Review article

Anti-COVID-19 drug candidates: A review on potential biological activities of natural products in the management of new coronavirus infection

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Abstract

Background and aim: The novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is now become a worldwide pandemic bringing over 71 million confirmed cases, while the specific drugs and vaccines approved for this disease are still limited regarding their effectiveness and adverse events. Since virus incidences are still on rise, infectivity and mortality may also rise in the near future, natural products are highly considered to be valuable sources for the discovery of new antiviral drugs against SARS-CoV-2. This present review aims to comprehensively summarize the up-to-date scientific literatures on biological activities of plant- and mushroom-derived compounds relevant to mechanistic targets involved in SARS-CoV-2 infection and inflammatory-associated pathogenesis, including viral entry, replication and release, and the renin-angiotensin-aldosterone system (RAAS).

Experimental procedure: Data were retrieved from a literature search available on PubMed, Scopus and Google Scholar databases and collected until the end of May 2020. The findings from in vitro cell and non-cell based studies were considered, while the results of in silico studies were excluded.

Results and conclusion: Based on the previous findings in SARS-CoV studies, except in silico molecular docking analysis, herein, we provide a total of 150 natural compounds as potential candidates for development of new anti-COVID-19 drugs with higher efficacy and lower toxicity than the existing therapeutic agents. Several natural compounds have showed their promising actions on multiple therapeutic targets, which should be further explored. Among them, quercetin, one of the most abundant of plant flavonoids, is proposed as a lead candidate with its ability on the virus side to inhibit SARS-CoV spike protein-angiotensin-converting enzyme 2 (ACE2) interaction, viral protease and helicase activities, as well as on the host cell side to inhibit ACE activity and increase intracellular zinc level.

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1. Introduction

On 31 December 2019, several cases of pneumonia were reported in Wuhan, the epicenter of the outbreak in Hubei province of China. The novel coronavirus was identified as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which causes Coronavirus Disease 2019 (COVID-19) pandemic. From the time of emergence until present, COVID-19 has spread worldwide in which a total of over 71 million confirmed cases with over 1.6 million death tolls has been reported by the World Health Organization (WHO). The COVID-19 positive cases continue rising and is widely distributed throughout the world with the prevalence ranging from highest in America, followed by Europe and South-East Asia, and lowest in Western Pacific region. Asymptomatic patients and patients with mild symptoms can be recovered under home care and isolation while patients with severe complications including acute respiratory distress syndrome (ARDS) require intensive care unit (ICU) which involves oxygen therapy. Currently, there is scant evidence from clinical trials for WHO to approve any standard drugs or vaccines as several trials have failed due to efficacy and safety concerns. Natural compounds from plant and fungi sources have been recognized in their antiviral properties with numerous mechanisms to prevent infection and strengthen host immunity. Herein, we reviewed potential antiviral compounds with multiple targets of action relating to coronaviruses including inhibiting of viral entry, replication and release, and compounds targeting renin–angiotensin–aldosterone system (RAAS) which exhibit promising effects against the disease. We also proposed future perspectives in adopting natural compounds to combat against the COVID-19.

2. Promising therapeutic strategies for the treatment of COVID-19 infection

Presently, there is no clinically approved therapeutics for treating COVID-19, while the rapid human-to-human transmission of this viral infection has expanded worldwide. As the efficacy and safety of natural products on the treatment of a number of viruses including SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), have been widely acknowledged for several years, the compounds derived from natural sources, e.g. plants and fungi, could have the potential to be a powerful anti-COVID-19 drug. In this review, we focused on four main categories of therapeutic strategies that aim to target the cellular machinery at each step of virus life cycle, starting from viral entry and replication to the release of viral progenies, as well as the RAAS which is a main target of the treatment of hypertension and has recently been proposed as another promising alternative in the treatment of COVID-19. The multiple potential therapeutic mechanisms, both specific and general, that could be capable of tackling COVID-19 infection are presented in Fig. 1.

The first therapeutic strategy targets on the mechanisms of virus entry in which the selective blockade of molecules that facilitates the internalization of virus into the host cells could be effective to prevent infection. Upon the binding of a virus surface spike (S) protein to a cellular receptor angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 generally enters into target host cells via two primary routes; viral membrane fusion and the more common endocytic uptake. The first entry mechanism is assisted by proteolytic activation of S protein by a host cell transmembrane protease serine 2 (TMPRSS2), which allows not only direct fusion of virus at the plasma membrane surface, but also release of viral genomic RNA into the cytoplasm. On the other hand, without the membrane bound protease TMPRSS2, the latter entry mechanism allows the whole viral particle to be uptake via receptor-mediated endocytosis, before subsequently uncoated following the S protein cleavage by cathepsin L within the endosome, to unveil its RNA genome into the cell.

The second and third therapeutic strategies focus on the inhibition of progeny virus production and release from infected cells. As far as the viral replication process is concerned, it begins with the translation of released genome of SARS-CoV-2, a single-stranded (positive-sense) RNA of approximately 30 kb in length, into two precursor polyproteins, pp1a and pp1ab. Both are further cleaved by virus-encoded proteases into several non-structural proteins (nsps) including two key replicative enzymes: the nsp12-RNA-dependent RNA polymerase (RdRp) and the nsp13-helicase, to form the replication-transcription complex (RTC) for synthesizing a full-length genomic RNA (replication) or a nested set of subgenomic mRNA (transcription). These mRNAs are translated into all relevant structural proteins, which together with the viral genome are subsequently assembled into new virions and finally released outside the cell through viroporin-mediated viral budding.

The last therapeutic strategy involves modulating the immune system with the RAAS which regulates blood pressure, fibrosis, and inflammation. In this system, angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II which is then converted to lung-protective angiotensin-(1–7) by ACE2. The angiotensin-(1–7) is further recognized by its receptor, the G-protein coupled receptor Mas, to reduce blood pressure, fibrosis, and inflammation. However, as SARS-CoV-2 enters the cells by binding to ACE2, the normal functions of ACE2 are then suppressed. Therefore, instead of converting to angiotensin-(1–7), the angiotensin II is largely bound to type 1 angiotensin II type 1 receptor (AT1R) which causes increased inflammation and other deleterious effects, particularly in the renal and cardiovascular systems.

3. Potential natural products as drug candidates against COVID-19

The data presented in this review were obtained from PubMed, Scopus and Google Scholar database up to May 2020. The terms of natural compound, natural product, plant and mushroom were individually searched along with the terms corresponding to each target molecule. Here, we summarize plant- and mushroom-derived compounds that have been reported of antiviral activity.

| List of abbreviations |
|-----------------------|
| 3CLpro 3-chymotrypsin-like main protease |
| ACE Angiotensin-converting enzyme |
| ARB Angiotensin-receptor blocker |
| ARDS Acute respiratory distress syndrome |
| AT1R Angiotensin II type 1 receptor |
| COVID-19 Coronavirus Disease 2019 |
| MERS-CoV Middle East Respiratory Syndrome Coronavirus |
| Nsp Non-structural protein |
| PIpro Papain-like protease |
| RAAS Renin–angiotensin–aldosterone system |
| RdRp RNA-dependent RNA polymerase |
| RTC Replication-transcription complex |
| SARS-CoV Severe Acute Respiratory Syndrome Coronavirus |
| SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus |
| TMPRSS2 Transmembrane protease serine 2 |
| V-ATPase Vacuolar-type H+–ATPase |
with known therapeutic mechanisms specifically against SARS-CoV-2 infection, performed by in vitro cell or non-cell based experiments but not in silico method, as potential candidates to be further researched. We also propose certain promising natural compounds targeting general mechanisms involved in coronavirus infection (see Fig. 1). Additionally, the reports on natural compounds against SARS-CoV with unidentified mechanism of action were included in this review.

