitalization, COVID-19-related Accident and emergency visits, and pneumonia when compared to the placebo group	NCT04400890	[320]
	A pilot randomized controlled clinical study of resveratrol for discharged COVID 19 patients in order to evaluate its therapeutic effects against fibrosis	Drug: resveratrol	Not posted yet	NCT04799743	–
	Can SARS-CoV-2 viral shedding in COVID-19 disease be reduced by resveratrol- assisted zinc ingestion, a direct inhibitor of SARS-CoV-2-RNA polymerase? a single blinded phase II protocol (reszinate trial)	Dietary supplement: zinc picolinate Dietary supplement: resveratrol	Not posted yet	NCT04542993	–
	Retrospective observational study to describe the evolution of SARS-CoV-2 disease and the profile of patients treated or not with Imuno TF and a combination of nutraceuticals and who have tested positive for COVID-19	Dietary supplement: ImmunoFormulation (ImmunoFormulation contains Imuno TF, selenium, zinc, ascorbic acid, vitamin D, Miodesin, resveratrol, Spirulina, ferulic acid, glucosamine, N-acetylcysteine, and SiliciuMax.)	Not posted yet	NCT04666753	–
Oleuropein	Assessment of the clinical effectiveness of standardized olive leaf capsules; as a co-therapy in the treatment of non-hospitalized COVID-19 patients; a randomized clinical trial	Dietary supplement: NusaPure standardized olive leaves capsule, 750 mg (50% oleuropein)	Not posted yet	NCT04873349	–
	Evaluation of the immunomodulatory and preventive effects of olive leaf tea against COVID-19	Dietary supplement: olive leaf tea	Not posted yet	NCT05222347	–

Quercetin

Quercetin is a flavonoid found in vegetables such as onions, dill, and cilantro and fruits such as capers, apples, and berries [131]. Molecular docking and SPR/FRET-based bioassays, as well as mutagenesis studies, indicated the potential antiviral effect of quercetin and its derivatives by inhibiting the Mpro of the SARS-CoV virus [132]. Considering the similarity of more than 95% of the gene encoding Mpro in SARS-CoV-2 with the same gene in the SARS-CoV virus, Mpro inhibitors are considered promising drugs for COVID-19 [114]. Quercetin exhibited more than 80% inhibitory activity on recombinant Mpro expressed in *Pichia pastoris* yeast in laboratory conditions (with an IC_{50} value of 73 µM) [133]. Recent computational studies and data from molecular docking also indicated that this molecule is one of the potential inhibitors of the Mpro of the SARS-CoV-2 virus [134–136].

According to Cherrak et al., quercetin-3-O-rhamnoside and quercetin-3-O-neohesperidoside display a strong inhibitory activity on SARS-CoV-2 Mpro [137]. Surprisingly, it has been shown that quercetin and quercetin-3-O-glucoside form better bonds with PLpro and Mpro viral proteins compared to remdesivir as a positive control [138]. Quercetin-3-O-glucoside had the highest PLpro binding score among the tested molecules [138]. In addition, a computer study conducted by Joshi et al. showed that quercetin-3-O-vicianoside, quercetin-3-O-glucuronide-7-O-glucoside, and quercetin-7-O-galactoside had low binding energy with the Mpro of the SARS-CoV-2 virus [139].

Quercetin and its derivatives show high binding energy with other drug targets such as S protein, ACE2 [140–144], and RdRp [145, 146]. Ascorbate and quercetin work synergistically to treat COVID-19 due to their shared antiviral and immunomodulatory effects, as well as ascorbate's ability to recycle quercetin [147].

Isoquercetin is the 3-O-glucoside of quercetin [148]. It has a higher accumulation rate than quercetin in the intestinal mucosa, where it is converted to quercetin, which is then absorbed by en-

terocytes, transported to the liver, released into circulation, and distributed to organs, primarily as metabolic conjugates [148]. In general, isoquercetin is less active than quercetin *in vitro* and *ex vivo*, but it is equally or more active *in vivo*, suggesting that it is largely a more absorbable precursor to quercetin, with better pharmacokinetics [148].

However, there are some aspects hampering the utilization of quercetin as a drug, such as its low absorption and bioavailability, quick metabolism, and interindividual variability [149, 150]. Serum albumin sequesters quercetin, contributing to its poor bioavailability [151]. Oral administration of isoquercetin, on the other hand, has much higher bioavailability than quercetin itself [152]. Isoquercetin also has a lower affinity for albumin, suggesting that it is less sequestered in the intestines and blood [151]. It has been shown that quercetin accumulates in red blood cells and may be removed by albumin, indicating that albumin may operate as a quercetin transporter in the body [149, 153]. Furthermore, quercetin metabolites, such as quercetin 3-O-glucuronide and isorhamnetin, have physiological features comparable to the aglycone form, including antiviral capabilities [154–156].

