MINIREVIEW

Phytochemicals for the treatment of COVID-19

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The coronavirus disease 2019 (COVID-19) pandemic has underscored the lack of approved drugs against acute viral diseases. Plants are considered inexhaustible sources of drugs for several diseases and clinical conditions, but plant-derived compounds have seen little success in the field of antivirals. Here, we present the case for the use of compounds from vascular plants, including alkaloids, flavonoids, polyphenols, and tannins, as antivirals, particularly for the treatment of COVID-19. We review current evidence for the use of these phytochemicals against SARS-CoV-2 infection and present their potential targets in the SARS-CoV-2 replication cycle.

Keywords: antivirals, alkaloids, coronaviruses, COVID-19, flavonoids, phytochemicals, natural products, SARS-CoV-2

Introduction

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 218 million and killed over 5.2 million people (WHO, 2020). The COVID-19 pandemic has underscored the limitations of the current pool of approved antivirals and has emphasized the need for further discovery and development of therapeutic and prophylactic agents for acute viral diseases. Plants have been utilized throughout human history for a variety of ailments and are considered inexhaustible sources of novel pharmacologically active compounds. Phytochemicals and their derivatives have already been approved for non-viral disease states. Among these compounds are paclitaxel from the Pacific yew tree (Taxus brevifolia), and vincristine and vinblastine from periwinkle (Catharanthus rosea) for cancer treatment; morphine from opium poppy (Papaver somniferum) and aspirin derived from salicylic acid from the bark of willow trees (Salix spp.) for pain management; and quinine from quina trees (Cinchona spp.) and artemisinin from sweet wormwood (Artemisia annua) for controlling parasitic infections. However, the majority of approved antivirals are synthetic small molecules, and a plant-derived antiviral is yet to be approved (Tompa et al., 2021). Unlike designed synthetic small molecules, plant secondary metabolites have evolved to exhibit biological activity, thereby increasing the likelihood of their interactions with other biological molecules, which is evident in the breadth of pharmacological activity exhibited by phytochemicals (Atanasov et al., 2021). Plant secondary metabolites, especially those that are used as food or as traditional medicine, may also be safer than synthetic molecules. Plants therefore remain rich but underutilized sources of antivirals. Here, we present some of the characterized secondary metabolites from vascular plants that have been observed to inhibit either SARS-CoV-2 replication or SARS-CoV-2 functional components at least in vitro.

Druggable Targets in the SARS-CoV-2 Replication Cycle

SARS-CoV-2 is a Betacoronavirus under the Coronaviridae family of relatively large positive-sense single-stranded RNA viruses. SARS-CoV-2 particles are spherical, with lipid envelopes surrounding an icosahedral capsid that protects the genomic RNA (around 29.9 kb). The 5’ end of the genome encodes 16 nonstructural proteins (NSP1–16), while the 3’ end encodes four structural proteins: spike (S), envelope (E), and membrane (M), and nucleocapsid (N). The homotrimeric glycosylated S protein is the predominant structure on the CoV envelope and is central to the CoV entry process. Each S protein consists of two noncovalently bound subunits: the surface-exposed S1, which contains the receptor-binding domain (RBD), and the transmembrane S2, which facilitates fusion with the host membrane. The infection cycle of SARS-CoV-2 is initiated by the interaction of the RBD with angiotensin-converting enzyme 2 (ACE2), the known SARS-CoV-2 receptor in humans (Fig. 1) (Yan et al., 2020). Proteolytic cleavage at the S1/S2 interface of the S protein triggers a series of conformational changes that lead to fusion of the viral envelope with the host membrane. SARS-CoV-2 S priming has been found to be dependent on transmembrane serine protease 2 (TMPRSS2) on the host cell surface (Hoffmann et al., 2020); however, in the absence of cell surface proteases, endosomal proteases, such as cathepsins B and L, may also facilitate SARS-CoV-2 S priming, suggesting that SARS-CoV-2 enters the host through both direct fusion with the plasma membrane and the endocytic pathway (Ou et al., 2020). Following fusion, the genomic RNA is uncoated in the cy-
Españo et al.

Nucleoside analogs that inhibit the RdRp or terminate the nascent viral RNA chains are among the primary candidates for SARS-CoV-2 inhibition. Considering the effectivity of inhibiting proteases in controlling human immunodeficiency virus and hepatitis C virus infections, proteases involved in the replication cycle of SARS-CoV-2 are also deemed important targets for controlling SARS-CoV-2 infection. These proteases include not only virus-encoded proteases (PL pro and Mpro) but also host proteases, such as TMPRSS2 and cathepsins L and B. Other targets for SARS-CoV-2 inhibition include the S protein and its interaction with ACE2; the endocytic pathway; lipid regulatory pathways; and the lysosomal trafficking pathway. Modulators of the immune response are also considered candidates for COVID-19 treatment, given the relative success of steroids in the treatment of the inflammatory stage of COVID-19 (The RECOVERY Collaborative Group, 2021). With these considerations, several groups have identified phytochemicals that inhibited SARS-CoV-2 production in vitro and have elucidated their targets in the SARS-CoV-2 replication cycle. Other groups have taken the reverse
route and have identified inhibitors of specific proteins involved in the SARS-CoV-2 replication cycle and determined whether these activities would translate to inhibiting virus production in cell culture models. Together, these efforts have led to the identification of vascular plant secondary metabolites that have the potential to treat COVID-19.

**Alkaloids**

Alkaloids are naturally occurring organic compounds that carry at least one nitrogen atom typically within a heterocyclic ring. The nitrogen atoms in alkaloids are in the negative oxidation state, lending alkaloids their basic properties (Kurek, 2019). Alkaloids are structurally diverse and comprise one of the largest groups of plant secondary metabolites. A number of alkaloids from plants (Table 1) have been observed to inhibit SARS-CoV-2 components or infection in *vitro*. In two separate studies using Vero E6 cells, berbamine inhibited SARS-CoV-2 S pseudovirus entry, reduced genome replication, and reduced infectious virus production (Huang et al., 2021; Xia et al., 2021). In one of these studies, berbamine was found to inhibit the ion channel activity of the SARS-CoV-2 E protein at a high concentration. In the same study, a berbamine derivative (BE-33) showed even more potent activity against SARS-CoV-2 infection (EC\textsubscript{90} of 0.94 μM for viral titers) and higher binding affinity to the E protein ion channel than did berbamine (Xia et al., 2021). This derivative also reduced viral loads in the lungs and reduced inflammatory cytokines in human ACE2 (hACE2)-transgenic mice, suggesting anti-inflammatory properties that may be beneficial to severe COVID-19 cases. Berberine, another alkaloid, was observed to reduce infectious virus production but not viral RNA levels in Vero E6 cells, indicating that berberine affects stages later than genome replication (Pizzorno et al., 2020; Varghese et al., 2021). An immunofluorescence-based screening for FDA-approved drugs that inhibit viral genome replication, as indicated by dsRNA production, revealed bromhexine and reserpine, and two antiarrhythmic drugs with antimarial activity, hydroquinidine and quinidine, as potential anti-SARS-CoV-2 agents (Ku et al., 2020). Other antimalarial alkaloids (quinarine and quinine) have also been reported to inhibit SARS-CoV-2 infection in *vitro* (Große et al., 2021; Salas Rojas et al., 2021).