3.1. Natural bioactive compounds targeting viral entry

3.1.1. The S protein-ACE2 interaction

The S protein plays a pivotal role in the entry of coronaviruses into host cells by recognizing and binding to the ACE2 via multivalent bonds. The attachment of S protein to ACE2 receptor leads to the fusion between the viral envelope and host cell membrane resulting in successful transfer of viral genome into infected cells. The S protein is composed of two functional subunits, S1 and S2. The S1 is responsible for binding to the host cell receptor through the receptor binding domain (RDB), while the S2 causes fusion of the viral and cellular membranes. Sequence alignment results showed that the homology of the S protein RBD sequence between the beta coronaviruses SARS-CoV and SARS-CoV-2 is 76%. A number of evidence revealed human ACE2 (hACE2) molecule as an entry receptor for both SARS-CoV and SARS-CoV-2 S proteins. Notably, S protein of SARS-CoV-2 was found to exhibit greater affinity to the ACE2 receptor than that of SARS-CoV. In addition, expression of ACE2 is ubiquitous with diverse functions, however its specific functions are demonstrated in several organs including lung, tongue, heart, kidney, gastrointestinal tract, pancreas and brain. Accordingly, multiple symptoms could be observed in COVID-19 patients. Several observations have been reported that the use of hydroxychloroquine, an ACE2 FDA-approved antagonist, was able to reduce mortality rate in hospitalized COVID-19 patients. Therefore, it is apparent that the S protein-hACE2 interaction complex is the most crucial target for searching appropriate inhibitors to inhibit entry of the virus in the host cell.

Several natural compounds have been demonstrated their activity to inhibit SARS-CoV entry to the host cell as shown in Table 1. According to the literature, an anthraquinone compound, emodin, showed the potency to inhibit viral infection by blocking the binding of SARS-CoV S protein to ACE2 in a dose-dependent manner. The plant sources which are likely to contain emodin as their active constituent were also found effective in blocking SARS-CoV S protein and ACE2 interaction, with showing IC50 values for aqueous extracts from the root of Rheum palmatum, the root and stem of Polygonum multiflorum, ranged from 1 to 10 µg/ml.

Another previous study using the high-throughput screening technique revealed more promising natural antiviral compounds consisted in the extracts from Chinese herbs. Those small herbal molecules could strongly bind to the SARS-CoV S2 protein and...
Table 1
List of bioactive compounds from natural sources as potential anti-COVID-19 drug candidates and their mechanisms of action.

| Compound                        | Class              | Source                     | Biological action/Efficacy          | Experiment                          | Reference |
|---------------------------------|--------------------|----------------------------|-------------------------------------|-------------------------------------|-----------|
| Emodin                          | Anthraquinone      | Rheum palmatum             | IC₅₀ = 200 µM                        | Cell-free assay (Competitive biotinylated ELISA) | 29        |
| Luteolin                        | Flavonoid          | Rhodiola kirilowii         | IC₅₀ = 4.5 µM                        | Cell-based assay (IFA)               | 30        |
| Quercetin                       | Flavonoid          | Allium cepa                | IC₅₀ = 83.4 µM                       | Cell-free and cell-based assay (FAC/MS and Luciferase assay) | 30        |
| Tetra-O-galloyl-β-d-glucose (TGG)| Tannin             | Galla chinensis            | IC₅₀ = 10.6 µM                       | Cell-free and cell-based assay (FAC/MS and Luciferase assay) | 30        |
| **Inhibiting the SARS-CoV S protein-ACE2 interaction** |                    |                            |                                     |                                     |           |
| 1-cinnamoyl-3,11-dihydroxy melicarpin | Terpenoid          | Melia azedarach            | increased endolysosomal pH (EC of 7.5 µM) | Cell-based assay (AO staining)       | 38        |
| 25-O-acetyl-7,8-didehydrocimigenol 3-O-beta-d-xylpropyloside (ADEX) | Terpenoid          | Cimicifugae rhi zona       | inhibited degradation activity by decreasing cathepsin expression, but not endolysosomal acidity (EC of 24 µM) | Cell-based assay (AO staining, DQ-BSA staining and WB) | 39        |
| Alantolactone                   | Sesquiterpene lactone | Inula helenium             | neutralized endo-lysosomal pH and reducing the expression and activity of cathepsins (EC of 10 µM) | Cell-based assay (LysoTracker Red and AO staining, WB and Cathepsin activity assay) | 76        |
| Cleistanthin A                  | Lignan glycoside   | Cleistanthus collini       | elevated the activity of V-type ATPase and elevated endolysosomal pH (EC of 0.1 µM) | Cell-based assay (AO staining, WB and Cathepsin activity assay) | 77,78     |
| Cleistanthoside A tetraacetate  | Lignan glycoside   | Phyllanthus ussulifolius   | neutralized endo-lysosomal acidity and decreased the activity of V-type ATPase (EC of 50 nM) | Cell-based assay (LysoTracker Red staining and V-type ATPase activity assay) | 78        |
| Dauricine                       | Alkaloid           | Rhizoma Menispermi        | elevated endo-lysosomal pH, decreased the levels of active cathepsins and inhibited the activity of V-type ATPase (EC of 10 µM) | Cell-based assay (LysoSensor Yellow/Blue staining, WB and V-type ATPase activity assay) | 42        |
| Daurisoline                     | Alkaloid           | Rhizoma Menispermi        | elevated endo-lysosomal pH, decreased the levels of active cathepsins and inhibited the activity of V-type ATPase (EC of 10 µM) | Cell-based assay (LysoSensor Yellow/Blue staining, WB and V-type ATPase activity assay) | 42        |
| Diphyllin                       | Lignan lactone     | Cleistanthus collini      | inhibited the activity of V-type ATPase (EC of 0.3 µM) | Cell-based assay (AO staining, V-type ATPase activity assay) | 79        |
| Ginsenoside Ro                  | Triterpenoid saponin | Punax ginseng             | raised endolysosomal pH and downregulating the expression and activity of cathepsins (EC of 50 µM) | Cell-based assay (AO staining, WB and Cathepsin activity assay) | 80        |
| Icariside II                    | Flavonoid          | Epimedium koreanum Nakai  | decreased endolysosomal acidity (EC of 25 µM) | Cell-based assay (AO staining)       | 81        |
| Leelamine                       | Terpene            | Pinus sylvestris          | decreased endolysosomal acidity and inhibited cellular endocytosis (EC of 3 µM) | Cell-based assay (LysoTracker Red staining and Internalization of fluorescent transferrin-A488) | 40        |
| Matrine                         | Alkaloid           | Sophora flavescens Ait    | inhibited endolysosomal acidification and reduced the expression and activity of cathepsins (EC of 2 nM) | Cell-based assay (LysoSensor Yellow/Blue, WB and Cathepsin activity assay) | 43        |
| Myrtrenal                       | Terpene            | Elettaria cardamomum      | inhibited the activity of V-type ATPase and reduced endolysosomal acidification (EC of 100 µM) | Cell-based assay (AO staining and V-type ATPase activity assay) | 41        |
| Oblongofolin C                  | Benzophenone       | Garcinia yunnanensis Hu   | inhibited endolysosomal acidification and downregulated the expression and activity of cathepsins (EC of 15 µM) | Cell-based assay (AO staining, WB and Cathepsin activity assay) | 82        |
| Pulsatilla saponin D            | Triterpenoid saponin | Pulsatilla chinensis      | elevated endolysosomal pH and downregulated the expression and activity of cathepsins (EC of 1.25 µM) | Cell-based assay (LysoSensor Yellow/Blue staining) | 83        |
| Tetrandrine                     | Alkaloid           | Stephanida tetrandra S. Moore | elevated endolysosomal pH in a concentration-dependent manner (EC of 1–10 µM) | Cell-based assay (LysoSensor Yellow/Blue staining) | 44        |
| **Inhibiting the SARS-CoV 3CL⁺⁺ activity** |                    |                            |                                     |                                     |           |
| 3’-(3-Methylbut-2-enyl)-7,4,7-trihydroxyflavane | Flavonoid          | Brassonienta papyrera     | IC₅₀ = 30.2 µM                       | Cell-free assay (FRET)              | 84        |
| 4-Hydroxyderricin               | Chalcone           | Angelica keiskei          | IC₅₀ = 81.4 µM, IC₅₀ = 50.8 µM       | Cell-free assay (FRET)              | 35        |
| Betulinic acid                  | Terpene            | Brennia fraticose         | IC₅₀ = 10 µM                         | Cell-free assay (FRET)              | 49,50     |
| Broussochalcone A               | Chalcone           | Brassonienta papyrera     | IC₅₀ = 88.1 µM                       | Cell-free assay (FRET)              | 84        |
| Broussochalcone B               | Chalcone           | Brassonienta papyrera     | IC₅₀ = 57.8 µM                       | Cell-free assay (FRET)              | 84        |
| Broussoflavan A                 | Flavonoid          | Brassonienta papyrera     | IC₅₀ = 92.4 µM                       | Cell-free assay (FRET)              | 84        |
| Dihydrotanshinone I             | Tanshinson         | Salvia militorrhiza        | IC₅₀ = 14.4 µM                       | Cell-free assay (FRET)              | 51        |
| Hesperetin                      | Flavonoid          | Isatis indigotica         | IC₅₀ = 60 µM                         | Cell-free assay (ELISA)             | 42        |