Kaempferol

Kaempferol is another flavonoid that belongs to the flavonol subclass. According to a study conducted by Schwarz et al. in 2013, kaempferol derivatives containing a rhamnose residue demonstrate significant effectiveness in inhibiting the 3a ion channel, a channel crucial to the intricate release mechanism of SARS-CoV [157]. The researchers propose that viral ion channels, in general, hold promise as targets for developing antiviral agents [157]. Specifically, they highlight kaempferol glycosides as strong candidates for targeting the 3a channel proteins of coronaviruses [157]. Moreover, in a study conducted by Shaldam et al. in 2021, it was found that kaempferol exhibits one of the strongest interactions with the target enzymes of SARS-CoV-2, namely Mpro and RdRp [158]. As a result, it may be considered an effective inhibitor for SARS-CoV-2 [158].

Catechins

Catechins and their derivatives, including (−)-epigallocatechin-3-gallate (EGCG), (−)-epicatechingallate (ECG), and (−)-epigallocatechin (EGC), belong to the subclass of flavanols and have many medicinal properties [159]. Considering the ability of catechins to bind to the viral S protein and ACE2 of the host cell, they can be considered as an option for treating COVID-19 [160].

In a study conducted by Henss et al. among the different catechins, EGCG was particularly effective in inhibiting the SARS-CoV-2 virus and showed no toxicity at effective concentrations [161]. EGCG also prevented SARS-CoV-2 from binding to ACE2 when used before COVID-19 infection [161]. EGCG was found to reduce virus infections *in vitro* by preventing the entry of SARS-CoV-2, as well as MERS-CoV and SARS-CoV pseudo-typed lentiviral vectors, indicating a more general antiviral effect of this compound [161]. In contrast, epicatechin (EC) did not show any effect in inhibiting SARS-CoV-2 and other coronaviruses [161]. In one study, catechin performed better than six conventional drugs, namely tenofovir, ritonavir, dolutegravir, boceprevir, tinofovirala-fenamide, and zanamivir, in serving as a multi-target drug because it exhibits the highest binding strength to the five proteins that the virus requires to infiltrate the host cell, namely the receptor-binding domain (RBD), cathepsin L, N protein, Mpro, and nonstructural protein 6 [162]. In a separate study, all types of catechins, including ECGC, indicated a considerable affinity to the S protein of the SARS-CoV-2 virus [163]. Moreover, Rabezanahary et al. demonstrated the inhibitory effects of EGCG and isoquercetin against SARS-CoV-2 *in vitro* and proved their substantial antiviral synergistic effects with remdesivir [164].

It is important to note that a clinical phase II/III trial is currently underway (NCT04446065) to evaluate the chemoprophylactic effects of EGCG on COVID-19 in healthy workers [165].

Baicalin and baicalein

Baicalin and baicalein are two compounds that are primarily obtained from the root of *Scutellaria baicalensis*, an East Asian plant [166]. In traditional Chinese medicine, this plant is used to treat obesity, hypertension, and dysentery, as well as inflammatory diseases, arteriosclerosis, and the common cold [167, 168].

When baicalin is metabolized in the intestine, it transforms into baicalein [169]. Numerous studies have reported that both of these compounds have an inhibitory effect against the SARS-COV-2 virus, particularly 3CLpro [170–173].

Zandi et al. have demonstrated that baicalein and its aglycon baicalein exhibit *in vitro* anti-SARS-CoV-2 activity, directly inhibiting the activity of SARS-CoV-2 RdRp [169]. They reported an EC_{50} of 4.5 µM and an EC_{90} of 7.6 µM for baicalein [169]. Su et al. found the binding activity of baicalein with Mpro and confirmed its anti-SARS-CoV-2 activity *in vitro* [172]. Moreover, their further study highlighted the presence of baicalin and baicalein, two bioactive ingredients of Shuanghuanglian (a Chinese traditional medicine), which provided supporting evidence for the potential antiviral activity of Shuanghuanglian [172]. However, the exact antiviral ability of baicalin and baicalein requires verification through animal models or clinical trials.

Luteolin

Luteolin is a flavonoid present in edible plants, including oregano, celery, parsley, and juniper berries [174]. Investigations into the properties of luteolin against the SARS-CoV virus have demonstrated its antiviral nature [175, 176]. Its potential in preventing the entry of SARS-CoV-2 into cells has been supported by various analyses, including the relaxed complex scheme analysis, classical molecular docking simulations, and metadynamics simulations [177]. Researchers such as Xie et al. conducted a comprehensive study employing system pharmacology and bioinformatic analysis, which revealed that luteolin holds significant promise as a treatment for COVID-19/asthma comorbidity [178]. This is attributed to its antiviral effects, regulation of inflammation and immune responses, reduction in oxidative stress, and modulation of blood circulation [178]. Clinical findings further suggest that oral supplementation of luteolin improves the recovery of olfactory function following COVID-19 [179].

