# Phytoconstituents in the Management of Covid-19: Demystifying the Fact

## Phytoconstituents Potential in COVID-19

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**ABSTRACT**

The 2019-nCoV (COVID-19; novel coronavirus disease-2019) outbreak is caused by the coronavirus, and its continued spread is responsible for increasing deaths, social and economic burden. COVID-19 created a chaotic situation worldwide and claimed the lives of over 5,027,183 and 248,467,363 confirmed cases have been reported so far as per the data published by WHO (World Health Organization) till 5th November 2021. Scientific communities all over the world are toiling to find a suitable therapeutic drug for this deadly disease. Although till date no promising drug has been discovered for this COVID-19. However, as per the WHO, over 102 COVID-19 vaccines are in clinical development and 185 in pre-clinical development. Naturally occurring phytoconstituents possess considerable chemical richness in the form of antiviral and anti-parasitic potential and have been extensively exploited for the same globally. Still, phytomedicine-based therapies are considered as the best available treatment option to minimize and treat the symptoms of COVID-19 because of the least possible side effects compared to synthetic drugs recommended by the physicians/clinicians. In this review, the use of plant chemicals as a possible therapeutic agent for severe acute respiratory syndrome coronavirus 2 (SARS CoV2) is highlighted with their proposed mechanism of action, which will prove fruitful and effective in finding a cure for this deadly disease.

**LIST OF ABBREVIATIONS**

| | |
|---|---|
| **COVID-19** | Novel coronavirus disease-2019 |
| **SARS CoV2** | Severe acute respiratory syndrome coronavirus 2 |
| **CoVs** | Coronaviruses |
| **RNA** | Ribonucleic acid |
| **MERS** | Middle East Respiratory Syndrome |
| **PLpro** | Papain-like protease |
| **3CL$^{pro}$** | 3-chymotrypsin-like protease |
| **M$^{pro}$** | Main protease |
| **ACE2** | Angiotensin-converting enzyme-2 |
| **TCM** | Traditional Chinese Medicine |
| **NCP** | Novel coronavirus pneumonia |
| **ARDS** | Acute respiratory distress syndrome |
| **RdRp** | RNA-dependent polymerase RNA |
| **3CLpro** | Chymotrypsin-like Cysteine Protease |

## Introduction

In late 2019 (31st December 2019), the first COVID-19 case was reported in Wuhan city, southern mainland China's Hubei province. COVID-19 disease is an acute respiratory tract inflammation caused due to SARS-CoV-2. It is incurable and characterized by a quick and unpredicted spread. In response to this COVID-19 virus outburst worldwide, the World Health Organization announced on 11th March 2020, stating that COVID-19 is a pandemic that has created chaos globally [1, 2]. It caused the death of over 5,027,183 and 248,467,363 confirmed cases worldwide so far as per the data published by WHO until 5th November 2021 [3].

Three epidemics resulting from coronavirus have occurred in the last two decades including, SARS in 2002-03, Middle East Respiratory Syndrome (MERS) in 2012, and COVID-19 in 2019 [4, 5]. Initially, severe acute respiratory syndrome (SARS-CoV) originated in Southern China in 2002-03, presenting a threat to the world and had infected more than eight thousand people with approximately eight hundred lives lost, mainly in China and nearby regions [6, 7]. The MERS coronavirus disease (MERS-CoV), initially reported in the Middle East, spread to several other countries, affects nearly twenty-three hundred people, and causes eight hundred forty-five deaths as of July 2019 [8]. Common symptoms of COVID-19 infection include high body temperature, weariness, coughing, myalgia, and difficulties in breathing. This disease can lead to severe illnesses like pneumonia, acute respiratory syndrome, kidney failure, and perhaps even death in extreme cases [9].

Scientific communities all over the world are toiling to find a suitable therapeutic drug for this deadly disease. Although to date, no promising drug has been discovered for this COVID-19. However, as per the WHO, over 102 COVID-19 vaccines are in clinical development and 185 in pre-clinical development [10]. Initially, hydroxychloroquine and chloroquine phosphate were prescribed to COVID-19 patients and also got encouraging outcomes. These two molecules work by various mechanisms, including alkalization of host cells' phagolysosomes [11, 12]. Subsequently, novel antiviral drugs such as lopinavir [13], remdesivir [14, 15], and arbidol [16] have been utilized widely. Additionally, many other drugs have been proposed, including nucleoside analogues, lopinavir/ritonavir, peptide EK1, and neuraminidase inhibitors [17].

