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A Mechanistic Review on Plant-derived Natural Inhibitors of Human Coronaviruses with Emphasis on SARS-COV-1 and SARS-COV-2

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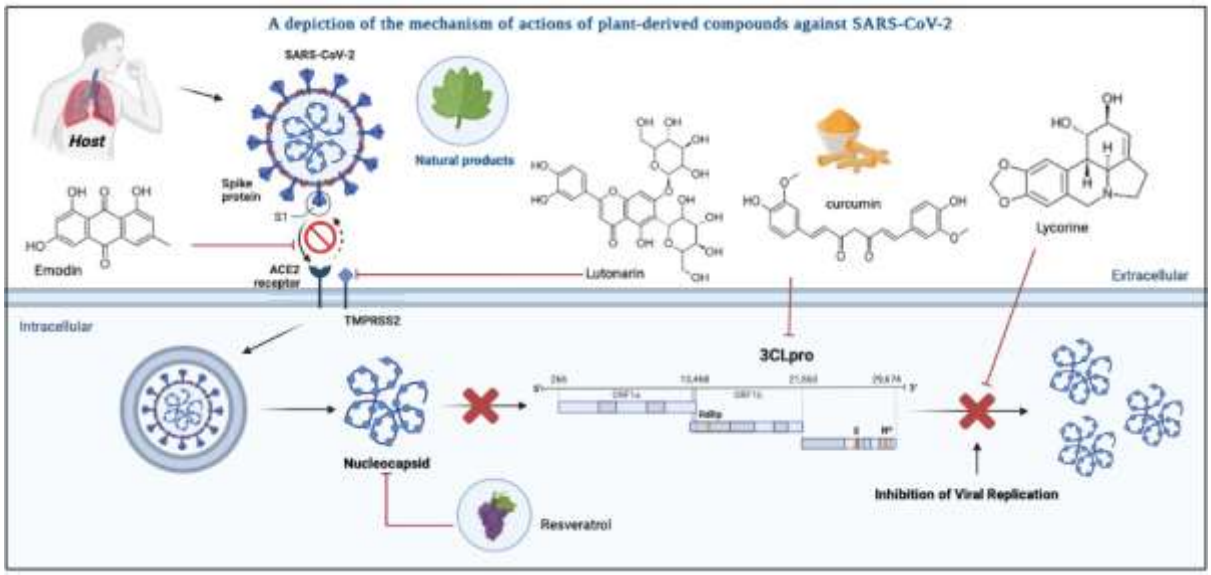
Abstract

Coronaviruses have been receiving continuous attention worldwide as they have caused a serious threat to global public health. This group of viruses is named so as they exhibit characteristic crown-like spikes on their protein coat. SARS-CoV-2, a type of coronavirus that emerged in 2019, causes severe infection in the lower respiratory tract of humans and is often fatal in immunocompromised individuals. No medications have been approved so far for the direct treatment of SARS-CoV-2 infection, and the currently available treatment options rely on relieving the symptoms. The medicinal plants occurring in nature serve as a rich source of active ingredients that could be utilized for developing pharmacopeial and non-pharmacopeial/synthetic drugs with antiviral properties. Compounds obtained from certain plants have been used for directly and selectively inhibiting different coronaviruses, including SARS-CoV, MERS-CoV, and SARS-CoV-2. The present review discusses the potential natural inhibitors against the highly pathogenic human coronaviruses, with a systematic elaboration on the possible mechanisms of action of these natural compounds while acting in the different stages of the life cycle of coronaviruses. Moreover, through a comprehensive exploration of the existing literature in this regard, the importance of such compounds in the research and development of effective and safe antiviral agents is discussed. We focused on the mechanism of action of several natural compounds along with their target of action. In addition, the immunomodulatory effects of these active components in the context of human health are elucidated. Finally, it is suggested that the use of traditional medicinal plants is a novel and feasible remedial strategy against human coronaviruses.

Graphical abstract



Keywords: Human Coronaviruses; SARS-CoV; SARS-CoV-2; MERS-CoV; COVID-19; Natural inhibitors

1. Introduction

Humans are prone to a wide range of viral infections, which leaves a possibility of the occurrence of pandemics similar to the COVID-19 outbreak in the future as well. Since the development of an effective novel vaccine requires years of research and additional years for patient reach, it is wise to explore the already reported natural compounds exhibiting promising antiviral activity as potential drugs against these viral infections.

At the end of the year 2019, a novel form of pneumonia outbreak occurred in Wuhan city, China, which subsequently spread rapidly to the other regions of the world. Initially, the virus that caused this novel form of pneumonia was transiently designated as 2019-nCoV (2019-novel coronavirus) by the World Health Organization (WHO) in January 2020. The COVID-19 outbreak was declared a pandemic by the WHO at the end of January 2020. After that, it was considered a situation of global health emergency of international significance. On 11th February 2020, the International Committee on the Taxonomy of Viruses (ICTV) formally termed the COVID-19 pandemic virus as SARS-CoV-2, while the disease arising from this virus was officially termed COVID-19. The SARS-CoV-2 virus spread across 200 countries worldwide [1, 2]. So far, six human coronaviruses (HCoVs) are reported, including alpha-CoVs (HCoVs-NL63 and HCoVs-229E), beta-CoVs (HCoVs-OC43 and HCoVs-HKU1), the severe acute respiratory syndrome coronavirus (SARS-CoV), and the Middle East Respiratory Syndrome coronavirus (MERS-CoV). While HKU1, NL63, OC43, and 229E are known to cause only mild symptoms, the infections of SARS-CoV, MERS-CoV, and SARS-CoV-2 are reported to cause severe illnesses [2, 3].

SARS-CoV-2comprises a RNA genome enclosed within an envelope of viral protein. The genome of SARS-CoV-2 is approximately 30 kb in size, the largest among all RNA viruses. [4,5]. The outer surface of the envelope in coronaviruses contains three types of proteins, among which the most important one is the spike protein or S-protein as it is necessary for binding to and penetrating the host cell (Fig.1). The S-protein is, therefore, crucial for the infectiveness of SARS-CoV-2. Similar to the spike protein of SARS-CoV, the SARS-CoV-2 spike protein also contains two subunits – S1 (13–680 aa) and S2 (681–1255 aa). While S1 is important for the attachment of the virus to the host cell, the fusion of the virus with the membrane of the host cell requires the S2 subunit, which further contains two heptad repeat domains [6]. The genomic data for SARS-CoV-2 indicates that there are certain distinctive adaptations in its spike protein for binding to the human receptor. These adaptations enable the spike protein of CoV-2 to acquire a unique ability of binding to the human transmembrane

receptor referred to as the angiotensin converting enzyme 2 (ACE-2) receptor. ACE-2 is expressed in the cells of most organs in the human body, thereby rendering these cells/organs highly vulnerable to viral infectivity [6]. Individuals with cardiovascular conditions exhibit particularly increased levels of ACE-2, which explains the high incidence of severe COVID-19 cases in this population [7].

The S1 subunit binds to the ACE-2 receptor located on the host cell surface, causing the host cell to be viral-bound. The S2 domain contain two heptal repeat regions, one located close to the N-terminal (HR1) and in the vincinity of fusion peptide whereas the other located near to the C-terminal (HR2) and adjacent to the transmembrane region of the spike protein. The HR1of h-1 interacts with the HR2 to form a six-helix bundle (6HB) that mediates the fusion of the viral membrane with the host cell membrane. Therefore, the configuration of the 6-HB fusion core S proteins of CoV-2 and other coronaviruses may also be contrasted based on the membrane fusion process mediated by their S proteins, which paves the way for the rational designing of fusion inhibitors [8]. The viral entry also depends on the initiation activity of host cell proteases, mainly transmembrane protease serine 2 (TMPRSS2) that primes the S protein by cleaving it between its sub-units, thereby exposing the S2 subunit of the fusion peptide for binding to the host cell membrane. This weakens the interactions between the S1 and S2 subunits, thereby enhancing the protease-mediated disassociation of these subunits. In this manner, S2 enables the fusion of the viral membrane with the host cell membrane. Studies have indicated that the S protein of SARS-CoV-2 contains a unique cleavage site-specific to the host cell proteases, such as furin which is lacking in other SARS viruses. [9].

The pre-activation or pre-cleavage of these unique sites in S1 and S2 by a furin-like enzyme in the infected cells promotes subsequent priming by TMPRSS2, and this mechanism facilitates viral entry into the host cells, particularly the cells with low levels of TMPRSS2. Furin is expressed in the cells of different organs of the human body, which could also explain the high transmissibility of SARS-CoV-2 [9, 10].

The fusion process is followed by the processing of a multidomain viral polyprotein by two cysteine proteases, viz., papain-like protease(s) (PLpro) and 3C-like protease (3CLpro), which are located within this polyprotein and catalyze its release. While PLpro catalyzes the cleavage of the first three cleavage sites of the viral polyprotein, the remaining 11 sites of the polyprotein are cleaved by 3CLpro. This initial phase is a critical one and generates 16 mature fragments referred to as non structural proteins (nsps), which later assemble into complexes that implement RNA synthesis [11]. Therefore, these two cysteine proteases (PLpro and 3CLpro)

are recognized as the most suitable drug targets against SARS Cov-2. Despite multiple biochemical, structural, and inhibitor-identification studies directed at 3CLpro, strong antivirals targeting 3CLpro specifically are yet to be developed [11]. The 3CLpro of SARS-CoV-2 is reported to play a significant role in the proteolytic production of viral polyproteins and is considered a prime target for the development of SARS-CoV drugs [11]. Since the recent availability and accessibility of the crystal structure of SARS-CoV-2 3CLpro, it has become a widely acceptable target for standardized rational drug design [12]. Although several structural and functional studies on PLpro have been conducted so far, the fundamental functions of PLpro, including its deubiquitination and its involvement in viral evasion of the immune checkpoints, have been characterized outside of the viral peptide cleavage process [13].
After the fusion of the viral membrane with the host cell membrane, the virion is internalized by the cells via endocytosis and then released into the cytosol, where it replicates its RNA using the host cell machinery. The viral RNA and proteins produced within the host cell are subsequently assembled into new virions, which are then released from the host cell to infect the surrounding cells [8].