Recent studies showed the significant inhibitory activity of luteolin against the Mpro of SARS-CoV-2, papainlike proteinase. In addition, luteolin prevents the coronavirus from binding to human cell receptors and entering the cells [180, 181].

Alkaloids

Alkaloids are a large group of natural compounds that contain at least one nitrogen atom, often located in a heterocyclic ring [182].

Alkaloids are abundant in the human diet [183]. Edible plants such as coffee, cocoa, tea, tomatoes, and potatoes contain alkaloid compounds [183]. In previous studies on the inhibitory effect of plant metabolites on the SARS-CoV virus, alkaloids such as berberrubine, berberine, berbamine, dicentrine, coptisine jatrorrhizine, palmatine, tetrandrine, fangchinoline, and cepharanthine have been reported as inhibitors of SARS-CoV proliferation [184–187]. Lycorine, found in the Amaryllidaceae family, also has a potential antiviral effect against SARS-CoV [188].

Schizanthine z is an alkaloid obtained from *Schizanthus porrigens*. This compound has an inhibitory effect against the PLpro of SARS-CoV-2 [189]. Cryptoquindoline and cryptospirolepine, two alkaloids from *Cryptolepis sanguinolenta*, showed an inhibitory effect against the Mpro of SARS-CoV-2 [190]. Other alkaloids that have an inhibitory effect against the Mpro of this virus are anisotine, adhatodine, vasicoline, and vasicine, which are found in the *Justicia adhatoda* plant [191]. In addition, an *in silico* investigation found that thalimonine and sophaline D may have antiviral activity against SARS-CoV-2 Mpro [192]. A number of alkaloids also showed an inhibitory activity against the RdRp of SARS-CoV-2 including several compounds from *Cryptolepis sanguinolenta* including cryptomisrine, cryptospirolepine, cryptoquindoline, and biscryptolepine [190].

Colchicine

Colchicine, one of the oldest anti-inflammatory medications, is a tropolone alkaloid derived from the plants *Colchicum autumnale* and *Gloriosa superba* [193]. Colchicine gained approval from the US FDA in 2009 for treating familial Mediterranean fever (FMF) and preventing and managing gout attacks [194]. According to a study by Karatza et al., colchicine is a promising drug for COVID-19 patients [193]. Through their research, various dosage regimens were explored, with the findings indicating that a safe and effective approach involves a dosage of 0.5 mg administered twice daily [193]. For patients with clearance impairment, lower doses of 0.25 mg twice or thrice daily should be used [193]. It is important to design dosage regimens based on individual patient needs since colchicine has a narrow therapeutic index [193].

Colchicine can indirectly obstruct the NLRP3 inflammasome, a large molecular complex responsible for detecting danger and initiating a localized or systemic inflammatory response by releasing pro-inflammatory cytokines, such as IL-1β [195–197]. Moreover, colchicine disrupts various inflammatory processes such as the movement, attachment, and activation of neutrophils, as well as the triggering of inflammasomes and the release of cytokines [198]. Considering the impact of colchicine on reducing the activity of various inflammatory pathways and its ability to adjust innate immunity, it is plausible to consider it as a potential treatment for COVID-19 [198]. This is particularly relevant because the autoinflammation of both the innate and adaptive immune systems is a distinguishing feature of the COVID-19 disease [198].

Notably, colchicine has been examined in both outpatient and inpatient settings for its effectiveness against COVID-19 [199–207].

Terpenoids

Terpenoids are the most abundant and diverse class of naturally occurring phytoconstituents [208]. They are responsible for the scent, flavor, and coloration of plants [208]. Their categorization is determined by the number of isoprene units (C_5H_8), which serve as the building blocks of terpenoids [208].

In a computational investigation, numerous components from essential oils, such as cinnamaldehyde, carvacrol, cinnamyl acetate, anethole, pulegone, and thymol, have been identified as obstructing the SARS-CoV-2 virus S protein [209]. In a study by Carino et al., betulinic and oleanolic acids were reported to reduce the binding of S protein RBD to the ACE2 receptor in a concentration-dependent manner [210]. An *in silico* study found that 3-oxoglycyrrhetinic acid inhibited SARS-CoV-2 Mpro [211].