The iminosugar castanospermine and its prodrug, celgosivir, protected Vero E6 cells from SARS-CoV-2-induced cytopathic effects (CPE) and reduced viral genome replication (Clarke et al., 2021). Celgosivir treatment led to lower S protein levels, probably owing to its ability to inhibit α-glucosidases, leading to improper S protein folding. A screening on natural products revealed the ability of cephalanthine, hernandezine, and neferine to inhibit SARS-CoV-2 S pseudovirus entry in ACE2-expressing HEK293T (HEK293/Ace2) cells (He et al., 2021). Other studies have also shown that cephalanthine can protect Vero E6 and Calu-3 cells from authentic SARS-CoV-2 infection; one of these studies has proposed that cephalanthine disrupts the S-ACE2 interaction (Jan et al., 2021; Ohashi et al., 2021). The anti-SARS-CoV-2 potential of neferine and its analogs (isoleisine and liesine) have also been corroborated in a different study, where neferine inhibited Ca\textsuperscript{2+}-dependent fusion of the viral envelope with the host membrane (Yang et al., 2021b).

Emetine, which has displayed inhibitory effects on Zika virus and Ebola virus (Yang et al., 2018), has been reported to reduce SARS-CoV-2 replication in a number of *in vitro* studies (Choy et al., 2020; Wang et al., 2020b; Jan et al., 2021; Kumar et al., 2021). A small observational study has also shown that, while emetine did not accelerate viral clearance, emetine appeared to improve blood oxygen concentrations and breathing difficulties among symptomatic COVID-19 patients (Fan et al., 2021). Meanwhile, homoharringtonine has been shown to protect Vero E6 cells from SARS-CoV-2 CPE and to reduce viral titers and RNA replication (Choy et al., 2020). Lycorine and oxyisorphin have also been shown to inhibit SARS-CoV-2 replication in Vero E6 cells (Zhang et al., 2020). Tetrandrine was demonstrated to inhibit the entry of SARS-CoV-2 S pseudoviruses in HEK293/Ace2 cells in a dose-dependent manner, likely owing to its ability to inhibit the two-pore calcium channel 2 (TPC2), which may be involved in the endocytic pathway of SARS-CoV-2 entry (Ou et al., 2020).

Derivatives of alkaloids have also exhibited anti-SARS-CoV-2 effects in a number of studies, indicating that alkaloid structures can be optimized for the development of anti-SARS-CoV-2 agents. Isatin-derived derivatives were observed to inhibit SARS-CoV-2 M\textsuperscript{pro} activity (Liu et al., 2020). Treatment with topotecan, an analog of the plant-derived alkaloid camptothecin, reduced morbidity and mortality rates in mice infected with SARS-CoV-2, with indications of reduced inflammatory responses (Ho et al., 2021). Derivatives of tylophorine, a naturally occurring alkaloid, have also demonstrated the ability to inhibit SARS-CoV-2 infection in *vitro* (Yang et al., 2020).

**Flavonoids**

Flavonoids comprise another large and structurally diverse group of secondary metabolites produced by plants. The basic flavonoid skeleton is characterized by 15 carbon atoms, wherein two primary aromatic rings (A and B) are connected by three carbon atoms (C\textsubscript{6}-C\textsubscript{3}-C\textsubscript{6}), which may be linked to a third ring (C) (Santos et al., 2017). Flavonoids often occur as aglycones (non-sugar forms), as well as glycosylated and methylated derivatives. Several flavonoids have displayed activity against SARS-CoV-2 infection (Table 2). Both baicalin and its aglycone baicalein have been observed to inhibit SARS-CoV-2 infection in *vitro* in several studies, some of which have shown that these flavonoids inhibit M\textsuperscript{pro} activity (Huang et al., 2020; Jo et al., 2020; Su et al., 2020; Liu et al., 2021). Furthermore, baicalin reduced lung damage and lung inflammation in hACE2 transgenic mice infected with SARS-CoV-2, and baicalin treatment protected the mice from infection-induced body weight loss (Song et al., 2021). Remarkably, a study has also shown that baicalin may inhibit the endoribonuclease activity of SARS-CoV-2 NSP15, which suggests an additional or alternative mode of action (Hong et al., 2021). Naturally occurring baicalin analogs (dihydromyricetin, myricetin, scutellarein, and quercetagetin) have also been demonstrated to inhibit M\textsuperscript{pro} (Liu et al., 2021).
| Compound   | Plant source(s) | Study                  | System            | Effects (EC50/IC50)                                                                 | Target/MoA*                  | Reference                  |
|------------|-----------------|------------------------|-------------------|------------------------------------------------------------------------------------|------------------------------|-----------------------------|
| Berbamine  | *Berberis amurensis* | *In vitro* Vero E6 cells | •Inhibited SARS-CoV-2 S pseudovirus entry •Reduced authentic SARS-CoV-2 RNA levels (EC50: 2.4 μM) and titers | ACE2                            | Huang et al. (2021)          |
| Berbamine  | *Berberis petiolaris, Berberis vulgaris* | *In vitro* Vero E6 cells | •Inhibited E protein ion channel activity (IC50: 111.5 μM) •Protected cells from CPE (EC50: 34.34 μM) •Reduced virus production (EC50: 14.5 μM) | E protein channel            | Xia et al. (2021)           |
| Berberine  | *Adhatoda vasica* | *In vitro* Vero cells  | •Reduced viral dsRNA production (EC50: 14.4 μM)                     |                                 | Ku et al. (2020)             |
| Castanospermine | *Castanospermum austrole* | *In vitro* Vero E6 cells | •Reduced CPE in a dose-dependent manner •Reduced viral RNA levels |                                 | Clarke et al. (2021)        |
| Cepharanthine | *Stephania spp.* | *In vitro* Vero E6 cells | •Reduced SARS-CoV-2 S pseudovirus entry (EC50: 0.315 μM) •Reduced CPE and RNA levels following authentic virus infection | Fusion, entry                | He et al. (2021)            |
| Cepharanthine | *Stephania spp.* | *In vitro* Vero E6/TMPRSS2 cells, Calu-3 cells | •Reduced CPE (EC50: 25.1 μM) and RNA levels (EC50: 0.035 μM) •Reduced N protein production | S-ACE interaction             | Ohashi et al. (2021)        |
| Emetine    | *Psychotria ipecacuanha* | *Observational clinical trial Hospitalized COVID-19 patients* | •No significant effect on qRT-PCR test conversion and symptoms after oral emetine administration •Showed tendency to improve oxygen levels and breathing difficulties (total n = 63; n = 37 for emetine group) | Replication, translation      | Fan et al. (2021)           |
| Emetine    | *Psychotria ipecacuanha* | *In vitro* Vero cells  | •Reduced viral RNA levels (EC50: 0.147 nM)                          |                                 | Kumar et al. (2021)         |
| Emetine    | *Psychotria ipecacuanha* | *In vitro* Vero E6 cells | •Reduced CPE (EC50: 1.56 μM), viral titers (EC50: 0.46 μM), and viral RNA levels (EC50: 0.5 μM) |                                 | Choy et al. (2020)          |
| Emetine    | *Psychotria ipecacuanha* | *In vitro* Vero cells  | •Reduced viral RNA levels upon full-time incubation (EC50: 0.007 μM) and during entry stage (EC50: 0.019 μM) |                                 | Wang et al. (2020b)         |
| Emetine    | *Psychotria ipecacuanha* | *In vitro* Vero E6 cells | •Reduced N protein production (EC50: 0.397)                          |                                 | Jan et al. (2021)           |
Table 1. Continued