Helicases are reported to be necessary for the replication of the viral genome and are, therefore, expected to have a potential application in antiviral therapies. The SARS-CoV helicase has been demonstrated to exhibit RNA5-triphosphatase activity, which could be responsible for its involvement in viral RNA capping [14]. Various potential nsp13 inhibitors are reported, and the interaction of a few of these inhibitors with nsp13 is facilitated by the unwinding and ATPase activities of nsp13 [15,16,17]. In addition, these inhibitors may interfere with the cellular ATPase or kinase function of the ATPase, ultimately affecting the cellular activity. According to a recent report, the duplex DNA-unwinding activity of SARS-CoV nsp13 could be inhibited selectively using an aryl diketoacid compound. However, the effect of this compound on the unwinding activity of nsp13 against double-stranded RNA (dsRNA) and SARS-CoV replication could not be determined [16]. Adedeji et al. identified a strong nsp13 inhibitor that could inhibit the unwinding activity of nsp13 while having no impact on the enzymatic and nucleic acid binding activity of the ATPase [18].

Evidence suggests that SARS-CoV nsp13 possesses the NTPase activity and RNA helicase activity of the helical superfamily-1 [14, 19]. Since there is a high level of amino acid sequence-homology among the nsp13 proteins of different coronaviruses, it is speculated that SARS-CoV-2 nsp13 might also possess the activities of NTPase and RNA helicase [20].

Therefore, to facilitate the timely development of antivirals against COVID-19, it becomes important to study the drugs already reported for the nsp13 of other coronaviruses. Shu et al. [20] reported the successful expression and purification of the recombinant nsp13 from SARS-CoV-2 and also the analysis of its biochemical activities. The authors observed that SARS-CoV-2 nsp13 exhibited NTPase and RNA helicase activities, with all types of NTPs being hydrolyzed and able to unwind the RNA helicase in an NTP-dependent manner. Moreover, the authors observed that bismuth salts could suppress both NTPase and RNA helicase activities of SARS-CoV-2 nsp13 in a dose-dependent manner. Therefore, the study indicated that SARS-CoV-2 nsp13 could serve as a valuable target for developing antivirals against this life-threatening virus [20].

The Nsp12 protein of coronavirus is an RNA-dependent RNA polymerase (RdRp) enzyme that is essential for its replication/transcription complex. At the C-terminus of this protein is located the RdRp polymerase domain that contains a conserved Ser–Asp–Asp motif [21]. Another protein referred to as nsp8 serves as a primer for the de-novo synthesis of nsp12-RdRp RNA of up to 6 nucleotides in length. Furthermore, the Nsp7–Nsp8 complex is reported to enhance the binding of nsp12 to RNA and increase the activity of the RdRp enzyme [22]. Nsp12–RdRp has been utilized as a highly important drug target in the study of SARS-CoV and MERS-CoV inhibitors, without any major toxicity and undesirable effects on the host cells [23,24]. The general life cycle of a pathogenic human coronavirus is illustrated in Figure 1B.

To date, no medications have been approved for SARS-CoV-2 therapy, and the existing treatment options are based on relieving the symptoms of the disease, such as dry cough, fever, and pneumonia. Several researchers are currently evaluating the effectiveness of the existing treatments for pneumonia in treating pneumonia caused by SARS-CoV-2 and other coronaviruses. Various previously reported antivirals, including fusion inhibitors (such as Arbidol), protease inhibitors (indinavir, saquinavir, and lopinavir/ritonavir), and RNP inhibitors (remdesivir) [25], are being tested against SARS-CoV-2. Arbidol, also referred to as umifenovir, is a membrane fusion inhibitor that prevents the entry of the influenza virus into the host cell by stabilizing the pre-fusion conformation of hemagglutinin [26]. According to a recent report, therapy based on arbidol alone had a better potential of treating the COVID-19 disease compared to the therapy based on lopinavir/ritonavir [27]. A clinical trial in China (NCT04287686) is also investigating the biological and physiological effects of recombinant hACE2 (APN01), which is an entry blocker of SARS-CoV-2 that acts by blocking the binding of the viral S protein to the host cell ACE2 [28].

Plants synthesize a wide range of natural compounds that have long been used as remedies for various health conditions. Several of these plants and natural compounds are now being studied for identifying potential sources of novel drugs. Several clinical drugs available these days are based on natural products exhibiting a broad range of chemical activities and biological properties. Approximately 200 antiviral agents have been introduced in the past 50 years, among which nearly 40% account for vaccines, and the remaining percentage involves natural or nature-inspired semi-synthetic compounds. Several compounds obtained from medicinal plants, including flavonoids, polyphenols, alkaloids, stilbenoids, and terpenes, are evaluated widely for their antiviral activity and have been categorized based on their ability to block adhesion, penetration, duplication, or replication of the viruses.

Several of the compounds listed in the present review have been demonstrated to be effective against similar viruses. In *in vitro* experiments, certain flavonoids such as quercetin, hesperetin, and catechin, are reported to be effective against Herpes simplex virus type 1 (HSV-1), poliovirus type 1, parainfluenza virus type 3, or respiratory syncytial virus in unique circumstances. Among these flavonoids, hesperetin has been demonstrated to reduce the intracellular replication of all the above-stated four viruses, while catechin inhibits the infectivity of RSV and HSV-1. Quercetin, in particular, is uniformly efficient in reducing viral infectivity [29]. Several stilbenoids, such as resveratrol and its analogs, have also been demonstrated to inhibit SARS-COV replication in Vero E6 cells [30].

Various phytochemicals possessing immunomodulatory and antiviral properties have been reported [25]. The difference in the antioxidant behavior of these phytochemicals enables categorizing their antiviral processes into the inhibition of DNA, RNA synthesis, viral entry, or replication [26,27]. Licorice is a recognized antiviral, with certain reports stating that a group of people who consumed licorice decoctions did not get infected during the SARS epidemic despite being exposed to the virus. This finding demonstrated the efficacy of the phytochemicals in licorice against the SARS virus [28]. The phytochemicals in *Cassia javanica* (Java cassia), which is reported to inhibit the replication of HSV-2, as well as those in *Phyllanthus urinaria*, may confer strong protection against viral infection. Furthermore, resveratrol may relieve the viral-induced symptoms in the respiratory tract of humans, including the inflammation of the airways [31]. In Ayurvedic treatment, *Andrographis paniculata* is used for treating various infectious illnesses, such as infections of the throat and urinary tract, influenza virus and HIV infections, as well as cough, fever, and different anti-inflammatory diseases. The medicinal benefits of *Andrographis paniculata* are attributed to the

properties of its active components known as diterpenoids, which include andrographolides, neoandrographolides, and 14-deoxyandrographolide [32,33]. According to the existing literature on drug development, a mixture of natural products and synthetic therapeutic chemicals could generate potent and effective medicines, such as the anti-cancer drugs vincristine and vinblastine. This approach could form the basis of developing therapeutic natural products intended for human consumption. Moreover, such plant-based natural products exhibiting elevated antiviral activity should be considered for application in the treatment of SARS-CoV-2 and COVID-19 infections. In this context, certain selected classes of natural compounds that have been previously reported to exhibit antiviral activity against similar viruses are discussed in the present review.

2. Search Methodology

A thorough literature search was conducted for retrieving the studies published until September 2020 in the following databases: PubMed, Science Direct, Google Scholar, and Clinicaltrials.gov. The obtained search results were refined by applying inclusion and exclusion criteria, which screened out 102 relevant papers. The "Similar Articles" option available in PubMed was used for obtaining additional specific papers, and the list of bibliographical reference material in each of these papers was also screened. The identified papers included extensive data on several recognized as well as novel natural compounds studied in relation to all human coronaviruses. A brief synopsis of each of these papers, including the mechanism of action of the natural inhibitors targeting viral components and host proteins, is provided in Table 1. The identified papers mainly concentrated on the bioactive plant-derived components obtained from different natural sources and the evaluation of their influence on the different stages of viral replication (viral attachment, viral entry, etc.). The obtained documents were included or excluded based on the following criteria:

i. Study of natural components exhibiting low or minimum toxicity levels.
ii. Review emphasizing the natural antiviral drugs for combating human coronaviruses.
iii. Potential metabolites exhibiting multi-site inhibitory effects along with their precise mechanism of action.

3. Natural inhibitors targeting viral components

The development of novel pharmaceuticals from natural materials has been in practice for decades, with approximately 50% of all medications being based on small molecules extracted or inspired by natural materials. Owing to the broad range of natural materials derived from various bacterial, vegetative, and fungal sources, these compounds form an important basis of drug development projects. Plant-derived chemicals exhibit different modes of action against different diseases. Several secondary metabolites, such as phenolics, alkaloids, carotenoids, organosulfur compounds, terpenoids, and nitrogen-containing compounds, and the other important phytochemicals secreted by plants, are known to possess a range of anti-infective and antioxidant properties [34]. Several classes of these phytochemicals, such as phenolics, alkaloids, and terpenoids, are known to possess antiviral characteristics as well [35,36]. Among these, certain phytochemicals with an established mechanism of action against human coronaviruses are discussed ahead.