The effect of bioactive molecules from *Withania somnifera* or "Indian ginseng" on the Mpro of SARS-CoV-2 indicated that the steroid compound withanoside V has the highest inhibitory effect on this viral protease among the molecules studied [212]. Other compounds from this plant, including quercetin-3-O-galactosyl-rhamnosyl-glucoside, withanoside X, ashwagandhanolide, dihydrowithaferin A, and withanolide N, showed a promising inhibitory effect on S glycoprotein and nonstructural protein 15 endoribonuclease of SARS-CoV-2 [213].

Recent *in silico* analysis showed the substantial affinity of terpenoids from *Nigella sativa*, including campesterol, cycloeucalenol, α-spinasterol, and β-sitosterol, for the viral N-terminal RNA-binding domain (NRBD) and PLpro of the SARS-CoV-2 virus [214]. Furthermore, The inhibitory activity of bioactive terpenes against SARS-CoV-2 proteins was investigated in another *in silico* study [215]. Based on the results, methyl tanshinonate, sugiol, and cadinol are potential SARS-CoV-2 Mpro inhibitors, and 8-hydroxyabieta-9,13-dien-12-one, dehydroabieta-7-one, and tanshinone I show promise as SARS-CoV-2 PLpro inhibitors [215]. Deacetylnomilin, ichangin, nomilin, and β-amyrin have a high binding affinity with the Mpro of SARS-CoV-2 [216]. Deacetylnomilin and ichangin, in particular, can interact directly with the catalytic dyad parts of Mpro [216].

Tanshinones, a class of terpene, have previously been found to have antiviral properties by inhibiting PLpro SARS-CoV-1 [217].

Saponins

Saponins are triterpenoid or steroidal glycosides with a wide range of medicinal effects, including anti-inflammatory, antiviral, and antifungal effects [218]. Due to the stimulation of the mammalian immune system, they are also considered as potential adjuvant vaccines [219, 220].

Glycyrrhizin obtained from the root of Glycyrrhizae radix is a saponin that has shown inhibitory effects against SARS-CoV [221]. This compound shows affinity with the ACE2 receptor of the cell, which is one of the drug targets of SARS-CoV-2 [222].

Tannins

Tannins are a group of large polyphenolic compounds consisting either of several flavan-3-ol units (known as proanthocyanidins) or of a sugar moiety esterified to a number of organic acids, typically gallic acid or ellagic acid (referred to as hydrolyzable tannins). They have many therapeutic properties, among which are antiviral properties [223]. Based on an *in silico* study conducted on 19 different tannins, three compounds, pedunculagin, tercatain, and castalin, showed a significant interaction with the catalytic dyad part (Cys145 and His41) of the Mpro of the SARS-CoV-2 virus [224]. According to the results of a recent study, tannic acid also has a significant inhibitory effect on the Mpro and TMPRSS2 of the virus [225].

Conclusion

The global healthcare landscape has undergone a significant transformation since the onset of the SARS-CoV-2 outbreak. While COVID-19 once posed a dire and widespread threat to human lives worldwide, the situation has evolved. Thanks to extensive research and the collective efforts of the scientific community and healthcare systems, the pandemic phase of COVID-19 has transitioned into a more manageable state. Despite the progress made, it is essential to acknowledge that only limited options are available for the treatment of COVID-19. Nevertheless, the development of antiviral drugs has expanded the arsenal of available therapeutic choices, and mortality rates, once on the rise, have stabilized. In this new phase, it is crucial to continue exploring therapeutic and preventative measures. Natural resources including plant SMs containing an antiviral agent have the potential to be used to develop medicinal targets and be considered as an efficient alternative for chemical drugs.

This comprehensive review has consolidated the latest investigations employing a triad of methodologies, *in vitro, in vivo*, and *in silico*, aimed at identifying prospective plants' secondary metabolites to combat SARS-CoV-2. Our inclusion of agents targeting both anti-SARS-CoV and anti-MERS-CoV was due to the striking similarity between these viruses and SARS-CoV-2. Hopefully, this compilation will facilitate forthcoming laboratory research in the pursuit of novel therapeutics against SARS-CoV-2.

Contributors' Statement

Data collection: Z. Alipour, S. Zarezadeh, A. A. Ghotbi-Ravandi; design of the study: Z. Alipour, S. Zarezadeh, A. A. Ghotbi-Ravandi; analysis and interpretation of the data: Z. Alipour, S. Zarezadeh, A. A. Ghotbi-Ravandi; drafting the manuscript: Z. Alipour, S. Zarezadeh; critical revision of the manuscript: A. A. Ghotbi-Ravandi.

Acknowledgements

We would like to thank Dr. Alireza Majd for his helpful comments.

Conflict of Interest

The authors declare no conflicts of interest.

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