| Compound     | Plant source(s) | Study | System          | Effects (EC50/IC50)                                                                 | Target/MoA* | Reference            |
|--------------|----------------|-------|-----------------|--------------------------------------------------------------------------------------|-------------|----------------------|
| Hernandezine | *Thalictrum podocarpum* | *in vitro* | HEK293/hACE2 cells, Vero E6 cells | • Reduced SARS-CoV-2 S pseudovirus entry (EC50: 0.111 μM)  
• Reduced viral RNA levels following authentic virus infection | Fusion, entry | He et al. (2021) |
| Homoharringtonine | *Cephalotoxus harringtonia* | *in vitro* | Vero E6 cells | • Reduced CPE (EC50: 3.125 μM), viral titers (EC50: 2.55 μM), and viral RNA levels (EC50: 2.14 μM) | | Choy et al. (2020) |
| Hydroquinidine | *Cinchona officinalis* | *in vitro* | Vero cells | • Reduced viral dsRNA production (EC50: 23.8 μM) | | Ku et al. (2020) |
| Isoliensinine | *Nelumbo nucifera* | *in vitro* | HEK293/hACE2 cells | • Inhibited SARS-CoV-2 pseudovirus entry (EC50: 3.31 μM) | | Yang et al. (2021b) |
| Liensinine | *Nelumbo nucifera* | *in vitro* | HEK293/hACE2 cells | • Inhibited SARS-CoV-2 S pseudovirus entry (EC50: 11.52 μM) | | Yang et al. (2021b) |
| Lycorine | *Amaryllidaceae spp.* | *in vitro* | Vero E6 cells | • Reduced viral RNA levels (EC50: 0.31 μM) and CPE  
• Reduced N protein production | | Zhang et al. (2020) |
| Neferine | *Nelumbo nucifera* | *in vitro* | HEK293/hACE2 cells, Vero E6 cells | • Inhibited SARS-CoV-2 S pseudovirus entry (EC50: 0.36 μM)  
• Blocked Ca2+-dependent fusion of pseudovirus with cells | Fusion | He et al. (2021) |
| Neferine | *Nelumbo nucifera* | *in vitro* | HEK293/hACE2 cells | • Inhibited SARS-CoV-2 S pseudovirus entry (EC50: 0.36 μM)  
• Blocked Ca2+-dependent fusion of pseudovirus with cells | Fusion | Yang et al. (2021b) |
### Table 1. Continued

| Compound       | Plant source(s)     | Study      | System               | Effects (EC\textsubscript{50}/IC\textsubscript{50})                                                                 | Target/MoA*                                                                 | Reference          |
|----------------|---------------------|------------|----------------------|---------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------|
| Oxysophoridine | Sophora alopecuroides | \textit{In vitro} | Vero E6 cells        | • Reduced viral RNA levels (EC\textsubscript{50}: 0.18 \(\mu\)M) and CPE                                                                                           |                                                                              | Zhang et al. (2020) |
| Quinacrine     | Cinchona officinalis  | \textit{In vitro} | Vero E6 cells        | • Reduced CPE (EC\textsubscript{50}: 0.582/1.88 \(\mu\)M for MOI of 0.01/0.1) • Reduced viral RNA levels (EC\textsubscript{50}: 0.579/1.373 \(\mu\)M for MOI of 0.01/0.1) |                                                                              | Salas Rojas et al. (2021) |
| Quinidine      | Cinchona officinalis  | \textit{In vitro} | Vero cells           | • Reduced viral dsRNA production (EC\textsubscript{50}: 13.3 \(\mu\)M)                                                                                               |                                                                              | Ku et al. (2020)    |
| Quinine        | Cinchona officinalis  | \textit{In vitro} | A549/ACE2 cells      | • Dose-dependent inhibition of SARS-CoV-2 infection in different A549-ACE2/TMPRSS2 constructs (EC\textsubscript{50}: 5.58–55.82 \(\mu\)M) |                                                                              | Große et al. (2021) |
| Reserpine      | Rauwolfia serpentina  | \textit{In vitro} | Vero cells           | • Reduced viral dsRNA production (EC\textsubscript{50}: 29.2 \(\mu\)M)                                                                                               |                                                                              | Ku et al. (2020)    |
| Tetrandrine    | Stephania tetrandra   | \textit{In vitro} | HEK293/hACE2 cells   | • Dose-dependent inhibition of SARS-CoV-2 S pseudovirus entry Entry, TPC2 inhibition                                                                                   |                                                                              | Ou et al. (2020)    |

*Targets or mode of action (MoA) are proposed based on the findings of the study.