Phenolics constitute a large group of secondary plant metabolites, which are broadly categorized into different subclasses of flavonoids, phenolic acids, and stilbenes.

Polyphenols are secondary plant metabolites characterized by the presence of one or more hydroxyl groups joining the aromatic benzene ring in their structure with the other aromatic structures. Polyphenols exhibit additional and contiguous mechanisms of action for inhibiting the replicationof viral DNA or RNA or to inhibit the reproductive activities of pathogens. The main targets of the antiviral activity of polyphenols are the viral envelope, viral nucleic acids, and viral constituent proteins [37].

Flavonoids are naturally occurring polyphenolic molecules distributed widely in plants and exhibiting highly effective antiviral activity [38]. To date, over 6,000 flavonoidswith the fundamental structure of C6–C3–C6 have been identified. These compounds exhibit a large spectrum of activities, including antiviral, anti-inflammatory, anti-ulcer, and anti-allergic activities. Moreover, these compounds are reported to exert a beneficial effect on capillary fragility and also inhibit the aggregation of human platelets [39]. Their mechanism of action occurs at different stages of the viral infection, particularly the viral growth stage, and involves blocking the entry, replication, translation, and polyprotein processing, all of which are vital for the spreading of the viral infection to the surrounding cells [40].

Stilbenoids are a group of non-flavonoid compounds that have been studied extensively for their biological activity. Stilbenoids are phytoalexins that are produced in defense against pathogens or stress factors. Stilbenoids occur as both monomers and dimers [41]. The antioxidant effects of stilbenoids are evoked through the inhibition of several important pathways, such as the NF-κB pathway. Their antiviral activity is based on functional inhibition

during several stages of the viral life cycle, such as viral replication, protein synthesis, nucleic acid synthesis, and gene expression [30].

3.1 Natural compounds targeting different entities within the viral entry process associated with coronaviruses

3.1.1 Spike Protein

The spike protein enables the coronaviruses to bind to the angiotensin-converting enzyme 2 (ACE2) receptor present on the host cell membrane. Flavonoids, when used against SARS-CoV, mostly target its spike protein. Flavonoids may be classified into different groups, including anthocyanidins, chalcones, flavonols, flavans, flavan-3-ols, flavanonols, and isoflavonoids. Flavanoids such as hesperidin, luteolin, catechin, and chrysin are potent in binding strongly to the viral spike protein and block the viral entry into the host cell. Hesperidin is an active anti-inflammatory flavonoid with a strong binding affinity to three primary SARS-CoV-2 protein receptors, namely SARS-CoV-2 protease domain, the receptor-binding domain of spike glycoprotein (RBD-S), and ACE2 receptor-binding domain (RBD-ACE2) [42]. Hesperidin targets the binding interface between the viral S-protein and the human ACE2 receptor, which leads to the superimposition of the hesperidin–RBD complex and the RBD-ACE2 complex [43]. Luteolin and catechin bind specifically to the viral S-protein and exhibit a dual binding effect toward papain-like proteases and ACE2, respectively. Luteolin exhibits a strong binding affinity to papain-like proteases [44]. Catechins bind to the S-proteins located close to the RBD and cause fluctuations in the amino acids of RBD and its neighboring region, in addition to being potent immunostimulants that induce autophagy, which is another mechanism of viral clearance [45]. Ho et al. identified two competent natural compounds – chrysin and emodin – to treat SARS-CoV-2. Chrysin is a flavonoid that acts as a weak inhibitor by binding to the viral spike protein fragment and may also serve as a capable ACE2 receptor-binding spike protein inhibitor with a binding energy of –6.87 kcal/mole [46]. A detailed analysis of the molecular binding site of chrysin revealed that this compound could be effective in treating SARS-CoV [47,48]. On the other hand, emodin has been described as a strong antioxidant quinone compound that inhibits the interaction between the viral S-protein and ACE-2, achieving 94.12% inhibition at a concentration of 0.5 mM [49].

Another compound named 6-gingerol, a bioactive phenolic phytochemical isolated from *Zingiber officinale*, was reported to inhibit viral replication by restricting the viral proteins onto the host cell. The highest binding affinity of this compound has been observed with COVID-19 viral RNA binding protein (6W4B) (–11.4082 kJ/mol), N-Terminal RNA Binding Protein

(6VSB) (–12.9523 kJ/mol), and spike glycoprotein (6M3M) (–12.8835 kJ/mol) [50,51]. Saikosaponins are glycosides of the triterpene named saponin present in several families of medicinal plants. Saikosaponin A, saikosaponin B2, saikosaponin C, and saikosaponin D are the triterpenoid saponins derived from *Bupleurum falcatum* L. (Umbelliferae) and exhibit good pharmacological activities. Among these, saikosaponin B2 is reported to exhibit *in vitro* antiviral activity against HCoV-229E by inhibiting the viral attachment to host cells in a dose-dependent manner, which prevents the virus from penetrating the cells, and also by interfering with viral replication [52,53]. Saikosaponin A is reported to inhibit 3Clpro, while saikosaponin C and saikosaponin D restrict the viral replication, although the underlying mechanism of the latter remains unknown.

Berbamine is a bis-benzylisoquinoline alkaloid isolated from *Coptis chinesis*. that is used in traditional Chinese medicine (TCM). It is known to possess the calcium channel blocker property. Berbamin has gained considerable attention due to its ability to act against the spike protein of HCoV-NL63 and restricts the viral entry with an IC_{50} value of 1.48 µM [54]. The above-stated findings corroborate that these spike inhibitors are suitable drug candidates for the treatment of SARS-CoV infection owing to their anti-inflammatory, immunomodulatory, and antiviral activities.

3.1.2 Host cell ACE2 receptor

ACE2 serves as a cellular gateway for COVID-19 and SARS and a receptor for both SARS-CoV-1 and SARS-CoV-2. Curcumin is a polyphenolic compound present in turmeric, a spice derived from the rhizomes of *Curcuma longa* Linn. Curcumin is considered a possible inhibitor of SARS-CoV-2 that acts by antagonizing the entry of the viral protein [55]. Utomo & Meiyanto et al. demonstrated through an *in silico* docking study that curcumin reduced the ACE-2 activity and suppressed the viral entry [56]. Recently curcumin's potential to prevent and treat diseases is receiving increasing attention from researchers owing to the evidence in support of its anti-inflammatory and anti-cancer activities. Glycyrrhizin, a triterpenoid saponin isolated from the components of licorice [57], is used in traditional Chinese medicine (TCM and is known to neutralize the SARS-CoV with less toxicity to host cells [58]. Owing to its cytokine-modulating activity, glycyrrhizin enhances the immune response during the early stages of the disease, which attenuates the excessive cytokine storms by downregulating the expression of the ACE2 receptor [59]. Glycyrrhetinic acid is the active metabolite of glycyrrhizin. It inhibits 11-beta hydroxysteroid dehydrogenase type 2 and activates mineralocorticoid receptors) by allowing cortisol to access the receptors in the aldosterone-

specific tissues, thereby inhibiting the binding of SARS-CoV-2 by reducing the ACE2 expression [60,61]. These findings elucidate that when formulating pharmaceutical products and administering them as a preventive measure against SARS-COV-2 transmission and infection among humans, it is important to consider the biological properties of the formulations, including the advanced mode of the drug delivery mechanism of glycyrrhizin [62,63].

3.1.3 Host TMPRSS2 receptor

TMPRSS2 is a transmembrane type II serine protease expressed in epithelial cells that is necessary for the pathogenesis of SARS-CoV-2 virus within an infected host cell [64]. Certain serine protease inhibitors, such as camostat and nafamostat, have been approved by the FDA as synthetic drugs capable of affecting the activation of TMPRSS2 and restricting the entry of the virus into the host cell [65]. In a study, the action of camostat mesylate against TMPRSS2 was mimicked using terpenoids, mainly withanone and withaferin-A [66]. The binding relationship of these two compounds with TMPRSS2 is the same as that of camostat mesylate, i.e., it demonstrates a downregulation of TMPRSS2 upon binding, which indicates the dual ability of withanone to block TMPRSS2 and the entry of SARS-CoV-2 into the host cell [67]. Lutonarin is a flavonoid isolated from the seedlings of barley, which is a food source. It is used for suppressing the function of TMPRSS2 by binding to it with an affinity of −8.8 and an inhibition constant of 348 nM at all of its three major binding sites. This binding is clear evidence that the proposed antioxidant compound is a TMPRSS2 inhibitor and could, therefore, reduce the severity of viral infection [68]. The structures of the natural inhibitors that influence the entry process of coronaviruses are provided in Figure 2.

