

Mini Review

# Phytochemicals candidates as promising preventives and/or curatives for COVID-19 Infection: A brief review

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## Abstract

The outbreak of new coronavirus acute respiratory disease (SARS-CoV-2) has been a major global challenge for the scientific community to save humanity. While, the unviability of the vaccine keeps most classes of society, especially African countries, suffer from the healthcare problem. Conventional medicine plants become the alternative method for the therapeutic because it contains valuable bioactive compounds. This brief review devoted the importance of medicinal plants such as citrus, olive, garlic, ginger, green tea, woad, broad-leaf privet, Japanese torreyia, and saffron crocus, by their antiviral effects (anti-SARS coronavirus, anti-HSV, and anti-HIV diseases) and their promising uses as probable boosters of the immune and anti-inflammatory response from SARS-CoV-2 infection. Based on scientific reports, bioactive compounds could inhibit 3-chymotrypsin-like cysteine protease and human protein ACE2, where these facts can be attractive to develop effective drugs.

## Introduction

A new severe pandemic pneumonia generated from a large seafood and animal market in the city of Wuhan (China) on December 2019 killed thousands of people around the world [1].

As of May 10, 2020, 61,165 cases confirmed and 2,239 deaths have been reported in Africa [2]. The spread out of this pandemic in Africa raise fears of the worst. In terms of healthcare, these countries face a large number of challenges, including lack of funds and poor infrastructures [3]. Besides, the availability of the vaccine or drug, if there is, will not be accessible to all layers of society.

Human coronavirus disease (COVID-19 or SARS-CoV-2) presents a severe acute respiratory, fever, dry cough, shortness of breath, fatigue and decreases of white blood cells and kidneys function. SARS-CoV-2 is an enveloped virus, classified

in the beta-corona viruses group with a single-stranded positive-sense RNA genome and high nucleotide similarity (89%) with SARS coronavirus (SARS-CoV) genes [4]. The viral 3-chymotrypsin-like cysteine protease is the major protease produced by the SARS-CoV-2 that plays a key role in the production of functional viral proteins, which maintains the virus replication [5]. This protease shares 96% of similarity with SARS coronavirus protease [6]. Studies showed that the receptor-binding domain of COVID-19 strongly interacts with type I integral membrane human protein ACE2, where it is easily able to enter the host cells [7]. Treatment of COVID-19 remains a big challenge and more attention due to (i) the adaptation of virus, (ii) the resistance of SARS-CoV-2 to antiviral drugs and (iii) the possible development of new viral and bacterial strains [1].

Currently, SARS-CoV-2 is treated using chloroquine and hydroxychloroquine knowing for their ability to inhibit the

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SARS coronavirus and to treat HIV infections [8]. Scientists believed that both drugs can inhibit the ACE2 protein, but their risk of toxicity and side effects is of great concern [8].

For decades, medicinal plants have gained wide popularity due to their beneficial effect in treating various diseases. All civilizations around the globe offer unlimited sources of traditional plants and herbs that provide numerous phytochemicals compounds used in pharmaceutical industry. Meanwhile, over than 40% of natural products have been used in the synthesis of pharmaceutical drugs [9]. Virtually, the use of medicinal plants or their phytochemicals have gained an attractive interest to prevent and to treat the viral infections. It was well established that the main antiviral mechanisms of natural compounds are the inhibition of viral replication, assembly of intracellular particles, RNA polymerase, viral neuraminidase, protease, reverse transcriptase and viral protein expression [10]. As well as, many traditional medicinal plants have shown promising results in treating the coronavirus as shown in figure 1 [11-13]. Moreover, phytochemicals compounds have shown their direct antiviral impact and their ability to biosynthesis nanoparticles with promising antiviral activity [1,14,15]. These facts can be attractive to develop effective drugs much safer than chemical drugs.



Figure 1: Some common medicinal plants and fruits.

This brief-review will provide information on the most effective medicinal plants in the treatment of coronavirus, as well as the mechanism *in silico* of their phytochemicals compounds against SARS-CoV-2 infection.