(continued on next page)
| Compound                  | Class                        | Source                                | Biological action/Efficacy | Experiment                                      | Reference |
|---------------------------|------------------------------|---------------------------------------|-----------------------------|-------------------------------------------------|-----------|
| Hirsuteneone              | Diarylheptanoid              | *Alnus japonica*                      | IC₅₀ = 8.3 μM               | Cell-based assay (Luciferase reporter assay)     | 85        |
| Isobavachalcone           | Chalcone                     | *Angelica keiskei*                    | IC₅₀ = 36.2 μM              | Cell-free assay (FRET)                           | 85        |
|                           |                              |                                       | IC₅₀ = 39.4 μM              | Cell-free assay (FRET)                           | 35        |
|                           |                              |                                       | IC₅₀ = 11.9 μM              | Cell-based assay (Luciferase reporter assay)     |           |
| Isoliquiritigenin         | Chalcone                     | *Glycyrrhiza glabra* *a*              | IC₅₀ = 61.9 μM              | Cell-free assay (FRET)                           | 84, 86    |
| Kazinol A                 | Flavonoid                    | *Broussonetia papyrifera*             | IC₅₀ = 84.8 μM              | Cell-free assay (FRET)                           | 84        |
| Kazinol F                 | Biphenyl propanoids          | *Broussonetia papyrifera*             | IC₅₀ = 43.3 μM              | Cell-free assay (FRET)                           | 84        |
| Kazinol J                 | Biphenyl propanoids          | *Broussonetia papyrifera*             | IC₅₀ = 64.2 μM              | Cell-free assay (FRET)                           | 84        |
| Methyl tanshinonate       | Tanshinone                   | *Salvia miltiorrhiza*                 | IC₅₀ = 21.1 μM              | Cell-free assay (FRET)                           | 51        |
| Quercetin                 | Flavonoid                    | *Allium cepa*                         | IC₅₀ = 52.7 μM              | Cell-free assay (FRET)                           | 64, 87, 88 |
| Quercetin-3-b-galactoside | Flavonoid                    | *Machilus zhaoensis* *a*              | IC₅₀ = 42.8 μM              | Cell-free assay (FRET)                           | 87, 88    |
| Rosmariquinone            | Tanshinone                   | *Salvia miltiorrhiza*                 | IC₅₀ = 21.1 μM              | Cell-free assay (FRET)                           | 51        |
| Savinin                   | Lignoid                      | *Chamomyparis obtuse var. formosana*  | IC₅₀ = 25 μM                | Cell-free assay (FRET)                           | 49        |
| Tanshinone I              | Tanshinone                   | *Salvia miltiorrhiza*                 | IC₅₀ = 38.7 μM              | Cell-free assay (FRET)                           | 51        |
| Tanshinone IIA            | Tanshinone                   | *Salvia miltiorrhiza*                 | IC₅₀ = 89.1 μM              | Cell-free assay (FRET)                           | 51        |
| Tanshinone III            | Tanshinone                   | *Salvia miltiorrhiza*                 | IC₅₀ = 24.8 μM              | Cell-free assay (FRET)                           | 51        |
| Xanthoangelol             | Chalcone                     | *Angelica keiskei*                    | IC₅₀ = 38.4 μM              | Cell-free assay (FRET)                           | 35        |
|                           |                              |                                       | IC₅₀ = 5.8 μM               | Cell-based assay (Luciferase reporter assay)     |           |
| Xanthoangelol B           | Chalcone                     | *Angelica keiskei*                    | IC₅₀ = 22.2 μM              | Cell-free assay (FRET)                           | 35        |
|                           |                              |                                       | IC₅₀ = 8.6 μM               | Cell-based assay (Luciferase reporter assay)     |           |
| Xanthoangelol D           | Chalcone                     | *Angelica keiskei*                    | IC₅₀ = 26.6 μM              | Cell-free assay (FRET)                           | 35        |
|                           |                              |                                       | IC₅₀ = 9.3 μM               | Cell-based assay (Luciferase reporter assay)     |           |
| Xanthoangelol E           | Chalcone                     | *Angelica keiskei*                    | IC₅₀ = 11.4 μM              | Cell-free assay (FRET)                           | 35        |
|                           |                              |                                       | IC₅₀ = 7.1 μM               | Cell-based assay (Luciferase reporter assay)     |           |
| Xanthoangelol F           | Chalcone                     | *Angelica keiskei*                    | IC₅₀ = 34.1 μM              | Cell-free assay (FRET)                           | 35        |
|                           |                              |                                       | IC₅₀ = 32.6 μM              | Cell-based assay (Luciferase reporter assay)     |           |
| Xanthokeistal A           | Chalcone                     | *Angelica keiskei*                    | IC₅₀ = 44.1 μM              | Cell-free assay (FRET)                           | 35        |
|                           |                              |                                       | IC₅₀ = 9.8 μM               | Cell-based assay (Luciferase reporter assay)     |           |