3.1.4 Main protease 3CL^{pr}°

The 3C-like protease, which is also referred to as C30 endopeptidase present in coronaviruses, corresponds to the nsp5 in coronaviruses that is involved in the processesing of the coronavirus replicase polyprotein. Owing to its important function in the processing of polyproteins translated from the viral RNA, the 3CLpro protease is considered a potential drug candidate against coronavirus infections. Kandeil et al. conducted *in vitro* experiments on curcumin and reported that curcumin exerted an inhibitory effect on SARS-CoV-2. Recently, another *in vitro* study conducted with Vero E6 cells suggested curcumin as a promising and effective 3CLpro inhibitor that presented an IC_{50} value of 0.44. In addition, curcumin was observed to exert a combination of inhibitory effects on SARS-CoV-2 at different stages of virus development,

particularly viral replication and adsorption [69]. Hesperetin (a 4'methoxy derivative of eriodictyol) is a flavanone commonly isolated from *Isatis tinctoria L.* (Cruciferae family). Hesperetin has been demonstrated to exhibit anti-3CLpro activity in a cell-free system (IC 50 = 132 µM). Interestingly, in the cell-based assay, hesperetin (CC_{50} = 2.7 mM) exhibited potent activity with an IC_{50} value of 8.3 µM, compared to the *in vitro* biochemical assay [70,71]. Amentoflavone**,** a bioflavonoid derivative isolated from *Torreya nucifera* has been demonstrated to inhibit SARS-CoV 3CLpro with an IC_{50} value of 8.3 µM in a docking assay [54,72]. Since amentoflavone is a ubiquitous bioflavonoid, it exhibits a large number of pharmacological functions, such as anti-inflammation, anti-oxidation, antivirus functions, among others. Therefore, amentoflavone could be employed as a drug for treating COVID-19 infection. Hinokinin is a dibenzylbutyrolactone lignan that inhibits the activity of 3CL-protease with IC_{50} values of over 100 µM. Savinin, another lignan and a member of benzodioxoles, forms several hydrogen bonds between the pharmcoreand the unique amino acid residues located at the active site pocket of the enzyme, thereby competitively inhibiting the 3CLpro activity [73]. A computer modeling study on hinokinin and savinin revealed that savinin fits better into the active site cavity by forming hydrogen bonds, exerting inhibitory effects on the 3CL protease activity with an IC_{50} value of 25 µM [74].

Theaflavin-3,3′-digallate, a theaflavin derivative present in black tea, inhibits 3CLpro with an IC_{50} value of <10 µM. Black tea contains the highest concentration (1.05%) of TF3 reported so far. It is noteworthy that TF3 contains two gallate groups attached to the position of 3,3'. A study reported that the gallate group attached to the 3' position in TF3 could be relevant for its interaction with the active site of 3CLPro [75]. Fortunellin (acacetin 7-O-neohesperidoside), a natural flavonoid O-glycoside isolated from the fruits of *Citrus japonica*, was reported to be an effective dimerization inhibitor of 3CLpro. In the *in silico* study, it was observed that fortunellin binds to the dimerization interface of 3CLpro with great affinity (ΔG = –13.9 kcal/mol) and inhibits the dimerization by interacting with the residues responsible for the dimerization of the protein. Fortunellin and its 16 known structural analogs may, therefore, serve as effective drug candidates against the COVID-19 disease caused by SARS-CoV-2 [76,77]. Pectolinarin belongs to the subclass of flavones and has received considerable attention due to its pharmaceutical properties. The seventh location of this compound contains an additional carbohydrate group, which is bulky and occupies substantial space. When encountering the SARS-CoV virus, these bulky groups occupy the S1 and S2 sites and effectively block the enzymatic activity of 3CLpro [78].

Baicalin and baicalein are flavonoids commonly isolated from the roots of *Scutellaria baicalensis*. These are used in TCM and were reported as the first non-covalent, non-peptidomimetic inhibitors of SARS-CoV-2 ‘s 3CLpro and exhibiting antiviral activity in SARS-CoV-2-contaminated Vero E6 cells. Baicalein interacts with the two catalytic residues, the essential S1/S2 subsites and the oxyanion loop, which enables it to settle perfectly inside the core of the substrate-binding pocket. In this manner, baicalein blocks the virus from entering the active site by behaving as a protector of the catalytic diad. The fluorescence resonance energy transfer (FRET) protease assay revealed that baicalin presented an IC_{50} value of 6.41 µM against protease, while baicalein presented an IC_{50} value of 0.94 µM. Therefore, both baicalin and baicalein are considered novel high-potency SARS-CoV-2 3CLpro inhibitors [60,79]. Furthermore, both baicalin and baicalein were observed to inhibit the replication of live SARS-CoV-2 in Vero E6 cells in a dose-dependent manner, exhibiting the EC_{50} values of 10.27 µM and 1.69 µM, respectively. These EC_{50} values are close to those reported for chloroquine (1.13 µM; SI > 88) and remdesivir (0.77 µM; SI > 129) [80,81].

In addition to the flavonoids and flavones discussed above, other potent compounds with anti-3CLpro and Mpro activity against SARS-CoV-1 are reported. One such compound is andrographolide, a labdane diterpenoid isolated from *Andrographis paniculate*, which is reported to inhibit the expression or function of mature proteins at multiple stages of the viral lifecycle. Studies have indicated that andrographolide attacks the non-structural proteins of SARS-CoV-2. The enzyme-based assays and *in silico* simulation prediction revealed that andrographolide inhibited the key protease (3CLPro) activities of SARS-CoV-2 with an IC_{50} value of 15 µM [82,83,84]. Another compound named aloe emodin, an anthraquinone isolated from the exudate of the aloe plant *Isatis tinctoria L.* (the Brassicaceae family), was reported to reduce the 3CLpro activity in a cell-free system (IC 50 = 132 µM). A variety of emodin inhibited the 3CLpro activity in a dose-dependent manner in a cell-based system (IC_{50} = 366 µM). β-sitosterol, a phytosterol (plant sterol) with a structure similar to that of cholesterol, inhibited the 3CLpro activity in a dose-dependent manner in a cell-based system (IC_{50} = 1210 µM). Indigo, commonly known as the indole dye, is isolated from *Isatis indigotica* Fort. (Cruciferae family). Indigo exhibits higher effectiveness (IC_{50} = 752 µM) in blocking the mechanism of 3CLpro cleavage compared to beta-sitosterol (IC_{50} = 1210 µM) in a cell-based system [86]. Sinigrin, a natural aliphatic glucosinolate present in the plants of the Brassicaceae family, demonstrated a strong association between its effects on the cell-free cleavage of

SARS-CoV 3CLpro and the cell-based cleavage of SARS-CoV 3CLpro. Sinigrin, as an antioxidant, is documented to exhibit inhibitory effects against *Bacillus subtilis* and Saccharomyces based on quinine reductase and glutathione S-transferase, antiproliferative effects against cancer cells, as well as antimicrobial activity. The afore-stated documentation pioneered in demonstrating that the cleavage of a viral protease could be substantially inhibited using sinigrin. In terms of blocking the cleavage processing of 3CLpro in a cell-based assay, sinigrin (IC_{50} = 217 μM) was more successful than indigo (IC_{50} = 752 μM) and beta-sitosterol (IC_{50} = 1210 μM). Therefore, in Vero cells, indigo (CC_{50} = 7.4 mM) and sinigrin (CC_{50} = >10 mM) remained harmless [70]. The structures of the chemical entities with anti-PLpro activities are provided in Figure 3.

3.1.5 Papain-like Protease PLpro

Unlike 3CLpro, PLpro possesses an additional significant characteristic, i.e., it suppresses the host immune response [85]. Kim et al. [86] identified two compounds isobavachalone and psoralidin with potent inhibitory activity against SARS-CoV PLpro, exhibited in a dose-dependent manner with the IC_{50} values of 7.3 ±0.8 μM and 4.2 ±1.0 μM, respectively. Isobavachalone is a naturally occurring chalone compound, while psoralidin is a naturally occurring phenolic compound (present in the seeds of *Psoralea corylifolia L.*). These two compounds have since been employed as principal contributors to PLpro inhibition. Moreover, intensive research revealed that the bioactive metabolites of *Psoralea corylifolia* exhibited antioxidant and anti-inflammatory activities [54]. Quercetin, a flavonoid compound abundant in *Torreya nucifera* (L.) Siebold. and *Zucc*. (the Taxaceae family) and plants such as *Allium cepa* L., Malus pumila Mill., etc., was demonstrated, by Ji-Young Park et al. [87], to reduce the activity of PLpro through the process of deubiquitination, in which the induction of type 1 interferon is antagonized. Ubiquitin and ISG15 exert significant effects on viral replication and pathogenesis. Quercetin exhibits mild inhibition of the *in vitro* cleavage of ubiquitin, with an IC_{50} value of 8.6 μM. Fortunately, the abundance, consistency, and wide availability of the quercetin and its effect on viral replication allow the opportunity to conduct further studies. Papyriflavonol A is a novel prenylated flavonol isolated from *Broussonetia papyrifera*.

Ji-Young Park et al. [87] demonstrated that Papyriflavonol A inhibits SARS-CoV PLpro and nullifies its potency by inhibiting the cleavage of both ubiquitin and ISG15 (IC_{50} values of 7.6 and 8.5 μM, respectively). In addition, this compound is reported to be a prenylated quercetin analog. Tomentin A and B are flavonoids isolated from the fruits of *Paulownia tomentosa*,

which is a well-recognized rich herb as its component polyphenol is used in TCM. Tomentin A and B were recently geranylated in NMR studies, exhibiting the 3,4-dihydro-2H-pyran moiety. Both the compounds exhibit higher efficiency in SARS CoV PLpro inhibition due to their high binding affinity to PLpro [54,88]. Therefore, it is clear that the PLpro inhibitors require, in addition to preventing the proteolytic, deubiquitinating, and deISGylating activities, to ensure the suppression of viral replication. The structures of the chemical entities with anti-PL^{pro} activities are provided in Figure 4.

3.1.6 RNA dependent RNA polymerase

RNA-dependent RNA polymerase (RdRp) is the most versatile enzyme for genome replication and transcription in all RNA viruses. Unlike the other SARS-CoV-2 proteins, RdRp lacks closely associated host cell counterparts. Therefore, targeting RdRp could enable bypassing the side effects caused by off-targeting. Favipiravir, an oral medication approved by the FDA, is a potent RdRp inhibitor that acts via a virus-containing cell disruption mechanism to treat patients with mild to moderate COVID-19 disease.