The development of novel antiviral therapy has often been led by conventional herbal medicines and extracted natural products. In other terms, it is possible to design more efficient drugs based on natural compounds structure which manifests the intended result. In addition, many patients in the current COVID-19 outbreak were found to be inclined towards complementary or traditional medicinal therapies such as Traditional Chinese Medicine (TCM), Ayurveda, Unani, etc., for treatment. The use of TCM in treating SARS-CoV2 is largely triggered SARS-CoV outbreaks in the Guangdong Province of China in 2003, with more than 8000 cases reported globally [18–20]. The laboratory findings have backed up the therapeutic potential of TCM. For instance, a recent research report published in The Lancet detailed that glycyrrhizin, a chief chemical constituent obtained from Liquorice root (*Glycyrrhiza glabra*), is the most frequently used traditional traditional traditional herb in China, strongly restricted the replication of SARS infection clinical confines [21]. One more independent investigation affirmed the antiviral activity of glycyrrhizin and baicalin, a Chinese herbal medicine by plaque reduction assay [22]. Furthermore, a recent study conducted by Luo et al. showed that TCM had been involved in fighting the novel coronavirus pneumonia (NCP) induced by this highly infectious COVID-19 virus in 54 NCP patients [23].

Countries like China and India are giving detailed information on how to use traditional medicines [24]. Several clinical trials in China and India are also under process [25, 26]. Furthermore, the WHO has encouraged researchers globally to work on repurposing drugs, customary prescriptions, and finding new treatments in the quest for potential medicines for COVID-19 [27].

Lin et al. (2014) briefly reviewed phytochemicals that showed therapeutic potential against known coronaviruses [28]. In contrast, the article by Pang et al. (2020) [29] and Lu (2020)[30] on COVID-19 medications made only a brief reference to natural therapies and the phytochemical components but have not explored their mechanism of action.

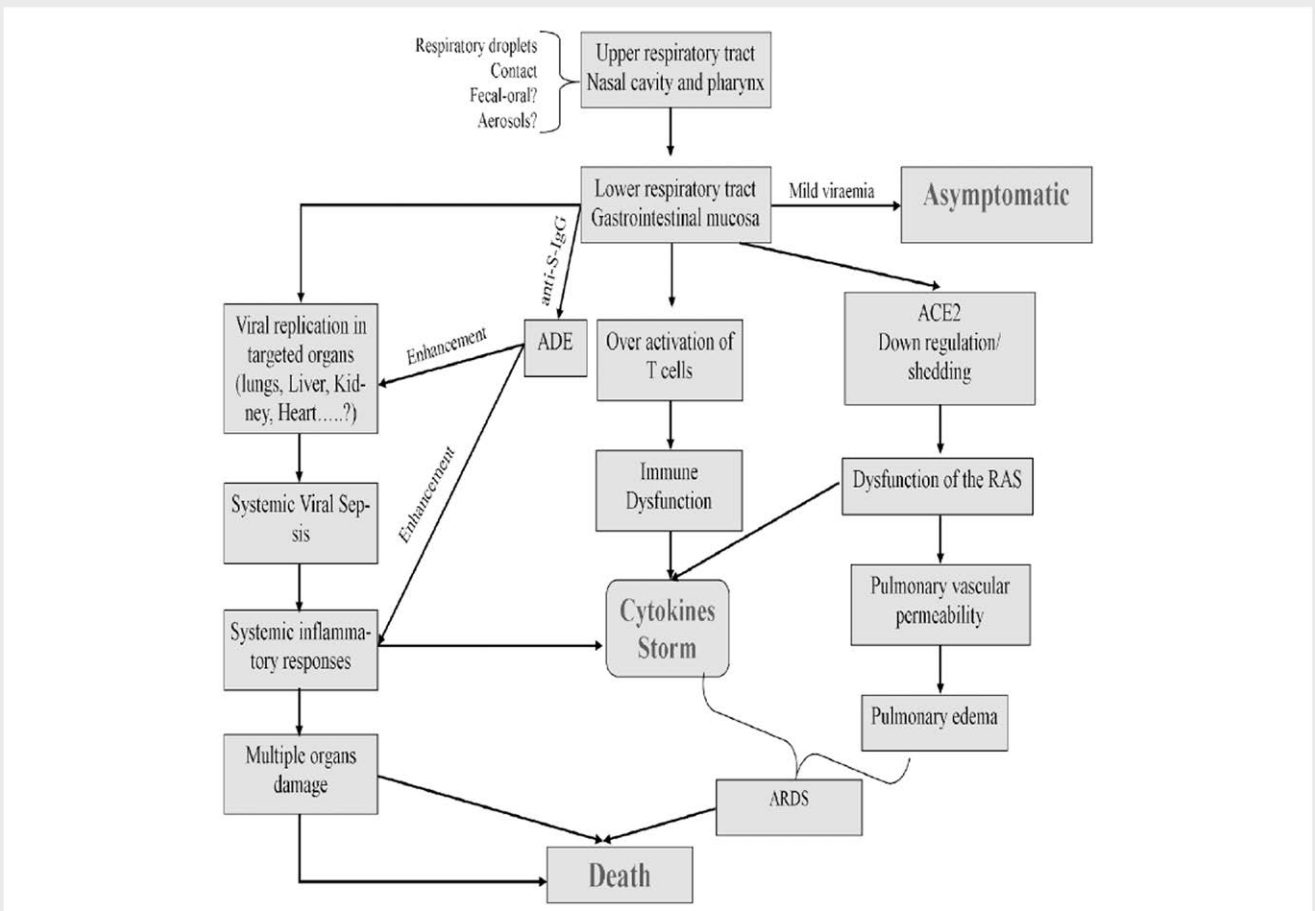
The recent review discussed the use of phytochemicals as a possible cure for COVID-19 with their proposed mechanism of action that will help find a suitable treatment for this life-threatening viral disease.