Abbreviations: ACE2, angiotensin-converting enzyme 2; CPE, cytopathic effects; E, envelope protein; dsRNA, double-stranded RNA; EC\textsubscript{50}, half-maximal effective concentration; hACE2, human ACE2; IC\textsubscript{50}, half-maximal inhibitory concentration; MOI, multiplicity of infection; M\textsuperscript{pro}, main protease; N, nucleocapsid protein; PL\textsuperscript{pro}, papain-like protease; S, spike protein; TMPRSS2, transmembrane serine protease 2; TPC2, two pore calcium channel 2.
| Compound  | Plant source(s)                                                                 | Study                                                                 | System                      | Effects (EC50/IC50)                                                                 | Target/MoA* | Reference          |
|-----------|--------------------------------------------------------------------------------|----------------------------------------------------------------------|-----------------------------|--------------------------------------------------------------------------------|-------------|--------------------|
| **Baicalein** | **Scutellaria baicalensis, Scutellaria lateriflora** | **In vitro**  
Protease assay, Vero E6 cells | • Inhibited Mpro (IC50: 0.94 μM)  
• Reduced viral RNA levels (EC50: 2.94 μM) | Mpro | Su et al. (2020) |
|           |                                                                                  | **In vitro**  
Vero E6 cells                                      | Reduced viral RNA levels (EC50: 10 μM) |                                |                         | Huang et al. (2020) |
|           |                                                                                  | **In vitro**  
Vero E6 cells                                      | • Inhibited Mpro (IC50: 0.39 μM)  
• Reduced viral RNA levels (EC50: 2.92 μM) | Mpro, entry | Liu et al. (2021) |
|           |                                                                                  | **In vitro, In vivo**  
Vero E6 cells, hACE2 transgenic mice | • Reduced CPE in vitro  
• Reduced lung damage, body weight loss, lung viral load, and lung inflammatory infiltration in mice (0.1–50 μM) |                                |                         | Song et al. (2021) |
| **Baicain** | **Scutellaria baicalensis, Scutellaria lateriflora** | **In vitro**  
Protease assay, Vero E6 cells | • Inhibited Mpro (IC50: 6.41 μM)  
• Reduced viral RNA levels (EC50: 27.87 μM) | Mpro | Su et al. (2020) |
|           |                                                                                  | **In vitro**  
Protease assay                                      | • Inhibited Mpro (IC50: 83.4) |                                | Mpro | Liu et al. (2021) |
|           |                                                                                  | **In vitro**  
Endoribonuclease inhibition assay, Vero cells | • Inhibited NSP15 endoribonuclease activity (IC50: 7.98 μM)  
• Reduced viral titers (EC50: 83.3 μM) | NSP15 | Hong et al. (2021) |
| **Brazilin** | **Paubrasilia echinata, Caesalpinia sappan** | **In vitro**  
A549/hACE2 cells | • Dose-dependent inhibition of SARS-CoV-2 RBD to hACE2  
• Dose-dependent inhibition of pseudovirus entry  
• Dose-dependent decrease in ACE2/TMPRSS2 activity | Binding/entry, TMPRSS2 | Goc et al. (2021) |
| **Catechin** | **Camellia sinensis** | **In vitro**  
Vero E6 cells | • Dose-dependent reduction in viral titers after virus incubation with catechin | Viral inactivation | Nishimura et al. (2021) |
| **Chrysanthemin** | **Olea europaea, Vaccinium spp.** | **In vitro**  
Protease assay | • Inhibited Mpro (IC50: 65.1 μM) | Mpro | Pitsillou et al. (2020a) |
|           |                                                                                  | **In vitro**  
Deubiquitinase inhibition assay  
Deubiquitinase inhibition assay | • Inhibited PLpro deubiquitinase activity | PLpro | Pitsillou et al. (2020b) |
| **Dihydromyricetin** | **Ampelopsis grossedentata** | **In vitro**  
Protease assay | • Inhibited Mpro (IC50: 1.20 μM) | Mpro | Liu et al. (2021) |
| Compound                  | Plant source(s) | Study          | System                              | Effects (EC50/IC50)                                      | Target/MoA*          | Reference          |
|--------------------------|-----------------|----------------|-------------------------------------|---------------------------------------------------------|----------------------|---------------------|
| Epigallocatechin-3-gallate | *Camellia sinensis* | *In vitro* Protease assay | • Inhibited Mpro (IC50: 7.58 μM) | Mpro                                                    | Jang *et al.* (2020) |
|                          |                 | *In vitro* HEK293/ACE2 cells | • Inhibited SARS-CoV-2 S pseudovirus entry; Inhibited RBD/AE2 binding; Early addition reduced viral RNA levels | Attachment/binding                                           | Henss *et al.* (2021) |
|                          |                 | *In vitro* Endoribonuclease inhibition assay; Vero cells | • Inhibited NSP15 endoribonuclease activity (IC50: 1.62 μM); Reduced viral titers (EC50: 0.20 μM) | NSP15                                                       | Hong *et al.* (2021) |
|                          |                 | *In vitro* Vero E6/TMPRSS2 cells | • Reduced SARS-CoV-2 titer and RNA levels | Viral inactivation                                        | Ohgitani *et al.* (2021) |
| Herbacetin               | *Linum usitatissimum* | *In vitro* Protease assay | • Inhibited Mpro (IC50: 53.9 μM) | Mpro                                                    | Jo *et al.* (2020)   |
| Isorhamnetin             | *Hippophae rhamnoides, Opuntia ficus-indica* | *In vitro* HEK293/hACE2 cells | • Reduced SARS-CoV-2 S pseudovirus entry | S-ACE binding                                               | Zhan *et al.* (2021) |
| Kaempferol               | *Capparis spinosa, Crocus sativus* | *In vitro* Vero E6 cells | • Reduced CPE (EC50: 34.46 μM) | Mpro                                                    | Khan *et al.* (2021) |
| Myricetin                | *Ceratonia siliqua, Vaccinium spp.* | *In vitro* Protease assay | • Inhibited Mpro (IC50: 2.86 μM) | Mpro                                                    | Liu *et al.* (2021)  |
| Naringenin               | *Citrus spp., Lycopersicum esculentum* | *In vitro* Vero E6 cells | • Dose-dependent reduction in CPE | TPC2                                                      | Clementi *et al.* (2021) |
| Panduratin A             | *Boesenbergia pandurate* | *In vitro* Vero E6 cells, Calu-3 cells | • Reduced viral titers in Vero E6 (EC50: 0.078 μM) and Calu-3 cells (EC50: 0.53 μM) | Pre-entry                                                  | Kanjanasirirat *et al.* (2020) |
| Compound                  | Plant source(s)                  | Study                | System                        | Effects (EC<sub>50</sub>/IC<sub>50</sub>)                                                                 | Target/MoA* | Reference               |
|--------------------------|---------------------------------|----------------------|-------------------------------|-------------------------------------------------------------------------------------------------------------|-------------|-------------------------|
| Pectolinarin             | Cirsium spp., Linaria spp.      | In vitro            | Protease assay                | • Inhibited M<sup>pro</sup> (IC<sub>50</sub>: 51.64 μM)                                                      | M<sup>pro</sup> | Jo et al. (2020)         |
| Quercetagetin            | Tagetes erecta                  | In vitro            | Protease assay                | • Inhibited M<sup>pro</sup> (IC<sub>50</sub>: 1.24 μM)                                                      | M<sup>pro</sup> | Liu et al. (2021)        |
| Quercetin                | Allium cepa, Vaccinium spp.     | In vitro            | Protease assay                | • Inhibited M<sup>pro</sup>                                                                                   | M<sup>pro</sup> | Abian et al. (2020)      |
| Rutin                    | Fagopyrum esculentum, Rheum spp. | In vitro            | Deubiquitinase inhibition assay | • Inhibited PL<sup>pro</sup> deubiquitinase activity                                                          | PL<sup>pro</sup> | Pitsillou et al. (2020b) |
| Scutellarein             | Scutellaria spp.                | In vitro            | Protease assay                | • Inhibited M<sup>pro</sup> (IC<sub>50</sub>: 5.8 μM)                                                      | M<sup>pro</sup> | Liu et al. (2021)        |
| Theaflavin 3,3'-di-O-gallate | Camellia sinensis              | In vitro            | Protease assay                | • Inhibited M<sup>pro</sup> (IC<sub>50</sub>: 8.44 μM)                                                      | M<sup>pro</sup> | Jang et al. (2020)       |
|                          |                                 | In vitro            | Vero E6/TMPRSS2 cells          | • Reduced SARS-CoV-2 titers and RNA levels                                                                   | Viral       | Ohgitani et al. (2021)   |
|                          |                                 | In vitro            | A549/hACE2 cells               | • Dose-dependent inhibition of SARS-CoV-2 RBD to hACE2                                                        | Binding/entry, TMPRSS2 | Goc et al. (2021)        |