**Inhibiting the SARS-CoV PL₃₀ activity**

| 3'-O-Methylidyplacol       | Flavonoid                    | *Paulownia tomentosa*                 | IC₅₀ = 9.5 μM               | Cell-free assay (Fluorescence-based deubiquitination) | 89        |
| 3'-O-Methyldiplacone      | Flavonoid                    | *Paulownia tomentosa*                 | IC₅₀ = 13.2 μM              | Cell-free assay (Fluorescence-based deubiquitination) | 89        |
| 4'-O-Methylbavachalcone   | Chalcone                     | *Psaurea corylifolia*                 | IC₅₀ = 10.1 μM              | Cell-free assay (Fluorescence-based deubiquitination) | 90        |
| 4'-O-Methyldiplacol       | Flavonoid                    | *Paulownia tomentosa*                 | IC₅₀ = 9.2 μM               | Cell-free assay (Fluorescence-based deubiquitination) | 89        |
| 6-Geranyl-4',5,7-trihydroxy-3',5'-dimethoxyflavonone | Flavonoid | *Paulownia tomentosa* | IC₅₀ = 13.9 μM | Cell-free assay (Fluorescence-based deubiquitination) | 89        |
| Broussonchalcone A        | Chalcone                     | *Broussonetia papyrifera*             | IC₅₀ = 9.2 μM               | Cell-free assay (Fluorescence-based deubiquitination) | 84        |
| Broussonchalcone B        | Chalcone                     | *Broussonetia papyrifera*             | IC₅₀ = 11.6 μM              | Cell-free assay (Fluorescence-based deubiquitination) | 84        |
| Cryptotanshinone          | Tanshinone                   | *Salvia miltiorrhiza*                 | IC₅₀ = 0.8 μM               | Cell-free assay (Fluorescence-based deubiquitination) | 51        |
| Curcumin                  | Polyphenol                   | *Curcuma longa*                      | IC₅₀ = 5.7 μM               | Cell-free assay (Fluorescence-based deubiquitination) | 85, 87, 88 |
| Dihydrorasthinone I       | Tanshinone                   | *Salvia miltiorrhiza*                 | IC₅₀ = 4.9 μM               | Cell-free assay (Fluorescence-based deubiquitination) | 89        |
| Diplacone                 | Flavonoid                    | *Paulownia tomentosa*                 | IC₅₀ = 10.4 μM              | Cell-free assay (Fluorescence-based deubiquitination) | 85        |
| Hirsutanonol              | Diarylheptanoid              | *Alnus japonica*                      | IC₅₀ = 7.8 μM               | Cell-free assay (Fluorescence-based deubiquitination) | 85        |
### Table 1 (continued)

| Compound                  | Class               | Source                          | Biological action/Efficacy                                      | Experiment                                         | Reference |
|---------------------------|---------------------|---------------------------------|------------------------------------------------------------------|----------------------------------------------------|-----------|
| Hirsutenone               | Diarylheptanoid     | *Alnus japonica*                | IC_{50} = 4.1 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 85        |
| Isobavachalcone           | Chalcone            | *Psoralea corylifoia*           | IC_{50} = 7.3 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 90        |
| Isoliquiritigenin         | Chalcone            | *Glycyrrhiza glabra*            | IC_{50} = 13.0 µM                                                | Cell-free assay (Fluorescence-based deubiquitination) | 35        |
| Kaempferol                | Flavonoid           | *Zingiber officinale*           | IC_{50} = 16.3 µM                                                | Cell-free assay (Fluorescence-based deubiquitination) | 84,92     |
| Kazinol J                 | Biphenyl propanoids | *Broussonetia papyrifera*       | IC_{50} = 15.2 µM                                                | Cell-free assay (Fluorescence-based deubiquitination) | 84        |
| Methyl tanshinonate       | Tanshinone          | *Salvia miltiorrhiza*           | IC_{50} = 9.2 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 51        |
| Mimulone                  | Flavonoid           | *Paulownia tomentosa*           | IC_{50} = 14.4 µM                                                | Cell-free assay (Fluorescence-based deubiquitination) | 89        |
| Neobavaisoflavone         | Flavonoid           | *Psoralea corylifoia*           | IC_{50} = 18.3 µM                                                | Cell-free assay (Fluorescence-based deubiquitination) | 90        |
| Papyriflavanol A          | Flavonoid           | *Broussonetia papyrifera*       | IC_{50} = 3.7 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 84        |
| Psoraladin                | Flavonoid           | *Psoralea corylifoia*           | IC_{50} = 4.2 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 90        |
| Quercetin                 | Flavonoid           | *Allium cepa*                   | IC_{50} = 8.6 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 84,87     |
| Rubranol                  | Diarylheptanoid     | *Alnus japonica*                | IC_{50} = 12.3 µM                                                | Cell-free assay (Fluorescence-based deubiquitination) | 85        |
| Rubransoxide A            | Diarylheptanoid     | *Alnus japonica*                | IC_{50} = 9.1 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 85        |
| Rubransoxide B            | Diarylheptanoid     | *Alnus japonica*                | IC_{50} = 8.0 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 85        |
| Tanshinone I              | Tanshinone          | *Salvia miltiorrhiza*           | IC_{50} = 8.8 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 51        |
| Tanshinone II A           | Tanshinone          | *Salvia miltiorrhiza*           | IC_{50} = 1.6 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 51        |
| Tanshinone II B           | Tanshinone          | *Salvia miltiorrhiza*           | IC_{50} = 10.7 µM                                                | Cell-free assay (Fluorescence-based deubiquitination) | 51        |
| Terrestramine             | Cinnamic amide      | *Tribulus terrestris*           | IC_{50} = 15.8 µM                                                | Cell-free assay (Fluorescence-based deubiquitination) | 93        |
| Tomentin A                | Flavonoid           | *Paulownia tomentosa*           | IC_{50} = 6.2 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 89        |
| Tomentin B                | Flavonoid           | *Paulownia tomentosa*           | IC_{50} = 6.1 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 89        |
| Tomentin C                | Flavonoid           | *Paulownia tomentosa*           | IC_{50} = 11.6 µM                                                | Cell-free assay (Fluorescence-based deubiquitination) | 89        |
| Tomentin D                | Flavonoid           | *Paulownia tomentosa*           | IC_{50} = 12.5 µM                                                | Cell-free assay (Fluorescence-based deubiquitination) | 89        |
| Tomentin E                | Flavonoid           | *Paulownia tomentosa*           | IC_{50} = 5.0 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 89        |
| Xanthoangelol             | Chalcone            | *Angelica keiskei*              | IC_{50} = 11.7 µM                                                | Cell-free assay (Fluorescence-based deubiquitination) | 35        |
| Xanthoangelol B           | Chalcone            | *Angelica keiskei*              | IC_{50} = 11.7 µM                                                | Cell-free assay (Fluorescence-based deubiquitination) | 35        |
| Xanthoangelol D           | Chalcone            | *Angelica keiskei*              | IC_{50} = 19.3 µM                                                | Cell-free assay (Fluorescence-based deubiquitination) | 35        |
| Xanthoangelol E           | Chalcone            | *Angelica keiskei*              | IC_{50} = 1.2 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 35        |
| Xanthoangelol F           | Chalcone            | *Angelica keiskei*              | IC_{50} = 5.6 µM                                                 | Cell-free assay (Fluorescence-based deubiquitination) | 35        |

**Inhibiting the SARS-CoV helicase activity**

| Myricetin                  | Flavonoid           | *Camellia sinensis*             | Inhibited ATPase activity of SARS-CoV helicase with IC_{50} of 2.71 µM | Cell-free assay (Colorimetry-based ATP hydrolysis assay) | 94        |
| Quercetin                  | Flavonoid           | *Allium cepa*                   | Inhibited duplex DNA-unwinding activity of SARS-CoV NTPase/helicase with IC_{50} of 8.1 µM | Cell-free assay (FRET-based dsDNA unwinding assay) | 95        |
| Scutellarein               | Flavonoid           | *Scutellaria baicalensis*       | Inhibited ATPase activity of SARS-CoV helicase with IC_{50} of 0.86 µM | Cell-free assay (Colorimetry-based ATP hydrolysis assay) | 94        |