### Pathogenesis of COVID-19

Understanding the structure of coronaviruses and SARS-CoV-2 is the first step in comprehending COVID-19's pathogenesis. Coronaviruses (CoVs) (Family: Coronaviridae) are large, enveloped, positive single stranded ribonucleic acid (RNA) viruses and the largest RNA virus genome (approximately 26–32 kilobases) causing infection equally in humans as well as in animals [4]. The size of the coronavirus is lying in the range of 65-125 nm in diameter. The SARS-CoV2 genome shows approximately 70 % similarity with the SARS-CoV genome which indicates its current name [9, 10]. SARS-CoV-2's primary drug targets include 3-chymotrypsin-like protease (3CL$^{pro}$), papain-like protease (PLpro), RNA-dependent polymerase, and spike (S) proteins [4]. The Spike proteins help the virus enter the cell by attaching it to human angiotensin-converting enzyme-2 (ACE2). The SARS-CoV2 virus predominantly affects the lungs, while other organs are implicated as well. Lower respiratory tract infection-related symptoms, including fever, dry cough, and dyspnea, have been observed in China's Wuhan study [31]. Headache, dizziness, general exhaustion, vomiting, and diarrhea have also been reported [32]. Respiratory symptoms of COVID-19 are now widely recognized as being highly diversified, varying from negligible health conditions to substantial hypoxia with acute respiratory distress syndrome (ARDS). In the above-mentioned Wuhan study, the incubation period was as short as nine days, indicating that perhaps respiratory diseases may advance rapidly [31]. ▶ **Fig. 1** depicts an explanation of the pathogenesis of SARS-CoV2 [33].

## Possible mechanism of action phytochemicals

SARS-CoV2 has structural similarity to coronavirus with spike protein and other polyproteins, membrane proteins, and nucleoproteins such as RNA polymerase, PLpro, 3CL$^{pro}$, glycoprotein, helicase, and accessory proteins (▶ **Fig. 2**) [34–36]. The SARS-CoV2 spike protein is composed of a 3-D structure in the receptor-binding domain (RBD) region for maintaining the Van der Waals forces [37].




▶ **Fig. 1** Pathogenesis of SARS-CoV2. ARDS: acute respiratory distress syndrome; ACE2: angiotensin-converting enzyme 2; Antibody-dependent enhancement (ADE); RAS: renin-angiotensin system. Words highlighted in red reflect significant pivotal moments in disease with SARS-CoV-2 [33].