*Targets or mode of action (MoA) are proposed based on the findings of the study.

Abbreviations: ACE2, angiotensin-converting enzyme 2; CPE, cytopathic effects; E, envelope protein; EC<sub>50</sub>, half-maximal effective concentration; hACE2, human ACE2; IC<sub>50</sub>, half-maximal inhibitory concentration; MOI, multiplicity of infection; M<sup>pro</sup>, main protease; N, nucleocapsid protein; NSP, nonstructural protein; PL<sup>pro</sup>, papain-like protease; RBD, receptor-binding domain; S, spike protein; TMPRSS2, transmembrane serine protease 2; TPC2, two pore calcium channel 2.
| Compound          | Class      | Plant source                          | Study          | System                  | Effects (EC50/IC50)                                                                 | Target/MoA * | Reference                           |
|-------------------|------------|---------------------------------------|----------------|-------------------------|----------------------------------------------------------------------------------|--------------|-------------------------------------|
| 6-Gingerol        | Gingerol   | Zingiber officinale                   | In vitro       | Vero E6 cells           | • Reduced viral titers (EC50: 1.38 μM)                                            |              | Kanjanasirirat et al. (2020)        |
| Acteoside         | Glycoside  | Scrophularia ningpoensis, Byblis liniflora | In vitro       | Protease assay          | • Inhibited Mpro (IC50: 43 nM)                                                    | Mpro         | Abdallah et al. (2021)              |
| Andrographolide   | Diterpenoid| Andrographis paniculata               | In vitro       | Calu-3 cells, Vero E6 cells | • Reduced viral titers in Calu-3 (EC50: 0.034 μM) and Vero E6 cells (EC50: 0.28 μM) | Late stage   | Sa-Ngiamsuntorn et al. (2021)       |
|                   |            |                                       | In vitro       | Protease assay          | • Inhibited Mpro (IC50: 15.05 μM)                                                 | Mpro         | Shi et al. (2020)                   |
| Betulin           | Triterpene | Betula pubescens, Ziziphus mauritiana | In vitro       | Protease assay          | • Inhibited Mpro (IC50: 89.67 μM)                                                 | Mpro         | Alhadrami et al. (2021)             |
| Betulinc acid     | Triterpene | Betula pubescens, Ziziphus mauritiana | In vitro       | Protease assay          | • Inhibited Mpro (IC50: 14.55 μM)                                                 | Mpro         | Alhadrami et al. (2021)             |
| Chebulagic acid   | Tannin     | Terminalia chebula                     | In vitro       | Vero E6 cells           | • Reduced viral titers (EC50: 9.76 μM) • Inhibited Mpro (IC50: 9.09 μM)         | Mpro         | Du et al. (2021)                    |
| Compound          | Class       | Plant source              | Study          | System                  | Effects (EC<sub>50</sub>/IC<sub>50</sub>)                                                                 | Target/MoA<sup>*</sup> | Reference           |
|-------------------|-------------|---------------------------|----------------|-------------------------|------------------------------------------------------------------------------------------------------------|------------------------|---------------------|
| Chlorogenic acid  | Quinic acid | Terminalia chebula        | In vitro       | Protease assay          | • Inhibited M<sup>pro</sup> (IC<sub>50</sub>: 39.48 μM)                                                   | M<sup>pro</sup>        | Su et al. (2020)    |
| Cleistanthin B    | Cleistanthin | Cleistanthus collinus     | In vitro       | Vero cells              | • Reduced viral titers (EC<sub>50</sub>: 6.51 μM)                                                          |                        | Stefanik et al. (2021) |
| Cryptotanshinone   | Diterpene   | Salvia miltiorrhiza       | In vitro       | Vero E6 cells           | • Inhibited PL<sup>pro</sup> (IC<sub>50</sub>: 5.63 μM) • Reduced viral titers (EC<sub>50</sub>: 0.70 μM) | PL<sup>pro</sup>       | Zhao et al. (2021)   |
|                    |             |                           | In vitro       | Protease assay          | • Inhibited PL<sup>pro</sup> (IC<sub>50</sub>: 1.336 μM)                                                   | PL<sup>pro</sup>       | Lim et al. (2021)   |
| Curcumin          | Diarylheptanoid | Curcuma longa              | RCT            | Symptomatic patients    | • Nano-curcumin reduced expression and serum levels of IL6 and IL1β (total n = 80; n = 40 COVID-19 patients; n = 20 curcumin group/placebo group) • Lower mortality rate in the curcumin (20%) than in the placebo (40%) group | Anti-inflammatory      | Valizadeh et al. (2020) |
|                    |             |                           | RCT            | Symptomatic hospitalized adult patients | • In combination with piperine (oral) • Earlier symptomatic recovery • Significantly lower hospitalization in the moderate and severe COVID-19 groups • Fewer deaths | Anti-inflammatory      | Pawar et al. (2021)  |
|                    |             |                           | In vitro       | A549/hACE2 cells        | • Dose-dependent inhibition of pseudovirus to hACE2 on A549 • Dose-dependent inhibition of syncytia in A549/hACE2 • Dose-dependent decrease in ACE2 and TMPRSS2 activity | Binding/entry, TMPRSS2 | Goc et al. (2021)    |
| Digoxin           | Glycoside   | Digitalis lanata          | In vitro       | Vero cells              | • Reduced viral RNA levels when added pre-infection and post-entry (EC<sub>50</sub>: 0.043 μM)             |                        | Cho et al. (2020)    |
| Dihydrotanshinone  | Diterpene   | Salvia miltiorrhiza       | In vitro       | Protease assay          | • Inhibited PL<sup>pro</sup> (IC<sub>50</sub>: 0.5861 μM)                                                   | PL<sup>pro</sup>       | Lim et al. (2021)   |
| Compound | Class      | Plant source | Study       | System          | Effects (EC50/IC50)                                      | Target/MoA* | Reference                      |
|----------|------------|--------------|-------------|-----------------|---------------------------------------------------------|-------------|--------------------------------|