**Increasing intracellular Zn^{2+}**

| Caffeic acid               | Phenolic acid       | *Ocimum basilicum*              | Increased intracellular Zn^{2+} level (3-fold increase at EC of 50 µM) | Cell-free assay (using liposome model) | 60        |
| Catechin                   | Flavonoid           | *Camellia sinensis*             | Increased intracellular Zn^{2+} level (2-fold increase at EC of 50 µM) | Cell-free assay (using liposome model) | 60        |
| Catechol                   | Phenol              | *Allium cepa*                   | Increased intracellular Zn^{2+} level (2-fold increase at EC of 50 µM) | Cell-free assay (using liposome model) | 60        |
| Epigallocatechin-3-gallate | Flavonoid           | *Camellia sinensis*             | Increased intracellular Zn^{2+} level (36-fold increase at EC of 50 µM) | Cell-free assay (using liposome model) | 60        |

(continued on next page)
Table 1 (continued)

| Compound | Class | Source | Biological action/Efficacy | Experiment | Reference |
|----------|-------|--------|---------------------------|------------|-----------|
| Gallic acid | Phenolic acid | Syzygium aromaticum | increased the uptake of Zn$^{2+}$ in both cell (4-fold increase at EC of 100 μM) and liposome model (16-fold increase at EC of 10 μM) | Cell-based assay (Fluorescent Zn$^{2+}$ indicator) and cell-free assay (using liposome model) | 62 |
| Genistein | Flavonoid | Glycine max | increased intracellular Zn$^{2+}$ level (8-fold increase at EC of 50 μM) | Cell-free assay (using liposome model) | 60 |
| Luteolin | Flavonoid | Rhodiola kirilowii | increased intracellular Zn$^{2+}$ level (12-fold increase at EC of 50 μM) | Cell-free assay (using liposome model) | 60 |
| Pyrithione | Organic sulfur compound | Allium stipitatum | increased intracellular Zn$^{2+}$ level (3-fold increase at EC of 10 μM) | Cell-based assay (Radioactive Zn$^{2+}$ uptake) | 66 |
| Quercetin | Flavonoid | Allium cepa | increased intracellular Zn$^{2+}$ level (18-fold increase at EC of 50 μM) | Cell-free assay (using liposome model) | 60 |
| Resveratrol | Polyphenol | Vitis vinifera | increased the uptake of Zn$^{2+}$ in both cell (2-fold increase at EC of 100 μM) and liposome model (8-fold increase at EC of 10 μM) | Cell-based assay (Fluorescent Zn$^{2+}$ indicator) and cell-free assay (using liposome model) | 62 |
| Rutin | Flavonoid | Morus alba | increased intracellular Zn$^{2+}$ level (7.5-fold increase at EC of 10 μM) | Cell-free assay (using liposome model) | 61 |
| Tannic acid | Phenolic acid | Camellia sinensis | increased intracellular Zn$^{2+}$ level (12-fold increase at EC of 50 μM) | Cell-free assay (using liposome model) | 60 |
| Taxifolin | Flavonoid | Silybum marianum | increased intracellular Zn$^{2+}$ level (4-fold increase at EC of 50 μM) | Cell-free assay (using liposome model) | 60 |
| β-thujaplicin (Hinokitiol) | Terpene | Chamaecyparis thujaplicin | inhibited the ion channel activity of SARS-CoV-3a protein with IC$_{50}$ of 20 μM | Cell-based assay (Voltage-clamp method in Xenopus oocyte model) | 65 |
| Azefin | Flavonoid | Houttuynia cordata | 3α protein (17% inhibition at EC of 10 μM) | Cell-based assay (Voltage-clamp method in Xenopus oocyte model) | 65,67 |
| Emodin | Anthraquinone | Rheum tanguticum | 3α protein with IC$_{50}$ of 20 μM | Cell-based assay (Voltage-clamp method in Xenopus oocyte model) | 65 |
| Juglanine | Flavonoid | Polygonum aviculare | 3α protein with IC$_{50}$ of 2.3 μM | Cell-based assay (Voltage-clamp method in Xenopus oocyte model) | 65 |
| Kaempferol | Flavonoid | Zingiber officinale | increased intracellular Zn$^{2+}$ level (4-fold increase at EC of 50 μM) | Cell-based assay (using liposome model) | 60 |
| Kaempferol-3-O-α-rambonopyranosyl (1→2)-β-glucopyranoside | Flavonoid | Cistus ternatea | increased intracellular Zn$^{2+}$ level (3-fold increase at EC of 125 μM) | Cell-based assay (Radioactive Zn$^{2+}$ uptake) | 66 |
| Tiliroside | Flavonoid | Althaea officinalis | inhibited the ion channel activity of SARS-CoV-3α protein (52% inhibition at EC of 20 μM) | Cell-based assay (Voltage-clamp method in Xenopus oocyte model) | 65,66 |
| Inhibiting the ACE activity | 25-O-methylsalol F | Alisma orientale | Reduced ACE and AT1R protein expression (~30% and ~10% inhibition at EC of 10 μM) | Cell-based assay (WB analysis) | 98 |
| 3,5-dihydroxy-4- methoxybenzoic acid | Phenolic acid | Tamarix hohenackeri | 46.2% inhibition at EC of 20 mg/mL | Cell-free assay (HHL degradation assay) | 99 |
| 4’-hydroxy Pd-C-III | Coumarin | Angelica decursiva | IC$_{50}$ = 9.4 μM | Cell-free assay (FAPGG degradation assay) | 100 |
| 4’-methoxy Pd-C→I | Coumarin | Angelica decursiva | IC$_{50}$ = 16 μM | Cell-free assay (FAPGG degradation assay) | 100 |
| Ampleopis C | Stilbenoid | Vitis thunbergii var. Taiwanian | IC$_{50}$ = 18.2 μM | Cell-free assay (FAPGG degradation assay) | 101 |
| Apigenin | Flavonoid | Adinandra nitida | 30.3% inhibition at EC of 500 μg/mL | Cell-free assay (HHL degradation assay) | 102 |
| Asparagine | Organic sulfur compound | Asparagus officinalis | IC$_{50}$ = 113 μM | Cell-free assay (3HB-GGG hydrolysis assay) | 103 |
| Caffeic acid | Phenolic acid | Echinacea purpurea | IC$_{50}$ = 0.1 μM | Cell-free assay (HHL degradation assay) | 71 |
| Camellianin A | Flavonoid | Adinandra nitida | 30.2% inhibition at EC of 500 μg/ml. | Cell-free assay (HHL degradation assay) | 102 |
| Camellianin B | Flavonoid | Adinandra nitida | 40.7% inhibition at EC of 500 μg/ml. | Cell-free assay (HHL degradation assay) | 104 |
| Carinoside | Flavonoid | Desmodium strychnifolium | IC$_{50}$ = 316 μM | Cell-free assay (HHL degradation assay) | 104 |
| Catechin | Flavonoid | Malus domestica | IC$_{50}$ = 109 μM | Cell-free assay (HHL degradation assay) | 105 |
| Chlorogenic acid | Phenolic acid | Echinacea purpurea | IC$_{50}$ = 0.1 μM | Cell-free assay (HHL degradation assay) | 71 |
| Chrysine | Flavonoid | Malus domestica | IC$_{50}$ = 146 μM | Cell-free assay (HHL degradation assay) | 105 |
| Chrysosanol | Flavonoid | Tamarix hohenackeri | 57.6% inhibition at EC of 20 mg/mL | Cell-free assay (HHL degradation assay) | 99 |
| Coretincone | Phenolic glycoside | Coreopsis tinctoria | IC$_{50}$ = 228 μM | Cell-free assay (HHL degradation assay) | 106 |
| Curcumin | Polyphenol | Curcuma longa | 76.9% inhibition at EC of 10 μM | Cell-free assay (HHL degradation assay) | 107 |
| Cyandin-3-O-glucoside | Flavonoid | Malus domestica | IC$_{50}$ = 174 μM | Cell-free assay (HHL degradation assay) | 105 |