Wan et al. demonstrated that the crucial lysine 31 on the human ACE2 receptor recognizes residue 394 (glutamine) in the SARS-CoV-2 RBD, which corresponds to residue 479 in SARS-CoV [38]. The whole virulence mechanism of SARS-CoV2 from attachment to replication has been explicitly depicted in ▶ **Fig. 3** [39]. The details of the possible mechanism by which the phytochemicals act are discussed below. A summary of phytochemicals with their mechanism is being summarized in ▶ **Table 1**.

## Proteases

### RNA dependent RNA polymerase

An alternative druggable target is defined by the RNA-dependent polymerase RNA (RdRp), the main enzyme responsible for both positive and negative-strand RNA synthesis. It has been shown that in docking studies Theaflavin from *Camellia sinensis* (*C. sinensis*) was able to inhibit RNA-dependent RNA polymerase [40].

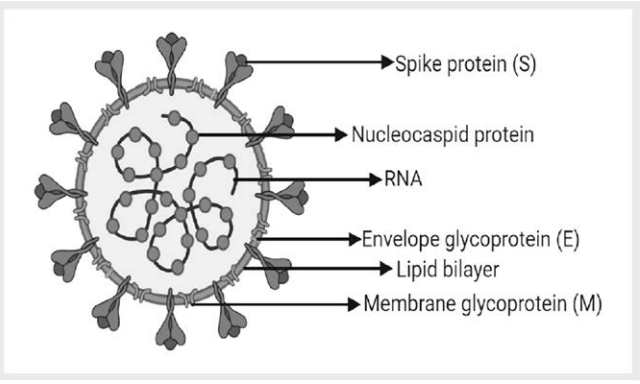
### Main protease ($M^{pro}$)

Main protease ($M^{pro}$) is an important drug target for coronaviruses due to its essential role in the processing of viral RNA translated polyproteins [62]. In a study, Sampangi-Ramaiah et al. have reported that 27 ligands, most of which form an integral component of many cuisines, both Indian as well as others out of which Curcumin, Coriandrin, Ursolic Acid, Hederagenin, Oleanolic Acid, Sageone, Apigenin, and Glabridin were able to inhibit $M^{pro}$ [41]. In another study, 25 natural compounds derived from plants were examined for their ability to inhibit $M^{pro}$, and Withaferin A was shown to be effective [44, 52]. Aanouz et al. studied 67 Moroccan medicinal plants and reported that *β*–Eudesmol, Digitoxigenin, and Crocin inhibited $M^{pro}$[45]. Similarly, Oleanic acid from *Anthocephalus cadamba* [46], Meliacinanhydride from *Azadirachta indica* [49], Absinthin, Quercetin, 3-glucuronide-7-glucoside, Quercetin 3-vicianoside [60], Rutin [44], Andrographolide [48], Scopodulcic acid, Dammarenolic acid [56], Allyl disulfide, Allyl trisulfide [61], and Ginkgolide A [51] were also found to inhibit enzyme successfully.

Moreover, the myricitrin, tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone, methyl rosmarinate from TCM [53], 22-Hydroxyhopan-3-one, 10-Hydroxyusambarensine Cryptoquindoline, and 6-Oxoisoiguesterin from native African medicinal plant [50], Baicalin and Baicalein from *Scutellaria baicalensis* [43] were found possess anti enzymatic activity against 3-Chymotrypsin-like Cysteine Protease (3CLpro). Furthermore, naturally occurring 8-Gingerol, 10 Gingerol, and 6-Gingerol were also able to inhibit the PLpro activity [42].