| Diphyllin| Lignan     | *Cleistanthus collinus* | *In vitro* | Vero cells      | •Reduced viral titers (EC50: 1.92 μM)                  |             | Stefanik et al. (2021)         |
| Ellagic acid | Tannin     | *Rubus fruticosus, Fragaria ananassa* | *In vitro* | Vero E6 cells   | •Inhibited RBD-ACE2 binding (IC50: 2.5 μg/mL)            | RBD-ACE2    | David et al. (2021)           |
| Glycyrrhizin | Saponin    | *Glycyrrhiza glabra* | *In vitro* | Vero E6 cells   | •Reduced viral titers (EC50: 0.44 mg/ml)                | MPro        | van de Sand et al. (2021)     |
| Hypericin | Anthraquinone | *Hypericum perforatum* | *In vitro* | Protease assay | •Inhibited MPro (IC50: 63.6 μM)                         | MPro        | Pitsillou et al. (2020a)      |
|           |            |              | *In vitro* | Deubiquitinase inhibition assay | •Inhibited PLPro deubiquitinase activity                | PLPro       | Pitsillou et al. (2020b)      |
| Maclurin  | Benzophenone | *Garcinia pedunculata, Gnidia involucrata* | *In vitro* | Protease assay  | •Inhibited MPro (IC50: 102 nM)                         | MPro        | Abdallah et al. (2021)        |
| Maslinic acid | Triterpene | *Olea europaea* | *In vitro* | Protease assay  | •Inhibited MPro (IC50: 3.22 μM)                         | MPro        | Alhadrami et al. (2021)       |
| Compound                  | Class      | Plant source                          | Study            | System                  | Effects (EC50/IC50)                                                                 | Target/MoA  | Reference                          |
|--------------------------|------------|---------------------------------------|------------------|-------------------------|--------------------------------------------------------------------------------------|-------------|------------------------------------|
| Nordihydroguaiaretic acid| Lignan     | Larrea tridentata                      | *In vitro*       | MALDI-TOF based assay   | • Inhibited PLpro (IC50: 1.06 μM)                                                   | PLpro       | Armstrong et al. (2021)            |
|                          |            |                                       |                  |                         | • Inhibited NSP3 (IC50: 1.62 μM)                                                     | NSP3        |                                    |
| Ouabain                  | Glycoside  | Acokanthera schimperi, Strophanthus gratus | *In vitro*       | Vero cells              | • Reduced viral RNA levels when added pre-infection and post-entry (EC50: 0.024 μM) |             | Cho et al. (2020)                  |
| Platycodin D             | Saponin    | Platycodon grandiflorum               | *In vitro*       | H1299/ACE2 cells        | • Reduced SARS-CoV-2 pseudovirus entry into H1299/ACE2 (EC50: 0.69 μM) and H1299/ACE2-TMPRSS2 cells (EC50: 0.72 μM) | Entry, ACE2/TMPRSS2 | Kim et al. (2021)                  |
| Pterostilbene            | Stilbenoid | Vaccinium spp., Pterocarpus marsupium  | *In vitro*       | Vero E6 cells, HPBECs   | • Reduced viral titers in Vero E6 (EC50: 19 μM)                                      | Post-entry  | ter Ellen et al. (2021)            |
|                          |            |                                       |                  |                         | • Inhibited infection in HPBECs                                                       |             |                                    |
| Punicalagin              | Tannin     | Punica granatum, Terminalia catappa   | *In vitro*       | Binding assay           | • Inhibited RBD-ACE2 binding                                                          | RBD-ACE2    | Tito et al. (2021)                 |
| Resveratrol              | Stilbenoid | Vitis vinifera, Ampelopsis cantoniensis | *In vitro*       | Vero E6 cells           | • Reduced viral titers in Vero E6 (EC50: 66 μM)                                      |             | ter Ellen et al. (2021)            |
|                          |            |                                       |                  |                         | • Inhibited infection in HPBECs                                                       |             |                                    |
|                          |            |                                       | *In vitro*       | Vero E6 cells           | • Dose-dependent reduction in viral RNA levels                                        |             | Pasquereau et al., (2021)          |
|                          |            |                                       |                  |                         | • Reduced viral RNA levels when added at post-infection stage (EC50: 4.48 μM)        |             | Yang et al. (2021a)                |
| Compound          | Class  | Plant source       | Study      | System                  | Effects (EC50/IC50)                                                                 | Target/MoA* | Reference           |
|-------------------|--------|--------------------|------------|-------------------------|------------------------------------------------------------------------------------|-------------|---------------------|
| Sennoside B       | Glycoside | Cassia fistula    | In vitro  | Protease assay          | • Inhibited Mmp (IC50: 104 nM)                                                      | Mmp         | Abdallah et al. (2021) |
| Tannic acid       | Tannin | Caesalpinia spinosa, Rhus semialata | In vitro  | HEK293/hACE2 cells, Vero E6 cells | • Dose-dependent inhibition of SARS-CoV-2 S pseudovirus entry into 293T/hACE2 and Vero E6 cells  
• Inhibited Mmp (IC50: 13.4 μM)  
• Inhibited TMPRSS2 (IC50: 2.31 μM) | Mmp, TMPRSS2 | Wang et al. (2020a) |
| Tanshinone I      | Diterpene | Salvia miltiorrhiza | In vitro  | Vero E6 cells          | • Inhibited PLpro (IC50: 5.63 μM)  
• Reduced viral titers (EC50: 2.26 μM)                                             | PLpro       | Zhao et al. (2021)  |
| Tanshinone II     | Diterpene | Salvia miltiorrhiza | In vitro  | Protease assay          | • Inhibited PLpro (IC50: 1.571 μM)                                                 | PLpro       | Lim et al. (2021)    |
| Ursolic acid      | Triterpenoid | Vaccinium spp. | In vitro  | Protease assay          | • Inhibited Mmp (IC50: 12.57 μM)                                                   | Mmp         | Alhadrami et al. (2021) |