| Compound                     | Class                | Source                | Biological action/Efficacy | Experiment                                      | Reference |
|-----------------------------|----------------------|-----------------------|-----------------------------|--------------------------------------------------|-----------|
| Cyanidin-3-O-galactoside    | Flavonoid glycoside  | Malus domestica       | IC₅₀ = 206 μM               | Cell-free assay (HHL degradation assay)           | 105       |
| Cyanidin-3-O-rhamnoloside   | Flavonoid glycoside  | Malus domestica       | IC₅₀ = 114 μM               | Cell-free assay (HHL degradation assay)           | 105       |
| Cyanidin-3-O-sambubioside   | Flavonoid glycoside  | Hibiscus sabdariffa   | IC₅₀ = 117.7 μM             | Cell-free assay (FAPGG degradation assay)         | 108       |
| Cyanidin-3-O-β-glucoside    | Flavonoid glycoside  | Rosa damascena        | IC₅₀ = 138.8 μM             | Cell-free assay (HHL degradation assay)           | 109       |
| Decursidin                  | Coumarin             | Angelica decursiva    | IC₅₀ = 20 μM                | Cell-free assay (FAPGG degradation assay)         | 100       |
| (+)-trans-Decursidinol      | Coumarin             | Angelica decursiva    | IC₅₀ = 4.7 μM               | Cell-free assay (FAPGG degradation assay)         | 100       |
| Decursinol                  | Coumarin             | Angelica decursiva    | IC₅₀ = 18.3 μM              | Cell-free assay (FAPGG degradation assay)         | 100       |
| Delphinidin-3-O-sambubioside| Flavonoid glycoside  | Hibiscus sabdariffa   | IC₅₀ = 141.6 μM             | Cell-free assay (FAPGG degradation assay)         | 108       |
| Epicatechin                 | Flavonoid            | Malus domestica       | IC₅₀ = 73 μM                | Cell-free assay (HHL degradation assay)           | 105       |
| Gallic acid                 | Phenolic acid        | Tamarix hohenackeri   | 43.1% inhibition at EC of 20 mg/mL | Cell-free assay (HHL degradation assay)       | 99        |
| Gluco-aurantioobtusin       | Anthraquinone glycoside | Cassia tora        | IC₅₀ = 30.2 μM             | Cell-free assay (FAPGG degradation assay)         | 110       |
| (+)-Hopeaphenol             | Stilbenoid           | Ampelopsis brevipedunculata var. hanceri | IC₅₀ = 1.6 μM | Cell-free assay (HHL degradation assay)           | 72        |
| Isoferulic acid             | Phenolic acid        | Tamarix hohenackeri   | 30.6% inhibition at EC of 20 mg/mL | Cell-free assay (HHL degradation assay)       | 99        |
| Isoqueretin                 | Flavonoid            | Troparolum majus     | Reduced plasmatic ACE activity in SHR rats (43% inhibition at EC of 10 mg/kg) | Cell-free assay (HHL degradation assay) | 111       |
| Isorutarine                 | Coumarin             | Angelica decursiva    | IC₅₀ = 68.4 μM             | Cell-free assay (FAPGG degradation assay)         | 100       |
| Junipediol A-8-O-β-d-glucoside | Phenylpropa- | Apium graveolens      | IC₅₀ = 210 μM               | Cell-free assay (HHL degradation assay)           | 112       |
| (5)-Malic acid 1’-O-β- | Organic acid glycoside | Luctus sativa   | IC₅₀ = 27.8 μM             | Cell-free assay (HHL degradation assay)           | 115       |
| Mangiferin                  | Xanthone glycoside   | Swertia chirayta     | 31.5% inhibition at EC of 500 μM | Cell-free assay (HHL degradation assay)       | 114       |
| Miquelianin                 | Flavonoid glycoside  | Cuphea glutinosa     | 32.1% inhibition at EC of 100 ng/mL | Cell-free assay (FAPGG degradation assay) | 115       |
| N³,N³,N⁸-tris (dihydrocaffeoyl) spermidine | Polyamine | Solarum quitensis     | IC₅₀ = 9.6 ppm              | Cell-free assay (3HB-GGG hydrolysis assay)        | 116       |
| Methyl gallate              | Phenolic acid        | Tamarix hohenackeri   | 35.7% inhibition at EC of 20 mg/mL | Cell-free assay (HHL degradation assay)       | 99        |
| Naringenin                  | Flavonoid            | Malus domestica       | IC₅₀ = 78 μM                | Cell-free assay (HHL degradation assay)           | 105       |
| Onopordia                   | Polyphenol           | Onopordum acanthium L. | IC₅₀ = 300 μM             | Cell-free assay (HHL degradation assay)           | 117,118   |
| Orotic acid                 | Organic acid         | Daucus carota        | 40.3% inhibition at EC of 5 μg/mL | Cell-free assay (HHL degradation assay)       | 119       |
| Pd—C—I                     | Coumarin             | Angelica decursiva    | IC₅₀ = 6.8 μM               | Cell-free assay (FAPGG degradation assay)         | 100       |
| Pd-C-II                     | Coumarin             | Angelica decursiva    | IC₅₀ = 12.4 μM              | Cell-free assay (FAPGG degradation assay)         | 100       |
| Pd-C-III                    | Coumarin             | Angelica decursiva    | IC₅₀ = 15.3 μM              | Cell-free assay (FAPGG degradation assay)         | 100       |
| Quercetin                   | Flavonoid            | Malus domestica       | IC₅₀ = 151 μM               | Cell-free assay (HHL degradation assay)           | 105       |
| Quercetin-3-O-galactoside   | Flavonoid glycoside  | Malus domestica       | IC₅₀ = 180 μM               | Cell-free assay (HHL degradation assay)           | 105       |
| Quercetin-3-O-glucoside     | Flavonoid glycoside  | Malus domestica       | IC₅₀ = 71 μM                | Cell-free assay (HHL degradation assay)           | 105       |
| Quercetin-3-O-glucuronic acid | Flavonoid conjugate | Malus domestica       | IC₅₀ = 27 μM                | Cell-free assay (HHL degradation assay)           | 105       |
| Quercetin-3-O-rhamnoside    | Flavonoid glycoside  | Malus domestica       | IC₅₀ = 100 μM               | Cell-free assay (HHL degradation assay)           | 105       |
| Quercetin-3-O-rutinoside    | Flavonoid glycoside  | Malus domestica       | IC₅₀ = 90 μM                | Cell-free assay (HHL degradation assay)           | 105       |
| Quercetin-3-O-sulfate       | Flavonoid conjugate  | Malus domestica       | IC₅₀ = 131 μM               | Cell-free assay (HHL degradation assay)           | 105       |
| Quercetin-4’-O-glucoside    | Flavonoid glycoside  | Malus domestica       | IC₅₀ = 211 μM               | Cell-free assay (HHL degradation assay)           | 105       |
| Schaftoside                 | Flavonoid glycoside  | Desmodium styracifolium | IC₅₀ = 58.4 μM          | Cell-free assay (HHL degradation assay)           | 104       |