## Angiotensin-converting enzyme-2

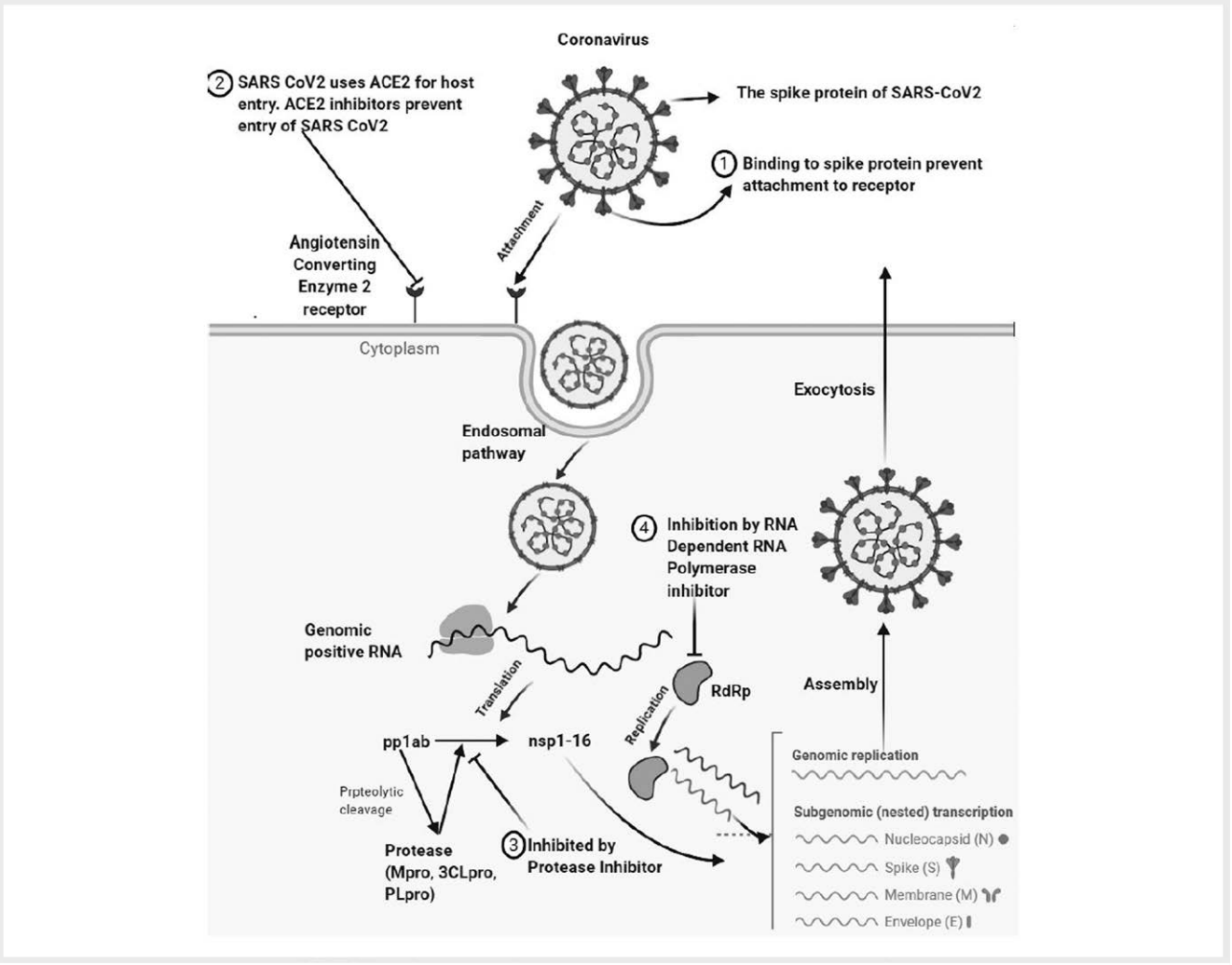
As with SARS-CoV and SARS-CoV2 utilizes the cellular entrance host ACE2 receptor [63]. The cellular entrance of SARS-CoV2, the leading cause for COVID-19, is assisted by binding viral spike proteins on the host membranes to ACE2 receptors [38]. This increases the prospect that perhaps the prevalence of infection may be related to target ACE2 receptor expression in virally exposed epithelium [64]. However, because of complex interaction, the associated SARS-CoV virus is being shown to de-regulate ACE2 after cell entry. This factor that contributes to the severe lung pathologies associated with this virus infection [64]. Resveratrol, stilbene based natural compounds, and natural garlic essential oil compounds substantially blocked the SARS-CoV S-protein and ACE2 interactions [58, 61].




▶ **Fig. 2** Structure of SARS-CoV2 [36].