Tryptanthrin, an alkaloidal indoloquinazoline compound isolated from *Strobilanthes cusia*, exhibits higher inhibitory activity toward the production of extracellular virions in the late stage (IC_{50} = 0.05 µM) than that in the early stage (IC_{50} = 6.99 µM). An assay combined with RT-qPCR analysis demonstrated that tryptanthrin decreased the number of post-infection RNA genomes of HCoV-NL63, which reduced the transcriptional action of HCoV-NL63 RdRp during viral replication [89]. Moreover, no major cytotoxic effect was observed in terms of the survival rate of normal human cells upon treatment with tryptanthrin [90].

In vitro studies suggest that Tylophorine, a phenanthroindolizidine alkaloid isolated from *Tylophora indica*, inhibits SARS-CoV with high potency at a low nanomolar concentration range. This activity is based on the ability of coronaviruses to inhibit a common or highly-conserved target involving the transcriptional complex of these viruses, such as RdRp, helicase, N-protein, and common cellular factors, which have important roles in coronavirus replication. Moreover, tylophorine was demonstrated to reduce, in a dose-dependent manner, the development of large syncytia (multinucleated giant cells) occurring as a result of the virus-induced fusion of cell membranes [91,92].

3.1.7 Compounds targeting NSP13 (Helicase)

Silvestrol, a rocaglate derivative containing a dioxanyl ring, is isolated from the fruits and twigs of *Aglaia foveolate*. It is an important and non-toxic cap-dependent viral mRNA translation

inhibitor in the human primary cells infected with coronavirus, which has exhibited an average EC_{50} value of 1.3 nM and 3 nM against MERS and HCoV-229E, respectively [93]. It inhibits the eIF4A helicase, which is necessary for the unwinding of the 5'-untranslated regions of mRNAs. In addition, it actively inhibits the expression of the structural and non-structural proteins (N; nsp8) of coronaviruses and also prevents the development of viral replication and transcription complexes at the concentration of 100 nM [94,95].

Scutellarin and myricetin are plant-derived flavonoids belonging to the class of polyphenols. Owing to their antioxidant properties, both the compounds have been reported to exert an inhibitory effect on the ATPase activity of nsp13, a helicase protein. Both the compounds strongly interfere with the protein activity occurring during SARS-CoV replication, presenting the IC_{50} values of 2.71 µM and 0.86 µM, respectively, in *in vitro* SPR/FRET-based assays [96,97].

3.1.8 Compounds targeting the replication of live coronaviruses

Lycorine**,** an alkaloid commonly isolated from *Lycoris radiata*, gained considerable attention recently due to its ability to act against the pathogenic Poliomyelitis virus and Herpes Simplex virus. Lycorine had previously been reported to inhibit the cytopathic effect induced by SARS-CoV, exhibiting potent anti-CoV action with the EC_{50} values ranging from 0.15 µM to 1.63 µM. These results suggest that lycorine could serve as a potential antiviral candidate for the treatment of SARS-CoV infection. However, the mechanism of its antiviral action remains unclear so far [98,99].

Cepharanthine, fangchinoline, and tetrandrine are bis-benzylisoquinoline alkaloids isolated from *Stephania tetrandra* and the other related species of Menispermaceae. These compounds exhibit potent anti-inflammatory, anti-cancer, and antiviral activities. The compounds gained attention recently when a study reported that certain bis-benzylisoquinoline alkaloids obstruct the translocation of MERS-pseudovirus via the endolysosomal system, which usually provides a route for the MERS-CoV entry into the host cell by inhibiting the NAADP-evoked Ca2+ release. Moreover, in the early stage of infection in human lung cells, tetrandrine, fangchinoline, and cepharanthine prevent the HCoV-OC43-induced cell death and reduce virus replication by blocking the expressions of viral S and N proteins [100]. Cepharanthine [101] is a potential drug candidate with evidence for its unique immunomodulatory property, while fangchinoline is one of the potential IC_{50}/EC_{50} alkaloids of 1.01 µM as recorded in several *in vitro* assays [102,103]. The enticing prospect of these alkaloids as anti-coronavirus drugs,

nonetheless, warrants further investigation. The structures of the viral replication inhibitors are provided in Figure 5.

3.1.9 Compounds targeting Nucleoprotein (N)

Resveratrol (trans-3,5,4'-trihydroxystilbene), a natural derivative of stilbene, is reported to decrease MERS CoV-induced apoptosis, thereby facilitating dose-dependent cell survival [104]. The probable antiviral mechanism of action of this compound has also been speculated in the same study. In response to DNA injury, resveratrol activates both ERK1 and ERK12 signaling pathways, promotes cell proliferation, and improves the SIRT 1 signaling, which is associated with cell survival and DNA repair. Resveratrol could modulate MERS-CoV-induced apoptosis by downregulating the FGF-2 signaling and directly inhibiting caspase 3 cleavage. It also minimizes inflammation by interfering with the NF-κB pathway. In addition, resveratrol could greatly inhibit the translation of MERS nucleocapsid protein which is important for the replication of this virus. Collectively, these results indicate that resveratrol suppresses MERS-CoV RNA replication, thereby inhibiting MERS CoV infection [105,106].

3.1.10 Compounds targeting DNA, RNA, and protein syntheses

Emetine, an alkaloid and the active ingredient of ipecac that is capable of inhibiting the replication of both DNA and RNA viruses, has also demonstrated potent anti-CoV activity and the highest anti-MERS-CoV activity with an EC_{50} value of 0.34 μM [107]. Emetine has been demonstrated to prevent the entry of the coronavirus by blocking the MERS-CoV-S-mediated infection [54,108].

Together, all the above-stated approaches could contribute to the development of broad-spectrum and safe therapeutics capable of simultaneously influencing the virus binding, replication, and synthesis processes to achieve the suppression of immune response against CoV.

3.2Authors' Insight On the Topic

The COVID-19 pandemic has emerged as a huge public health crisis exerting a great threat to global health and safety worldwide. In this context, the development of potent antiviral therapeutics against COVID-19 is a major and the most urgent challenge to the researchers currently. Several researchers have attempted to successfully identify the inhibitors of coronaviruses, including peptides, vaccines, small molecule compounds, and even natural products exhibiting anti-coronavirus activity. One solution to this pandemic is the natural

inhibitors of coronaviruses as most of such compounds are already being used in the pharmaceutical industry owing to their bioactivity, including their antiviral activity. The present review was, therefore, an attempt to search the existing literature for potential natural inhibitors against human coronaviruses to provide an overview that could assist in further investigations related to this topic of concern. The natural inhibitors discussed in the present report are suitable for managing coronavirus infections through the modulation of a wide range of molecular targets. Several plant varieties contain biologically active substances that could inhibit the coronaviruses through various mechanisms. The focus of the present review was the natural plant-derived compounds capable of inhibiting the human coronaviruses with minimum toxicity and effective mechanisms of action (Table 1). The compounds exhibiting low activity have been excluded from the discussion, and only those with favorable efficacy are included. Overall, the data collected from various sources indicated the availability of different classes of compounds, which included flavonoids, flavanones, flavanols, alkaloids, polyphenols, and terpenes.

LIST OF ABBREVIATIONS

SARS-CoV = Severe Acute Respiratory Syndrome-Corona Virus

MERS-CoV = Middle East Respiratory Syndrome-Corona Virus

COVID-19 = Corona Virus Disease-2019

NSP-Non-Structural proteins

ACE2 = Angiotensin Converting Enzyme 2

TMPRSS2 = Transmembrane protease, serine 2

RdRp = RNA Dependent RNA Polymerase

NF-KB = **Nuclear factor** kappa light chain enhancer of activated B cells

ERK = Extracellular signal Regulated Kinase

EC_{50} = Effective Concentration

IC_{50} = Inhibitory Concentration

CC_{50} = Cytotoxic Concentration

RT-qPCR = Quantitative **reverse transcription** PCR

IFN = Interferon

FRET = Fluorescence Resonance Energy Transfer

RBD = Receptor Binding Domain

TCM = Traditional Chinese Medicine

Contribution

Conceptualization: SSKD;. Methodology: SSKD, SKG SS, JD, HZ; Collection of articles: SKG, RR, LAR, TC, SSKD, KR; Writing original draft: SSKD, SKG, RR, LAR; Writing review and editing: SKG, LAR, RR SSKD, KR, JD, SS, TR.

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Conflict of interest

The authors declare that there is no conflict of interest with respect to the current study.

Figure legends:

Figure 1. Schematic representation of (A) a coronavirus and (B) its life cycle and the probable targets of different natural products.

Figure 2. Structures of the natural inhibitors that regulate the entry process of coronaviruses by binding with the coronavirus spike and the host ACE2 and TMPRSS2.

Figure 3. Structures of the natural chemical inhibitors of 3CLpro.

Figure 4. Structures of the natural inhibitors of PLpro.