(continued on next page)
Table 1 (continued)

| Compound            | Class             | Source                          | Biological action/Efficacy | Experiment                          | Reference |
|---------------------|-------------------|---------------------------------|-----------------------------|-------------------------------------|-----------|
| Tannic acid         | Phenolic acid     | Camellia sinensis              | IC50 = 230 µM              | Cell-free assay (HHL degradation assay) | 126       |
| Taxifolin           | Flavonoid         | Coreopsis tinctoria            | IC50 = 145.7 µM            | Cell-free assay (HHL degradation assay) | 106       |
| Vicenin 1           | Flavonoid         | Desmodium styracifolium        | IC50 = 8.25 µM             | Cell-free assay (HHL degradation assay) | 104       |
| Vicenin 2           | Flavonoid         | Desmodium styracifolium        | IC50 = 43.8 µM             | Cell-free assay (HHL degradation assay) | 104       |
| Vicenin 3           | Flavonoid         | Desmodium styracifolium        | IC50 = 46.9 µM             | Cell-free assay (HHL degradation assay) | 104       |
| (+)-α-Viniferin     | Flavonoid         | Vitis thunbergii var. taiwanian| IC50 = 35.5 µM             | Cell-free assay (FAPGG degradation assay) | 101       |
| (+)-Vitisin A       | Flavonoid         | Vitis thunbergii var. taiwanian| IC50 = 3.3 µM              | Cell-free assay (FAPGG degradation assay) | 101       |
|                    |                   | Ampelopsis brevipedunculata var. hancei | IC50 = 1.5 µM          | Cell-free assay (HHL degradation assay) | 72        |

3HB-GGG = 3-hydroxybutyryl-Gly-Gly-Gly; AAS = Acidine orange; ATP = Adenosine triphosphate; DQ-BSA = Dye quenched-bovine serum albumin; EC = The effective test concentration; ELISA = Enzyme Linked Immunosorbent Assay; FAC/MS = Frontal affinity chromatography-Mass spectrometry; FAPGG = furylacryloyl-phenylalanyl-glycyl-glycine; FRET = Fluorescence resonance energy transfer; HHL = hippuryl-L-histidyl-L-leucine; IC50 = The half maximal inhibitory concentration; IFA = Immunofluorescence assay; SHR = spontaneously hypertensive rat; WB = Western Blot.

* The study used commercial products. Here provides a natural source of compound as an example.

inhibited the pseudovirus entry, possibly by interfering with the function of the S protein.30

3.1.2. The plasma membrane protease TMPRSS2

Recognized as a host trypsin-like serine protease, TMPRSS2 highly expressed in alveolar cells has been demonstrated to facilitate viral entry by priming of viral S protein. Inhibition of TMPRSS2 activity could prevent infection of coronaviruses including MERS-CoV, SARS-CoV and SARS-CoV-2.31 Now, several synthetic drugs like camostat mesylate, nafamostat mesylate and bromhexine which are serine protease inhibitors showed potential to inhibit SARS-CoV-2 infection.32 TMPRSS2 is recognized as a host trypsin-like serine protease, TMPRSS2 activity may also inhibit SARS-CoV-2 infection of SARS-CoV using cell-based assays.46 Zhuang et al. also demonstrated that butanol crude fraction from C. cortex was able to inhibit the clathrin-dependent endocytosis pathway as well as the infection of SARS-CoV using cell-based assays.46

3.2. Natural bioactive compounds targeting viral replication

3.2.1. The 3-chymotrypsin-like main protease (3CLpro)

The 3CLpro is an enzyme that plays important role in replication of coronaviruses. It is responsible for the cleavage of polyproteins to functional proteins. Base on the protein structures, 3CLpro of SARS-CoV and SARS-CoV-2 show similarity of amino acid sequence at 96%, and both enzymes exhibit high conservation of active residues.47 Therefore, small molecules with SARS-CoV 3CLpro inhibitory activity may also inhibit 3CLpro of SARS-CoV-2. Numerous studies have revealed for plant and mushroom derived natural compounds that could suppress SARS-CoV replication by blocking 3CLpro activity with IC50 range from 8.3 to 92.4 µM in either cell-free or cell-based assays. Among them, hesperetin, a phenolic compound isolated from *Isatis indigotica* root exhibited the greatest inhibitory impact. In addition, the inference dose of 3CLpro activity ranged from 8.3 to 40 µM.48 Other phytochemicals that have shown promise in the inhibition of 3CLpro are lignoid, terpenoid, tanshinone and chalcone with IC50 less than 25 µM.49–52 Interestingly, the lignoid savinin was able to reduce both viral replication (Selective index > 667) and cytopathic effect on SARS-CoV-infected Vero E6 cells.45 The summary of bioactive compounds against SARS-CoV 3CLpro inhibitory activity is tabulated in Table 1. Regarding to the similarity between 3CLpro of SARS-CoV and SARS-CoV-2, these natural compounds are interesting substances to screen as inhibitors of SARS-CoV-2 3CLpro activity.

3.2.2. The papain-like protease (PLpro)

Similar to 3CLpro, the function of PLpro is essential for coronavirus replication by generating RTC through proteolytic processing of viral polyprotein. Hence, PLpro could be served as another attractive target of drug discovery for treatment of coronavirus infection, especially SARS-CoV-2. At present, there is no FDA
approved PL\textsuperscript{PRO} inhibitor available, therefore identification of bioactive compounds from medicinal plants that specifically inhibit PL\textsuperscript{PRO} has been focused to develop a new class of anti-coronavirus drug. According to high similarity of protein sequences and active residues between SARS-CoV and SARS-CoV-2 PL\textsuperscript{PRO} (83%),\textsuperscript{47} the compounds that have been reported as inhibitors of SARS-CoV PL\textsuperscript{PRO} may also be effective against SARS-CoV-2. Table 1 lists many interesting compounds from natural sources that exhibited SARS-CoV PL\textsuperscript{PRO} inhibitory activity. The IC\textsubscript{50} values of the compounds ranged from 0.8 to 19.3 µM, demonstrating their strong inhibitory potential. Among them, the cryptotanshinone and tanshinone IIA were regarded as two most excellent inhibitors.\textsuperscript{54}

### 3.2.3. The replication/transcription complex (RTC)

The replication of full-length genomic RNA and the discontinuous transcription of subgenomic RNA transcripts are crucial for the production of new coronavirus particles inside the host cell. Both processes are mediated by the coronavirus RTC composed of multiple viral nsps including two key replicative enzymes like the RdRp (nsp12) and helicase (nsp13),\textsuperscript{52} which are now considered as potential targets for COVID-19 therapy. Considering a strikingly high homology of nucleotide sequence, amino acid sequence and protein structure between SARS-CoV and SARS-CoV-2 RdRps,\textsuperscript{53} the natural compounds with previous reports of inhibitory activities towards RdRp of SARS-CoV could also have the potential to suppress the activities of those enzymes of the SARS-CoV-2. It was shown that the water extract from Houttuynia cordata exhibited a dose-dependent inhibition on SARS-CoV RdRp activity with the highest decrease by 74% in the treatment of 800 µg/mL.\textsuperscript{54} That activity of H. cordata was confirmed in another study by Fung et al.,\textsuperscript{55} along with Sinomenium acutum, Coriolus versicolor and Ganoderma lucidum, a traditional Chinese herbal formula Kwan Du Bu Fei Dang. Their IC\textsubscript{50} values were 251.1, 198.6, 108.4, 41.9 and 471.3 µg/mL, respectively.\textsuperscript{55}

The inhibitors of SARS-CoV helicase also serve as a potential drug candidate since this enzyme has a highly conserved sequence among coronaviruses and shares the similar structure to that of SARS-CoV-2.\textsuperscript{56} Herein, three plant-derived bioactive compounds that could be natural inhibitors of SARS-CoV-2 helicase are listed in Table 1.