## Inhibitors of spike (S) proteins

Spike protein is a protein in the shape of a clove, type I transmembrane (TM). The spike protein has three segments: TM region, ectodomain (ED) region, and an intracellular domain, comprising the short tail portion of the intracellular domain [65]. The ED is comprises of the receptor-binding S1 domain (three S1 heads) and the membrane fusion subunit S2 (trimeric stalk) at C-terminal together. Spike proteins gather on the outer surface of the virion in the trimeric form, giving it the appearance of a crown by which it is re-




▶ **Fig. 3** Mechanism of action of different phytochemicals on 1. Binding of spike protein prevents attachment of the virus to ACE2 receptor, 2. Inhibition of the ACE2 receptor prevents the entry of viruses into the human body, 3. Inhibitors of protease prevent the reproduction of SARS-CoV2 by stopping the process of translation, 4. Inhibition of RNA dependant RNA polymerase hastens the replication of the viral genome [39].

▶ **Table 1** Glimpse of some phytochemicals with their mechanism of action against SARS-CoV-2.

| Possible mechanism of action | | Lead Phytochemical/s active against SARS-CoV-2 | References |
|---|---|---|---|
| Inhibition of Proteases | Binding to RNA-dependent RNA polymerase | Theaflavin | [40] |
| | Inhibition of SARS-CoV2 main proteases. | Curcumin, Coriandrin, Ursolic Acid, Hederagenin, Oleanolic Acid, Sageone, Apigenin, Glabridin | [41] |
| | Inhibition of SARS-CoV2 PLpro | 8-Gingerol, 10-Gingerol, and 6-Gingerol | [42] |
| | Inhibition of SARS-CoV2 3C-like protease (3CLpro) | Baicalin and Baicalein | [43] |
| | Inhibition of SARS-CoV2 3CLpro/Mpro | Withaferin A | [44] |
| | Inhibition of Coronavirus (2019-nCoV) main protease | β–Eudesmol<br>Digitoxigenin, Crocin | [45] |
| | Inhibition of Coronavirus (2019-nCoV) main protease | Oleanic Acid | [46] |
| | Inhibition of Coronavirus (2019-nCoV) main protease | Rutin | [47] |
| | Inhibition of Coronavirus (2019-nCoV) main protease | Andrographolide | [48] |
| | Inhibition of Coronavirus (2019-nCoV) main protease | Meliacinanhydride | [49] |
| | Inhibition of SARS-CoV2 3C-like protease (3CLpro) | 10-Hydroxyusambarensine, Cryptoquindoline, 6-Oxoisoiguesterin, and 22-Hydroxyhopan-3-one | [50] |
| | Inhibition of Coronavirus (2019-nCoV) main protease | Ginkgolide A | [51] |
| | Inhibition of Coronavirus (2019-nCoV) main protease | Withaferin A, Withanolide B, Withanolide, Withanone, Campesterol, Cyclocurcumin, Somniferine A, Stigmasterol, Eriodictyol, Isopiperine, Oleanolic acid, Rhamnetin, Orientin, Quercetin, Piperine, Vicenin | [52] |
| | Inhibition of SARS-CoV2 3C-like protease (3CLpro) | 5,7,3',4'-tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone, myricitrin, and methyl rosmarinate, | [53] |
| Binding to Spike protein | Binding to Spike protein of SARS-Cov-2 | Biochanin A, Linoleic, Chlorogenic Acid, Cinnamaldehyde, and Thymoquinone | [54] |
| | Binding to Spike protein of SARS-Cov-2 | Saikosaponin V | [55] |
| | Binding to Spike protein of SARS-Cov-2 | Scopodulcic acid and Dammarenolic acid | [56] |
| | Binding to Spike protein of SARS-Cov-2 | 6-Gingerol | [57] |
| Inhibition of Angiotensin-converting enzyme-2 receptor | Inhibition of Coronavirus ACE2 receptor complex. | Resveratrol | [58] |
| | Inhibition of Coronavirus ACE2 receptor complex. | Isothymol | [59] |
| | Inhibition of Coronavirus ACE2 receptor complex. | Absinthin, Quercetin 3-glucuronide-7-glucoside, and Quercetin 3-vicianoside | [60] |
| | Inhibition of Coronavirus ACE2 receptor complex. | Allyl disulfide<br>Allyltrisulfide | [61] |

ferred to as CoV. The spike protein plays a major role throughout the accession of viruses further into the host [65].