Figure 5. Structures of the natural RdRp and helicase inhibitors**.**

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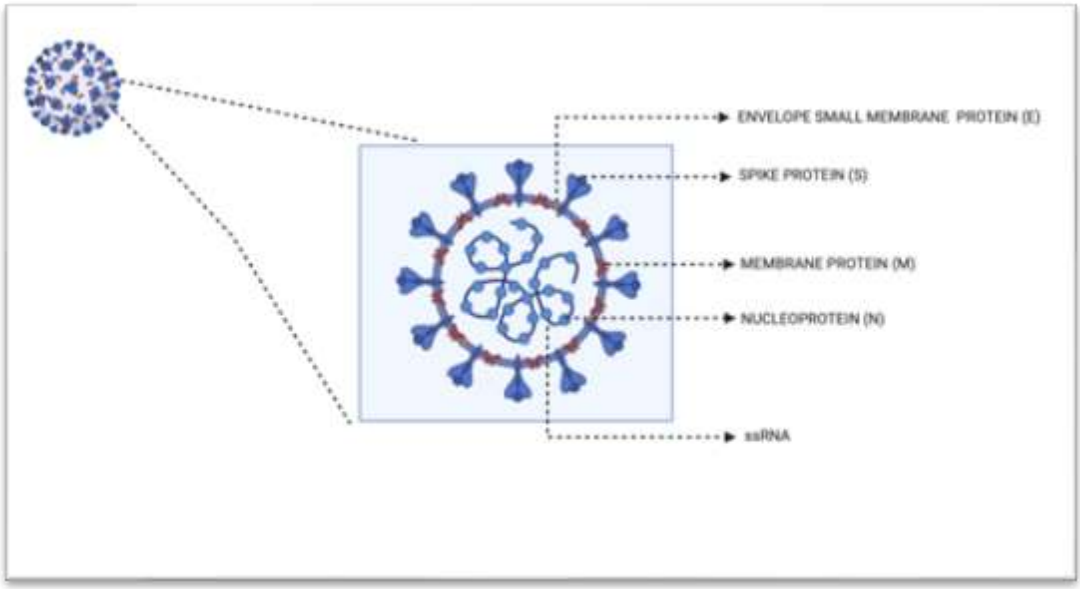
Figure 1

A.


ENVELOPE SMALL MEMBRANE PROTEIN (E)
SPIKE PROTEIN (S)
MEMBRANE PROTEIN (M)
NUCLEOPROTEIN (N)
ssRNA

B.

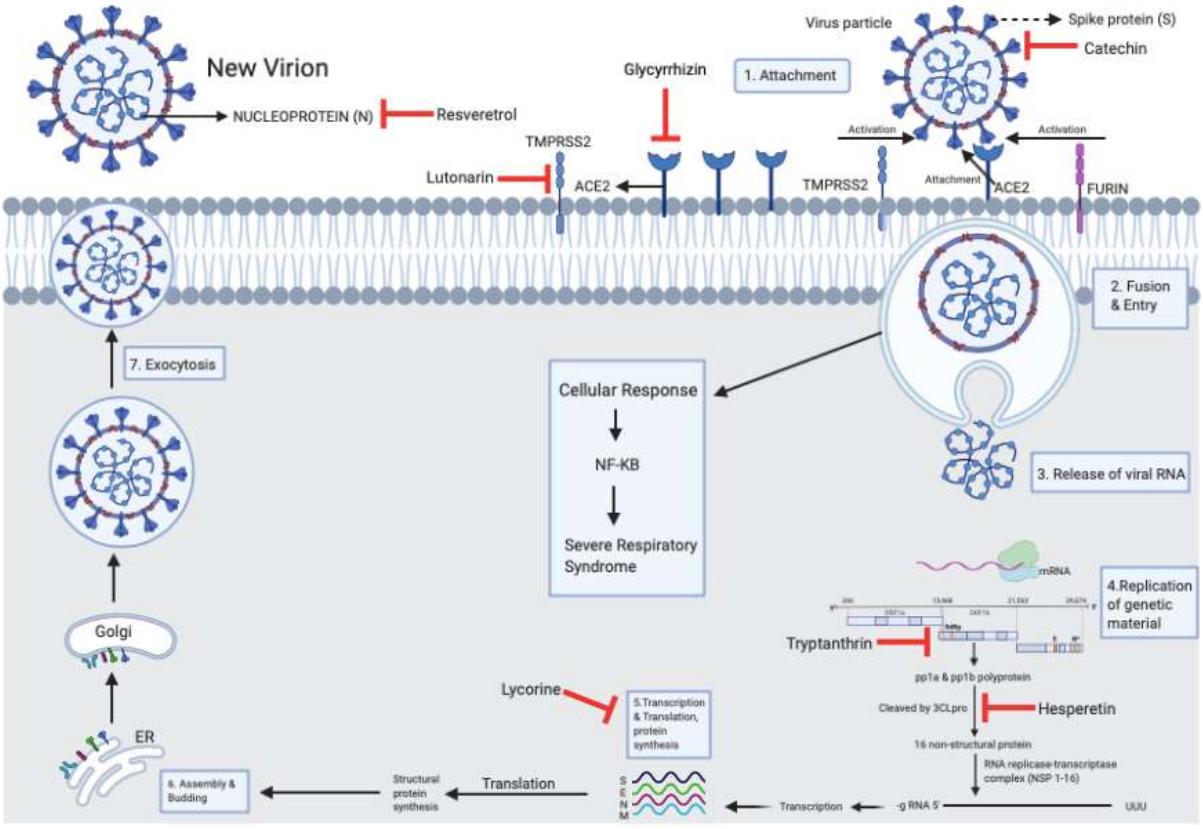

New Virion
NUCLEOPROTEIN (N)
Resveretrol
Glycyrrhizin
1. Attachment
TMPRSS2
Lutonarin
ACE2
Virus particle
Spike protein (S)
Catechin
Activation
Activation
TMPRSS2
Attachment
ACE2
FURIN
2. Fusion & Entry
7. Exocytosis
Cellular Response
NF-KB
Severe Respiratory Syndrome
3. Release of viral RNA
mRNA
4.Replication of genetic material
Tryptanthrin
pp1a & pp1b polyprotein
Cleaved by 3CLpro
Hesperetin
16 non-structural protein
RNA replicase-transcriptase complex (NSP 1-16)
Lycorine
5.Transcription & Translation, protein synthesis
Golgi
ER
6. Assembly & Budding
Structural protein synthesis
Translation
Transcription
-g RNA 5'
UUU

Figure 2

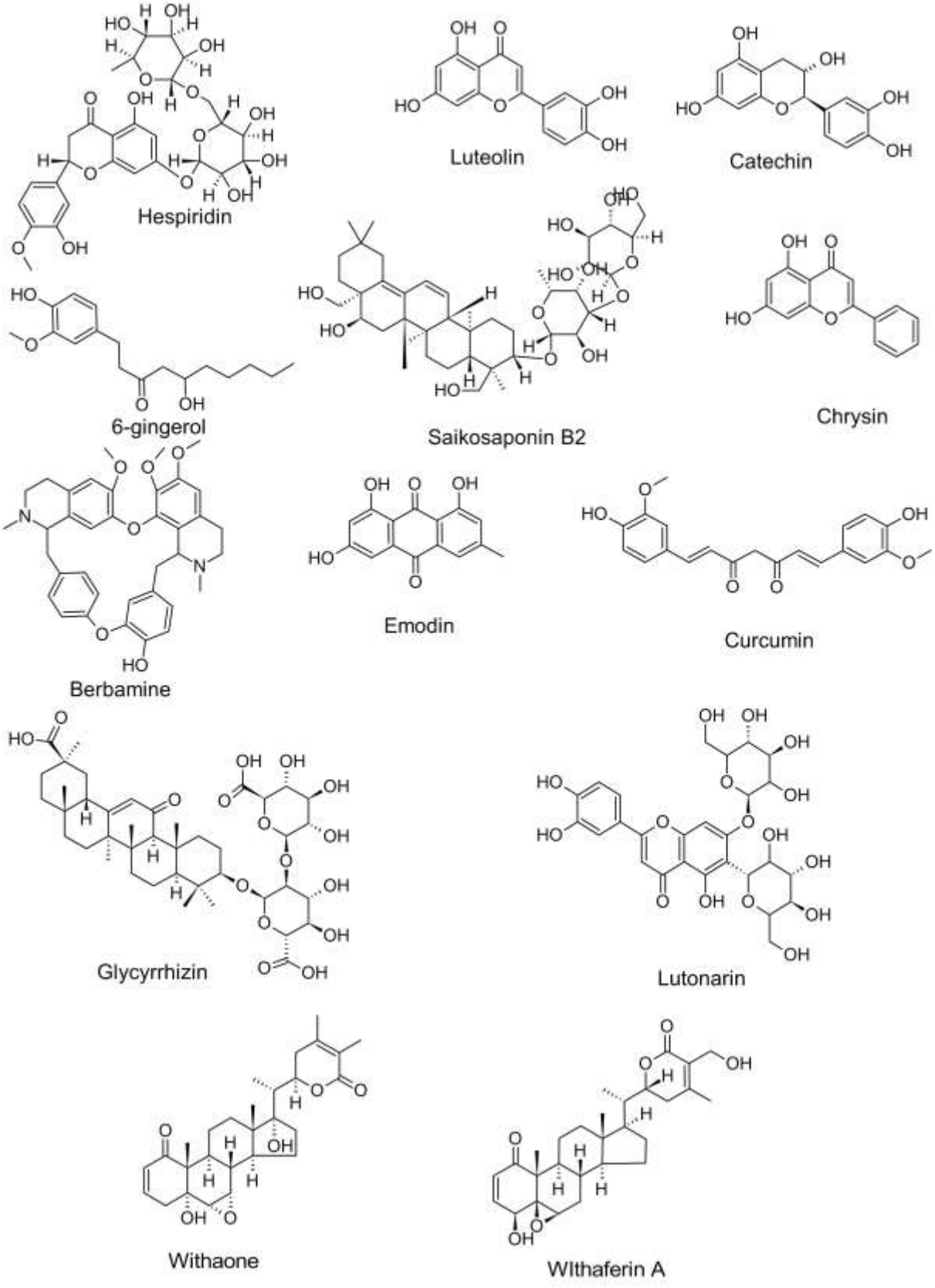

Hespiridin
Luteolin
Catechin
6-gingerol
Saikosaponin B2
Chrysin
Berbamine
Emodin
Curcumin
Glycyrrhizin
Lutonarin
Withaone
WIthaferin A