### 3.2.4. The zinc ion

Zinc is an essential micronutrient that is required for various cellular metabolic processes, not only in human immunity but also in the replication of many viruses.\textsuperscript{56-58} Although Zinc ion (Zn\textsuperscript{2+}) acts as a cofactor for several important viral enzymes such as RdRp, 3CL\textsuperscript{PRO} and PL\textsuperscript{PRO}, it is interesting that its high intracellular concentration was found to inhibit those enzyme activities of a variety of RNA viruses including SARS-CoV\textsuperscript{56-58} thus leading to subsequent decrease in the production of new virions. Therefore, Zn\textsuperscript{2+} possesses antiviral properties through generating host immune responses and inhibiting viral replication. As of now, several researchers have suggested the use of Zn\textsuperscript{2+} ionophore, a compound that stimulates cellular import of Zn\textsuperscript{2+} (e.g., chloroquine and its derivatives), as a possible option for the treatment of COVID-19.\textsuperscript{59}

### 3.3. Natural bioactive compounds targeting viral release

#### 3.3.1. The viroporin 3a

Viroporins are small, pore-forming, viral-encoded accessory proteins with ion channel activity that have been known to play an essential role in mediating several processes in the life cycle of many viruses, including coronaviruses.\textsuperscript{52} Viroporin 3a functions are strongly involved in the regulation of viral budding and release from infected cells.\textsuperscript{60} Interestingly, this protein was found unique to SARS-CoV and SARS-CoV-2 and not present in other known coronaviruses,\textsuperscript{64} thus the viroporin 3a protein can be an important potential therapeutic target for COVID-19. Summary of natural compounds with inhibitory effect on viroporin 3a activity is presented in Table 1. Schwarz et al. revealed that flavonoid compounds like kaempferol and its derivatives were capable of blocking the ion channel activity of SARS-CoV viroporin 3a protein. Among them, the most potent one is the glycoside juglanine, kaempferol 3-O-arabinopyranoside, exhibiting IC\textsubscript{50} of 2.3 µM.\textsuperscript{64} Another kaempferol glycoside tiliroside and the anthraquinone emodin also showed good inhibitory activity with and IC\textsubscript{50} of 20 µM.\textsuperscript{62}

### 3.4. Natural bioactive compounds targeting inflammation-related pathogenesis

Upon binding to SARS-CoV-2 S protein, the ACE2 function is downregulated which leads to increased angiotensin II level and overactivation of the AT1R signaling, causing the deleterious effects associated with excessive inflammation on several tissues.\textsuperscript{65} Therefore, suppressing angiotensin II production by ACE inhibitors and blocking of AT1R by angiotensin-receptor blockers (ARBs) may be of benefit to ameliorate Ang II/AT1R-mediated inflammation in COVID-19 patients. Moreover, it was shown that an ARB could not only reduce AT1R activation, but also activate the AT2R, thus resulting in a production of vasodilation benefit.\textsuperscript{68}

Currently, ACE inhibitors and ARBs are commonly prescribed in COVID-19 patients with severe symptoms. Even though risks of the use of hypertensive drugs were concerned, accumulating evidence has not suggested the association between the drugs and worse clinical outcomes.\textsuperscript{66,67} Interestingly, a great number of natural compounds have been identified as potent ACE inhibitors and ARBs. Given that there are minimal side effects of using drugs from natural sources, those compounds with potential activity should be considered and investigated. Bioactive compounds derived from...
natural sources which possess ACE inhibitory activity are summarized in Table 1. Among them, the excellent inhibitory properties against ACE were exerted by the phenolic caffeic acid and chlorogenic acid, and the stilbene hopeaphenol and vitisin A, with IC50 less than 2 \( \mu \text{M} \). These two stilbenoids were also found to be resveratrol tetramers exhibiting multifaceted properties including anti-inflammation and antiviral infection as a potent inhibitor of hepatitis C virus helicase. However, only few compounds have shown the ability to block AT1R which one of them is \([6]\)-gingerol, the major bioactive compounds present in \textit{Zingiber officinale}. According to the report by Liu and colleagues, it could inhibit AT1R activity with IC50 of 8.2 \( \mu \text{M} \) as detected by cell-based calcium mobilization assay.

3.5. Anti-SARS-CoV natural compounds with unidentified mechanism of action

Some natural occurring compounds have been reported their beneficial effect to inhibit SARS-CoV, even though their mechanisms of action have not yet been identified (Table 2). Accordingly, the compounds from those previous studies might also have a potency to inhibit COVID-19 infection. Using HIV/SARS-CoV S pseudovirus and wild-type SARS-CoV, three anthocyanins derived from \textit{Cinnamomum cortex}, cinnamtannin B1, procyanidin A2 and procyanidin B1, were reported their inhibitory activities against the infection of both viruses, but at least not through the inhibition of clathrin-mediated endocytosis. This study also investigated the effects of some crude plant extracts and found that aqueous extract of \textit{Caryophyllus Flos} exhibited moderate inhibition to pseudovirus (IC50 = 58.8 \( \mu \text{M} \)) and wild-type virus (IC50 = 50.1 \( \mu \text{M} \)). In addition, the natural alkaloid lycorine, isolated from \textit{Lycoris radiate}, has been suggested as an anti-SARS-CoV compound with an IC50 value of 15.7 nM.
4. Conclusion and further prospects

Emerged as the most devastating viral infection in this era for the human race, the COVID-19 pandemic has introduced “new normal” for changing life as we recognize it. As numbers of new COVID-19 infected cases are rising globally, disruption of the transmission chain to minimize this spread is seriously unavoidable. This rise in COVID-19 infection is hardly disrupted unless its infective mechanisms including entry, replication and release, and modification of RAAs can be properly eliminated by humans. Certainly, we are waiting for effective strategies including drugs and vaccines to fight against COVID-19. Due to the unavailability of drugs to treat this infection, natural compounds are a main area of anti-COVID-19 research discovery. Our review suggests that 24 natural compounds have shown their potential actions on multiple therapeutic targets, which should be further explored for anti-COVID-19 plant/mushroom-based medicines (Fig. 2). The classes of these phytochemical compounds include chalcones (n = 7), flavonoids (n = 5), tanshinones (n = 5), phenolic acids (n = 3), polyphenol (n = 1), anthraquinone (n = 1), diarylheptanoid (n = 1) and bipherpylenpropanoid (n = 1). Among them, a natural flavonoid quercetin is found as a lead candidate with its ability on the virus.

Together with proper proactive investments, it is our great hope that qualified natural compound-based medicines from promising leads described here will be developed as anti-COVID-19 soon to benefit the human race in this “new normal” era.

Taxonomy (classification by EVISE)

Emerging Infectious Disease, Viral Infection of Respiratory System, Severe Acute Respiratory Syndrome Coronavirus, Cell culture, Molecular Biology, Traditional herbal medicine, Natural Product Analysis.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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