Only a few studies evaluated and reported the spike protein (S) blockers. The potential compound derived from plants, such as Biochanin A, Linoleic, Chlorogenic Acid, Cinnamaldehyde, Thymoquinone [54], and Saikosaponin V from roots of *Bupleurum chinense* [55] were found to block the spike protein efficiently.

## Potentials of phytochemicals in COVID-19

For centuries, natural products have been regarded as significant sources of medicinal agents. Conventional medicines from various geographic locations and habitats are suggested as promising sources of natural drugs as an antiviral therapy for viral infection, especially those caused by SARS-CoV2. Some preliminary reports of the activity against SARS-CoV2 include a phytochemical called theaflavin found in *C. sinensis* [40]. The outbreak of SARS-CoV2 contributed to disastrous incidents, as no effective treatment at the time was available. This culminated in the worldwide hunt for therapeutic agents that can be a precautionary measure against SARS-CoV2 to avoid the potential threats to humans. Some Chinese herbs have long been known for their antiviral effects in this context and were therefore investigated for a potential function against SARS-CoV2. A data set having 32,297 potential antivirals and 10 phytochemicals from TCM were tested of which phytochemicals namely Myricitrin, 5,7,3',4'-tetrahydroxy-2'-(3,3-dimethylallyl) Isoflavone and Methyl Rosmarinate found to be effective against SARS-CoV2 protease [53]. A paper published by Neda Shaghaghi showed that Ginkgolide A exerts inhibitory action against SARS-CoV2 protease [51]. In a study, Das et al. reported that the rutin, a naturally occurring flavonoid, shows the highest inhibitory potential against SARS-CoV2 protease among the 33 molecules studied [47]. Recent findings showed that Curcumin, Coriandrin, Ursolic Acid, Hederagenin, Oleanolic Acid, Sageone, Apigenin, and Glabridin were seen to act against SARS-CoV2 with the help of computational studies [41]. In addition, 6-Gingerol, 8-Gingerol, and 10-Gingerol inhibited SARS-CoV2 PLpro [42]. Andrographolide reported from the plant *Andrographis paniculata* inhibited Coronavirus (2019-nCoV) main protease [48]. Similarly, Withaferin A [44], Withanolide, Withanolide

B, Campesterol, Withanone, Somniferine A, Cyclocurcumin, Eriodictyol, Stigmasterol, Oleanolic acid, Isopiperine, Orientin Rhamnetin, Piperine, Quercetin, and Vicenin from Indian traditional medicine Kadha [52], Baicalin and Baicalein from *Scutellaria baicalensis* [43], β–eudesmol, Digitoxigenin, Crocin from Moroccan Medicinal plants [44], Meliacinanhydride from *Azadirachta indica* [49], Oleanic Acid from *Anthocephalus cadamba* [46] were found effective against *n*COVID-19 protease. An in-silico study of terpenoids and alkaloids from medicinal herbs in Africa suggested Cryptoquindoline, 10-Hydroxyusambarensine, 22-Hydroxyhopan-3-one, 6-Oxoisoiguesterin, Isoiguesterin, Cryptospirolepine, and 20-Epibryonolic acid were found successful in inhibiting the SARS 3CLpro [50].

Researchers across the globe are continually focusing on elucidating the path through which naturally occurring phytoconstituents can be used. Natural compounds such as Biochanin A, Linoleic, Chlorogenic Acid, Cinnamaldehyde, and Thymoquinone effectively inhibit surface-binding spike protein. They can, therefore, be utilized to minimize the hazard of COVID-19 for high-risk people such as the elderly and cancer patients or actively engaged medical personnel [54]. Similar phytochemicals like Saikosaponin V, Scopodulcic acid, and Dammarenolic acid can be utilized to inhibit the surface binding spike protein [55, 56].