Figure 3

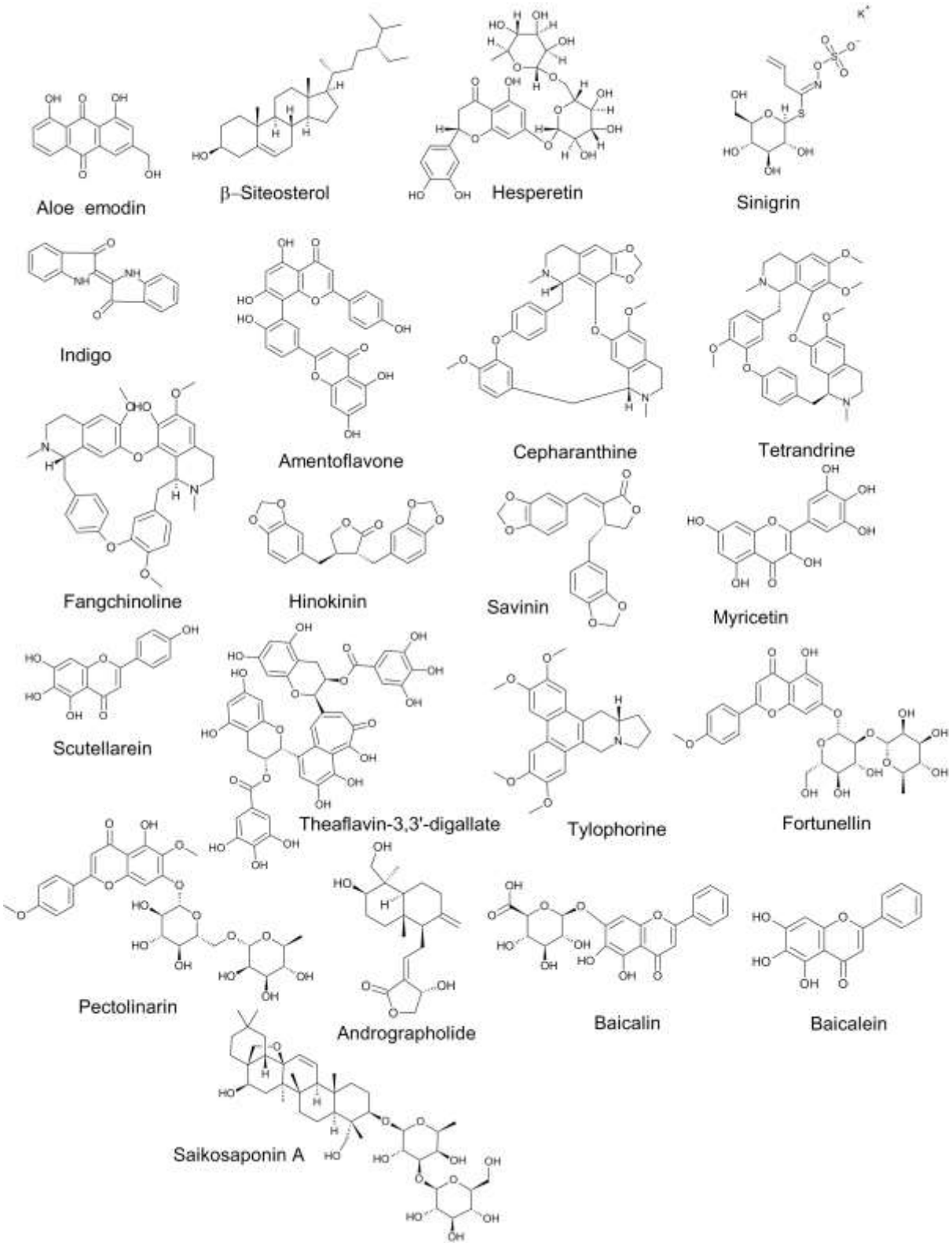

Aloe emodin
β–Siteosterol
Hesperetin
Sinigrin
Indigo
Amentoflavone
Cepharanthine
Tetrandrine
Fangchinoline
Hinokinin
Savinin
Myricetin
Scutellarein
Theaflavin-3,3'-digallate
Tylophorine
Fortunellin
Pectolinarin
Andrographolide
Baicalin
Baicalein
Saikosaponin A

Figure 4

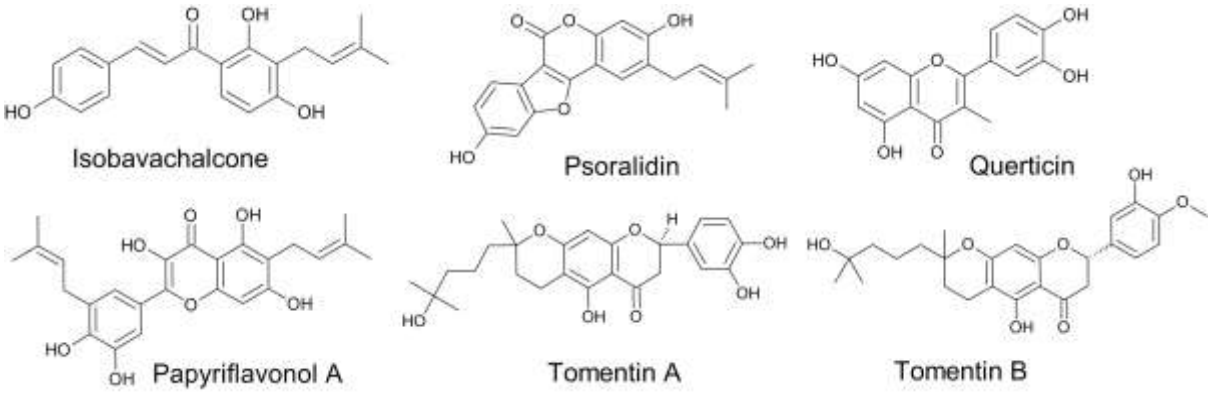

Isobavachalcone
Psoralidin
Querticin
Papyriflavonol A
Tomentin A
Tomentin B

Figure 5

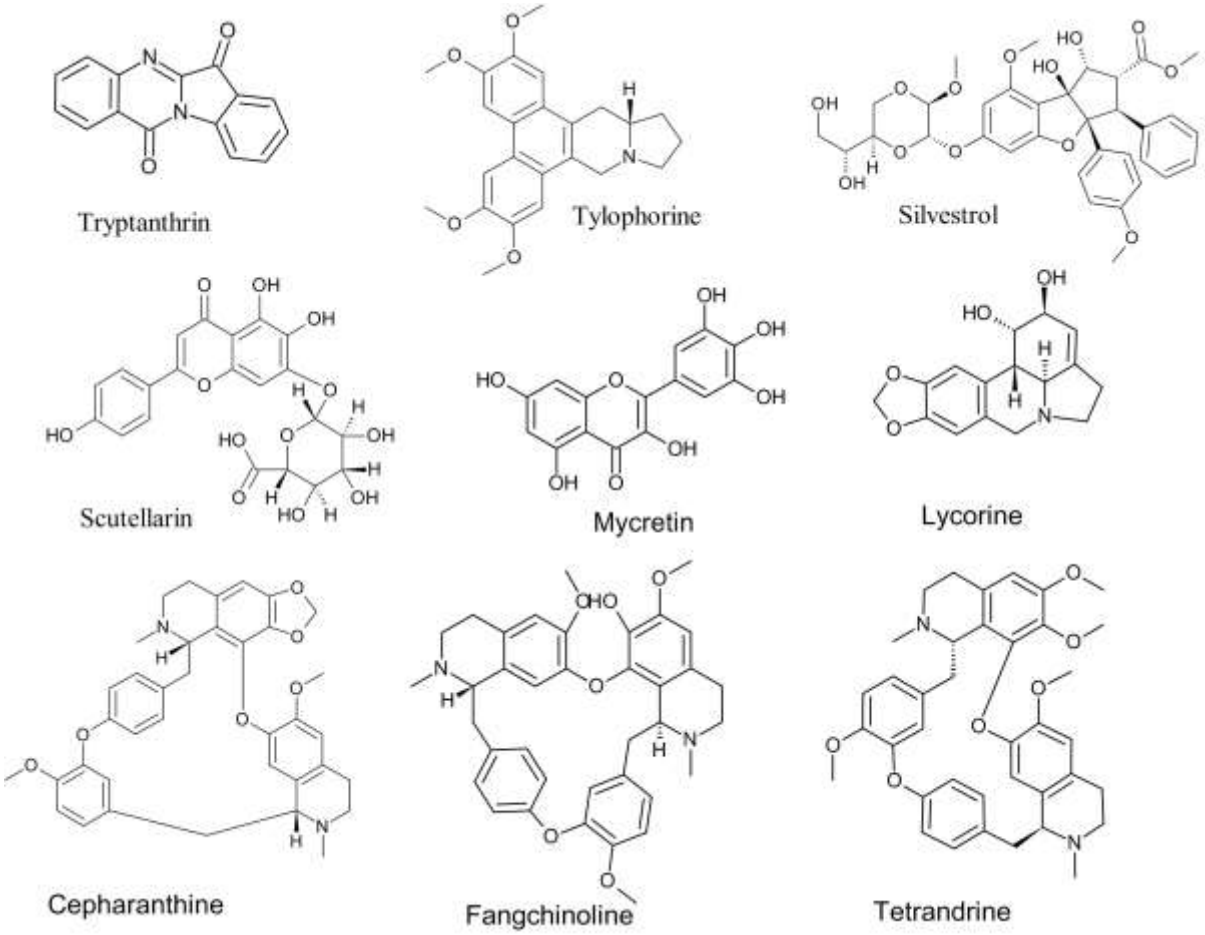

Tryptanthrin
Tylophorine
Silvestrol
Scutellarin
Mycretin
Lycorine
Cepharanthine
Fangchinoline
Tetrandrine

Table 1. List of the natural compounds with anti-CoV activities along with their mechanisms of action.