*Targets or mode of action (MoA) are proposed based on the findings of the study.

Abbreviations: ACE2, angiotensin-converting enzyme 2; CPE, cytopathic effects; E, envelope protein; EC50, half-maximal effective concentration; hACE2, human ACE2; HPBECs, human primary bronchial epithelial cells; IC50, half-maximal inhibitory concentration; IL, interleukin; MOI, multiplicity of infection; Mmp, main protease; N, nucleocapsid protein; NSP, nonstructural protein; PLpro, papain-like protease; RBD, receptor-binding domain; RCT, randomized controlled clinical trial; S, spike protein; TMPRSS2, transmembrane serine protease 2; TPC2, two pore calcium channel 2.
Brazilin has been shown to inhibit SARS-CoV-2 S pseudovirus entry into A549/ACE2 cells, likely owing to its ability to inhibit the RBD-ACE2 interaction or to inhibit ACE2 or TMPRSS2 activity (Goc et al., 2021). Isorhamnetin also inhibited SARS-CoV-2 S pseudovirus entry in HEK293/ACE2 cells, suggesting an ability to disrupt the S-ACE2 interaction (Zhan et al., 2021). Meanwhile, the addition of panduratin A to SARS-CoV-2-infected Vero E6 in Calu-3 cells reduced viral production in these cell culture models (Kanjanasirirat et al., 2020). Notably, pre-incubation of panduratin A with SARS-CoV-2 particles reduced the infectivity of the virus in Vero E6 cells, suggesting that it affects pre-entry stages of infection.

Chrysanthenin, the 3-glucoside of cyanidin, has been reported to inhibit Mpro and PLpro in separate studies (Pitsillou et al., 2020a, 2020b). Other flavonoids (herbacetin, kaempferol, pectolinarin, and quercetin) with the capacity to inhibit SARS-CoV-2 Mpro also have been reported in different studies (Abian et al., 2020; Jo et al., 2020; Khan et al., 2021). Meanwhile, rutin, a rutinose-bound form of quercetin, has been found to inhibit the deubiquitinase activity of PLpro (Pitsillou et al., 2020b). Naringenin was observed to protect Vero E6 cells from SARS-CoV-2-induced CPE and has been suggested to inhibit Mpro and TPC2 (Abdallah et al., 2021; Clementi et al., 2021).

Flavonoids from the leaves of *Camellia sinensis* have shown inhibitory activity against a variety of viruses and have likewise shown inhibitory effects on SARS-CoV-2 infection *in vitro* (Xu et al., 2017). Epicatechin-3-gallate (EGCG) and the-aflavin-3-3′-di-O-gallate (TF3) have displayed virucidal effects on SARS-CoV-2 particles (Nishimura et al., 2021; Ohgiti et al., 2021). Both have also been shown to inhibit SARS-CoV-2 binding, entry, and Mpro activity (Jang et al., 2020; Goc et al., 2021; Henss et al., 2021). EGCG also inhibited the endoribonuclease activity of NSP15 (Hong et al., 2021), whereas TF3 appeared to downregulate cathepsin L levels, which may contribute to its inhibitory effects on SARS-CoV-2 entry (Goc et al., 2021). Whether EGCG or T3G inhibits all or some of these targets remains to be determined. However, the findings listed here emphasize the breadth of pharmacological activities of some of these phytochemicals.

### Other Groups of Phytochemicals

#### Terpenes and terpenoids

Several other groups of phytochemicals have also displayed anti-SARS-CoV-2 activity *in vitro* (Table 3). Among these are terpenes and terpenoids, which form one of the largest families of plant secondary metabolites. All terpenes are composed of isoprene units ($C_5H_8$) and are further classified depending on the number of isoprene units (e.g., diterpenes have four isoprene units, while triterpenes have six) (Ferveen, 2021). Terpenes that have additional functional groups or oxidized methyl groups are called terpenoids. The diterpenoid andrographolide and its fluorescent derivative have been reported to inhibit Mpro (Shi et al., 2020). Andrographolide also reduced SARS-CoV-2 production in Vero E6 and Calu-3 cells and has been proposed to inhibit late stages of infection (Sa-Ngiamwunthorn et al., 2021). Diterpenes cryptotanshinone, tanshinone I, tanshinone II, and dihydrotanshinone I have all demonstrated the capacity to inhibit PLpro in separate studies (Lim et al., 2021; Zhao et al., 2021). Furthermore, cryptotanshinone and tanshinone I reduced SARS-CoV-2 production in Vero E6 cells (Zhao et al., 2021). Triterpenoids from olive leaves (betulin, betulinic acid, maslinic acid, and ursolic acid) were found to inhibit Mpro through an enzyme assay (Alhadrami et al., 2021). Triterpene glycosides, also known as saponins, such as glycerrhizizin and platycodin D, have also been observed to have anti-SARS-CoV-2 activity. In particular, glycerrhizizin inhibited the production of infectious virus particles in Vero E6 cells and inhibited Mpro in a dose-dependent manner (van de Sand et al., 2021). Meanwhile, platycodin D reduced SARS-CoV-2 S pseudovirus entry into H12299/ACE2 and H12299/ACE2-TMPRSS2 cells (Kim et al., 2021).