Resveratrol, a stilbene based natural compound found to inhibit the ACE2 receptor which processes the SARS-CoV2 virus into the human body [58]. Similarly, researchers are attempting to identify possible therapeutic targets for the COVID-19 virus utilizing bioactive molecules from *Ammoides verticillata* (Desf.) Briq, an antiviral and antimicrobial plant that is being widely grown in western Algeria. From the essential oil of *Ammoides verticillata* plant, several phytochemicals have been isolated such as, Thymol, Isothymol, Limonene, γ-terpinene, and *P*-cymene. The study revealed that the Isothymol, a major component of this plant essential oil, inhibits the ACE2 receptor [59]. In another study, 318 phytochemicals have been reported as an antiviral, antibacterial, and antifungal activity, out of which Absinthin, Quercetin 3-glucuronide-7-glucoside, and Quercetin 3-vicianoside were found to inhibit ACE2 and $M^{pro}$ receptor [60]. Recent findings indicated that Allyl disulfide and Allyl trisulfide from garlic essential oil inhibit angiotensin-converting enzyme-2 receptors in docking studies [61].

Flavonoids are abundant in a wide range of fruits and vegetables, including citrus fruits and tomatoes. It makes up the biggest category of ACE2 inhibitors found in natural products. Several studies have already shown that certain flavonoids have been shown to suppress ACE2 activity. Apigenin, for example, has been shown to increase the expression of the ACE2 gene in hypertensive rats [66]. Additionally, Wei and colleagues found that baicalin, a natural flavone, ameliorates angiotensin-II-induced endothelial dysfunction via regulating ACE2 expression both at mRNA and protein levels [67]. Naringenin, a flavanone present in grapefruit, may similarly protect the reno-vascular system from hypertension-induced injury in vivo by inhibiting ACE2 expression [68]. These findings suggest that flavonoids may be useful in preventing SARS-CoV-2 viral infection via ACE2 regulation. Notably, flavonoids such as naringenin, naringin, nobiletin, hesperidin, hesperetin, neo-hesperidin, pinocembrin, quercetin, myricetin, and kaempferol have shown a possible affinity for ACE2 binding to SARS-CoV-2 S protein residues [66].

The steroids and steroid glycosides are another family of natural compounds having ACE2 modulatory effects. Ginsenosides are naturally occurring steroid glycosides that are abundant in the rhizome of ginseng. In vivo studies have shown that ginsenoside Rg3, a tetracyclic triterpenoid saponin, increases ACE2 levels and protects against Ang II-mediated renal damage [69]. Following the SARS-CoV-2 epidemic, a recent virtual screening indicated that arundoin and a few steroid glycosides (azukisaponin I, 20(S),24(R)-ocotillol, and ginsenoside Rg6) may modify ACE2 activity [70].

Concerning alkaloids, a recent research shown that cepharanthine, a naturally occurring alkaloid, may bind to spike protein and disrupt the viral interaction with the ACE2 protein computer simulation [71]. Another research found that nicotianamine, a non-proteinogenic alkaloid, had a comparable action on ACE2 as Takahashi et al. demonstrated *in vitro* [66, 72].

## Conclusions

Natural resources, predominantly plants, offer an essential and potential reserve of chemical compounds with antiviral properties. Currently, the COVID-19 virus and its treatment have become a big challenge for drug discovery scientists and researchers globally. The outbreak of this virus is spreading worldwide and causing several deaths. As we know that no therapeutic drugs have been discovered to date for the management of this disease. The naturally occurring phytochemicals can be helpful to inhibit the dissemination of coronavirus and, at the same time, enhance immunity. Natural products can be used both ways to prevent viral disease and stop the virus from spreading. Despite the general hunt for SARS-CoV2 inhibitors, antiviral agents from natural sources that effectively inhibit SARS-CoV2 should provide a good point of reference for identifying substances that are very effective in SARS-CoV2. Using computer-based docking simulations, computer-based docking simulations, additional modification of such phytochemicals can improve their potency and/or selectivity. There is also a need for comprehensive *in vitro* and *in vivo* research to determine their activities. As a suggestion, since there are no effective drugs against coronavirus, the infected people should keep the immune system strong because a healthy immune system reduces the chance of viral infection and helps the body to clear the virus rapidly. Many such medicinal plants are available with antiviral, antibacterial, and antifungal activity and act as an immunity booster. The phytochemicals of these medicinal plants can be used against coronavirus. The scientific community is hoping to benefit from this review, which will ideally aid in developing safe and effective coronavirus medicines derived from naturally occurring chemicals.

## Authors' contributions

All the authors contributed equally.

### Conflict of Interest

The authors declare no conflict of interest.

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