S.No	Compound Name	Plant Source	Virus	Target protein	Mechanism of action	IC_{50}/ EC_{50} (μM)	References
1.	Hesperidin	*Citrus sinensis*	SARS-CoV-2	Spike	Inhibitory action- Strong binding affinity toward protein receptors	NR	[43]
2.	Luteolin	*Reseda luteola*	SARS-CoV	Spike	It binds to the SARS-CoV surface spike protein and can thus interact with the virus's entry into the host cells.	NR	[44]
3.	Catechin	Cocoa bean (*Theobroma cacao*), argan oil (*Argania spinosa*), leaves of tea plant (*Camellia sinensis*)	SARS-CoV-2	Spike	Binds to the viral s-protein, thereby inhibiting viral entry to the host cell	0.22–2.26 (1.39)	[45]
4.	6-gingerol	ginger rhizome	SARS-CoV-2	Spike	Hydrogen bond interaction with s protein inhibiting viral entry	NR	[50]
5.	Saikosaponin B_2	*Bupleurum chinense DC (Apiaceae)*	HCoV-229E	Spike	Inhibits viral attachment and penetration stages	5–25(1.7)	[53]
6.	Chrysin	*Scutellaria baicalensis Georgi.*	SARS-CoV	Spike	Restrict viral entry	0–400 (200)	[48]

		(Lamiaceae)					
7.	Berbamine	*Berberis amurensis Rupr. (Berberidaceae)*	HCoV-NL63	Spike	Restrict viral entry	0.01–20 (1.48)	[54]
8.	Emodin	*Rheum & Polygonum*	SARS-CoV	Spike	Restrict viral entry	0.1–400 (200)	[46]
9.	Glycyrrhizin	*Glycyrrhiza glabra*	SARS-CoV; SARS-CoV-2	ACE2	Downregulation of ACE2	0.1–1000(365)	[59]
10.	Withanone & withaferin-A	*Withania somnifera (Ashwagandha) (Solanaceae*)	SARS-CoV-2	TMPRSS2	Downregulation of TMPRSS2	NR	[67]
11.	Lutonarin	*Hordeum vulgare* L	SARS-CoV-2	TMPRSS2	Binds to the key residues	NR	[68]
12.	Curcumin	*Curcuma longa*	SARS-CoV-2	Mpro/3CLpro	Restricts Viral Replication and adsorption stages	0.44	[69]
13.	Aloe emodin	*Isatis tinctoria L. (Brassicaceae)*	SARS-CoV	$3CL^{pro}$	Dose-dependently inhibited cleavage activity	3.70–370.3 (8.3)	[70]
14.	β-sitosterol	*Isatis tinctoria L. (Brassicaceae)*	SARS-CoV	$3CL^{pro}$	Dose-dependently inhibited cleavage activity	3.70–370 (12.10)	[70]
15.	Hesperetin	*Isatis tinctoria L. (Cruciferae)*	SARS-CoV	$3CL^{pro}$	Dose-dependently inhibited cleavage activity	3.31–331.1 (36.50)	[70]
16.	Indigo	*Isatis. indigotica Fort. (Cruciferae)*	SARS-CoV	$3CL^{pro}$	Dose-dependently inhibited cleavage activity	0.1–1000 (752)	[70]

17.	Amentoflavone	*Torreya nucifera (L.) Siebold & Zucc. (Taxaceae)*	SARS-CoV	3CL^{pro}	Enzymatic inhibition assay	1–1000 (8.3)	[72]
18.	Hinokinin	*Phyllanthus amarus Schumach. & Thonn. (Phyllanthaceae)*	SARS-CoV	3CL^{pro}	Binding affinity with 3CL^{pro}	8–80 (>100)	[74]
19.	Savinin	*Chamaecyparis obtuse var. formosana (Cupressaceae)*	SARS-CoV	3CL^{pro}	Binding affinity with 3CL^{pro}	1–10 (9.1)	[74]
20.	Theaflavin-3,3'-digallate	*Camellia sinensis (L.) Kuntze (Theaceae)*	SARS-CoV	3CL^{pro}	Inhibition of 3CL^{pro} (fluorogenic substrate assay)	4–20 (9.5)	[75]
21.	Fortunellin	*Citrus japonica*	SARS-CoV	3CL^{pro}	Inhibitor of 3cl-pro dimerisation	NR	[76]
22.	Pectolinarin	*Cirsium subcoriaceum*	SARS-CoV	3CL^{pro}	Competitive inhibition	NR	[78]
23.	Andrographolide	*Andrographis paniculate*	SARS-CoV; SARS-CoV-2	3CL^{pro}	Restrict protein expression	NR	[82]
24.	Baicalin and Baicalein	*Scutellaria baicalensis*	SARS-CoV-2	3CL^{pro}	Competitive inhibition	6.41 µM and 0.94 µM, respectively	[80]
25.	Saikosaponin A	*Bupleurum chinense DC (Apiaceae)*	HCoV-22E9	3CL^{pro}	Inhibition of 3CL^{pro}	5–25 (8.6)	[53]
26.	Sinigrin	*Brassica nigra (Brassicaceae)*	SARS-CoV	3CL^{pro}	Dose-dependently inhibited cleavage activity	217	[70]
27.	Isobavachalcone	*Cullen corylifolium (L.) Medik. (Fabaceae)*	SARS-CoV	PL^{pro}	Dose-dependently inhibited of PL^{pro}	1–150 (18.3)	[86]

28.	Psoralidin	*Cullen corylifolium (L.) Medik. (Fabaceae)*	SARS-CoV	PL^{pro}	Dose-dependently inhibited of PL^{pro}	1–150 (4.2)	[86]
29.	Quercetin	*Torreya nucifera (L.) Siebold & Zucc. (Taxaceae)*	SARS-CoV	PL^{pro}	Deubiquitination of PL^{pro}	1–200 (8.6)	[87]
30.	Papyriflavonol A	*Broussonetia papyrifera*	SARS-CoV	PL^{pro}	cleavage of both ubiquitin and ISG15	3.7μM	[87]
31.	Tomentin A	*Paulownia tomentosa Steud. (Paulowniaceae)*	SARS-CoV	PL^{pro}	Binding affinity with PL^{pro}	0.1–100 (6.2)	[88]
32.	Tomentin B	*Paulownia tomentosa Steud. (Paulowniaceae)*	SARS-CoV	PL^{pro}	Binding affinity with PL^{pro}	0.1–100 (6.1)	[88]
33.	Tryptanthrin	*Strobilanthes cusia*	HCoV-NL63	RdRp	It reduces the transcriptional acton of Rdrp during viral replication.	0.05	[90]
34.	Tylophorine	*Tylophora indica (Apocynaceae)*	SARS-CoV	RdRp	Inhibit highly conserved regions of coronavirus transcription complex thereby inhibiting viral replication	(0.008–1.47) (0.018)	[91]
35.	Saikosaponin C	*Bupleurum chinense DC (Apiaceae*	HCoV-22E9	-	Restricts replication	5–25 (19.9)	[53]
36.	Saikosaponin D	*Bupleurum chinense DC (Apiaceae*	HCoV-22E9	-	Restricts replication	5–25 (13.2)	[53]

37.	Silvestrol	*Aglaia foveolata Pannell (Meliaceae)*	HCoV-229E	Nsp13	Inhibition of Cap-mRNA Translation	0.6–20 (40)	[94]
38.	Myricetin	*Isatis tinctoria L. (Brassicaceae)*	SARS-CoV	Nsp13	Inhibits the ATPase activity of NSP-13	0.01–10 (2.74)	[96]
39.	Scutellarein	*Scutellaria baicalensis Georgi (Lamiaceae)*	SARS-CoV	Nsp13	Inhibits the ATPase activity of NSP-13	0.01–10 (0.08)	[96]
40.	Lycorine	*Lycoris aurea (L ' Hér.) Herb (Amaryllidaceae)*	HCoV-OC43; HCoV-NL63; MERS-CoV	-	Restricts Replication	0.01–5 (0.15, 0.47, 1.63, 0.31)	[98]
41.	Cepharanthine	*Stephania cepharantha* Hayata	HCoV-OC43; HCoV-HKU1	-	Competitive inhibition	0.35	[100]
42.	Fangchinoline	*Panax ginseng C.A.Mey. (Araliaceae)*	HCoV-OC43	-	Inhibits protein Expression & replication	2–20 (1.01 ± 0.07)	[100]
43.	Tetrandrine	*Bisbenzylisoquinoline cyclic alkaloids*	HCoV-OC43	-	Restricts Replication N protein expression	0.33 ±0.03	[100]
44.	Resveratrol	*Vitis vinifera, Polygonum cuspidatum* and *Vaccinium macrocarpon*	MERS-CoV	N-protein	Inhibits MERS nucleocapsid protein translation	NR	[105]
45.	Emetine	*Carapichea ipecacuanha (Brot.) L. Andersson (Rubiaceae)*	HCoV-OC43; HCoV-NL63; MERS-CoV	RNA, DNA and protein synthesis.	Inhibits the replication	0.1–5 (0.30, 1.43, 0.34, 0.12)	[108]