#### Curcumin

Curcumin, which has demonstrated a broad spectrum of pharmacological activities, including anti-inflammatory and antiviral effects (Amalraj et al., 2017), has also been reported to inhibit SARS-CoV-2 S pseudovirus entry into A549/hACE2 cells (Goc et al., 2021). Curcumin is insoluble in water, and, consequently, has poor bioavailability (Anand et al., 2007); several formulations of curcumin have been designed to improve its bioavailability for clinical application. Two small randomized controlled clinical trials have reported the potential benefits of different curcumin formulations to COVID-19 patients (Table 3). In one of these studies, an oral nanomicellar formulation of curcumin was given for 14 days to newly diagnosed COVID-19 patients who also received standard of care (interferon beta-1b, bromhexine, and atorvastatin) (Valizadeh et al., 2020). Curcumin treatment among COVID-19 patients resulted in decreased interleukin (IL)-1β and IL-6 mRNA and serum levels relative to baseline, whereas the mRNA and serum levels of these pro-inflammatory cytokines did not significantly decrease in the placebo group. Mortality due to COVID-19 was also lower in the curcumin treatment group (20%) than in the placebo group (40%). In another study, an oral formulation containing curcumin and piperine (added to improve curcumin bioavailability) was observed to accelerate symptom recovery, shorten hospital stay, and reduce mortality rates among hospitalized COVID-19 patients who received COVID-19 standard of care, indicating that the formulation is a suitable adjuvant therapy for symptomatic patients (Pawar et al., 2021).

#### Other phytochemicals

Cardiac glycosides digoxin and ouabain (Table 3) have been reported to inhibit viral genome replication in Vero E6 cells (Cho et al., 2020). Sennoside B and acteoside, both glycosides, have been reported to inhibit Mpro (Abdallah et al., 2021). Phytochemicals belonging to other groups, such as maclurin (benzophenone) and chlorogenic acid (quinic acid) have also been reported to inhibit Mpro activity (Su et al., 2020; Abdallah et al., 2021). Tannins, which are high molecular-weight polyphenols from plants, such as chebulagic acid, punicalagin, and tannic acid, have all displayed the ability to inhibit Mpro activity (Wang et al., 2020a; Du et al., 2021; Tito et al., 2021). Punicalagin and ellagic acid were also observed to interfere
with the S protein or RBD interaction with ACE2 (David et al., 2021; Tito et al., 2021). The lignan diphyllin reduced SARS-CoV-2 titers in Vero cells (Stefanik et al., 2021). Nordihydroguaiaretic acid, another lignan, has been reported to inhibit NSP3 and one of its domains, PL^{pro}, in a matrix-assisted laser desorption ionization time-of-flight-based deubiquitylase assay (Armstrong et al., 2021). The stilbenoid resveratrol has been observed to inhibit viral genome replication and virus production in Vero and Vero E6 cells, and has been found to inhibit SARS-CoV-2 infection in human primary bronchial epithelial cells (Pasquareau et al., 2021; ter Ellen et al., 2021; Yang et al., 2021a). Pterostilbene, another stilbenoid, has likewise been reported to reduce virus production in Vero E6 cells and to inhibit SARS-CoV-2 infection in human primary bronchial epithelial cells (ter Ellen et al., 2021). Gingerol, a polyphenol from ginger, has been reported to reduce viral titers in Vero E6 cells. Meanwhile, hypericin, an anthraquinone, has been revealed to inhibit M^{pro} and PL^{pro} in separate screening assays (Pitsillou et al., 2020a, 2020b).

**Perspectives and Conclusion**

The diversity of plant secondary metabolites lend them a huge breadth of pharmacological activities and have made them a rich source of drugs for several disease states. However, the structural complexity of phytochemicals makes them difficult to produce and synthesize in the industrial scale, which is part of the reason why most pharmaceutical companies favor synthetic small molecules for antiviral screening and development. Phytochemicals may also possess suboptimal activity (i.e., require high concentrations that are not achievable in human plasma) and may have poor bioavailability. However, steady progress in synthetic chemistry and in biotechnology have recently allowed the synthesis or semisynthesis of large, complex natural products (Beutler, 2009; Atanasov et al., 2021). Furthermore, even for synthetic molecules, the identification of pharmacophores is imperative to allow derivatization of compounds for improved efficacy and bioavailability and even for structural simplicity, so the requirement for optimization is not unique to phytochemicals. Advancements in the field of drug delivery, as exemplified by the orally administered nano-curcumin that we have cited here, have also improved the systemic bioavailability and pharmacological profiles of phytochemicals in pre-clinical models (Rahman et al., 2020). The technologies for compound optimization and biosynthesis continue to improve and may eventually address some of the limitations to the clinical application of plant-derived antiviral compounds. Thus, we must continue to build our repository of plant-based antivirals, so that the semi-synthetic/biosynthetic techniques could be applied to these plant products as soon as the technology becomes available. Furthermore, studies identifying phytochemicals with broad-spectrum antiviral potential should be performed as they may allow us to focus our efforts on optimizing semi- and biosynthetic techniques to pathways relevant to these compounds.

As we have presented, plants provide a vast array of candidates for the treatment of COVID-19. Although we have not named them here, several of these phytochemicals have exhibited activity against other coronaviruses (Islam et al., 2020), indicating that they may be used against future coronavirus outbreaks. Some of these compounds (e.g., catechin and emetine) have also demonstrated the ability to inhibit infection with viruses belonging to other families, which suggests their potential as broad-spectrum antivirals (Ali et al., 2021). Based on the relative successes of plant secondary metabolites in other disease states, such as cancer and antiparasitic infections, the development of plant bioactive compounds from bench-to-bedside is not impossible. Likely, the lack of plant antivirals stems from the parallel lack of impetus to develop treatment agents for acute viral diseases, which is one of the reasons for the slow global response to the COVID-19 pandemic. Concerted efforts are needed to maximize resources, including phytochemicals, for the development of treatment agents for COVID-19 and other viral diseases to ease the blow of large viral outbreaks in the future.

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**Conflict of Interest**

The authors have no conflict of interest to disclose.

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