## Methodology

Literatures were collected from the online bibliographical databases: PubMed, Scopus, Google Scholar, and Web of Sciences. The following keywords were used to search recent papers: “anti-coronavirus”, “antiviral activity”, “medicinal plants”, “COVID-19”, “phytochemical compounds”, “bioactive compounds”, “anti-SARS activity”, “anti-HIV”, and “Anti-HSV”. In this brief review, we cited forty-three papers that are tightly correlated with the main objective of this work.

## Medicinal plants and their bioactive compounds

1. *Citrus* sp [mandarin orange, sour orange, pomelo, and sour orange]

Several *citrus* fruits such as *Citrus aurantium* (Sour orange), *Citrus grandis* (Pomelo), *Citrus reticulata* (Mandarin orange), and *Citrus sinensis* (Sweet orange) are rich in flavonoids compounds, which are highly recommended to block beta coronavirus (Figure 2) [13]. Hesperetin, a major flavonoid, has showed an anti-SARS-coronavirus activity through the inhibition of 3-chymotrypsin-like cysteine protease [16]. In addition, rutin (quercetin-3-O-rutinoside) and neodiosmin have revealed an inhibition of the 3-chymotrypsin-like

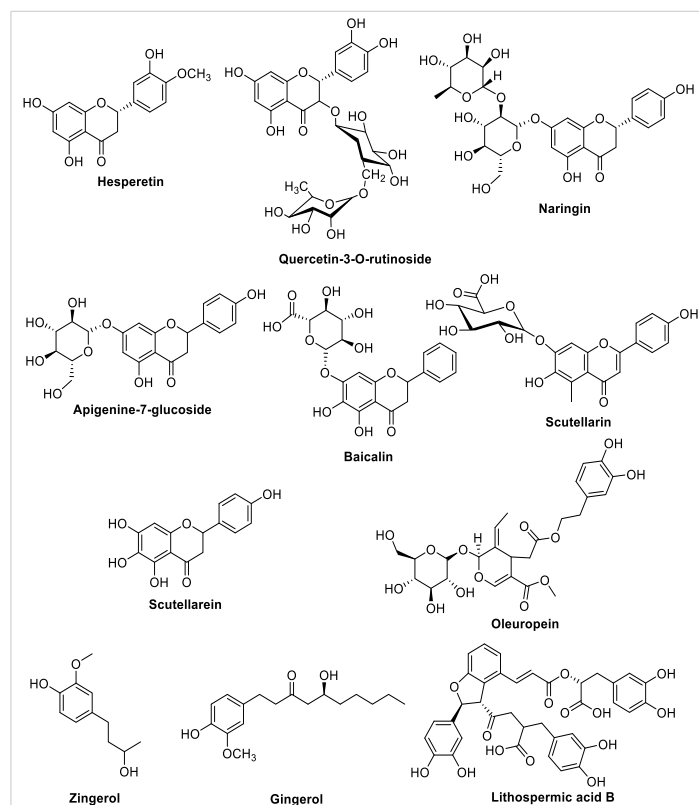


Figure 2: Chemical structure of flavonoids (hesperetin, quercetin 3-O-rutinoside, naringin, apigenine-7-glucoside, baicalin, scutellarin, scutellarein), tannins (oleuropein), simple and polyphenolic compounds (zingerol, gingerol, lithospermic acid B).

cysteine protease [5]. Thereby, naringin and rutin were used to prevent and decrease plasma cytokines levels of TNF- $\alpha$ , IL-1 $\beta$ , IL-10, IFN $\gamma$  in-patient with SARS-CoV-2. Moreover, naringin and hesperetin revealed a potential binding with the ACE2 protein, which could prevent COVID-19 infection [17].

## 2. *Olea europaea* L [Olive]

*Olea europaea* is among the oldest trees grown in the world known by its therapeutic properties. The bioactive compounds extracted from *Olea europaea* fruits such as oleuropein, apigenin-7-glucoside, and luteolin-7-glucoside showed a potential inhibition of SARS-CoV-2 infection pathway through blocking the 3-chymotrypsin-like cysteine protease [6].

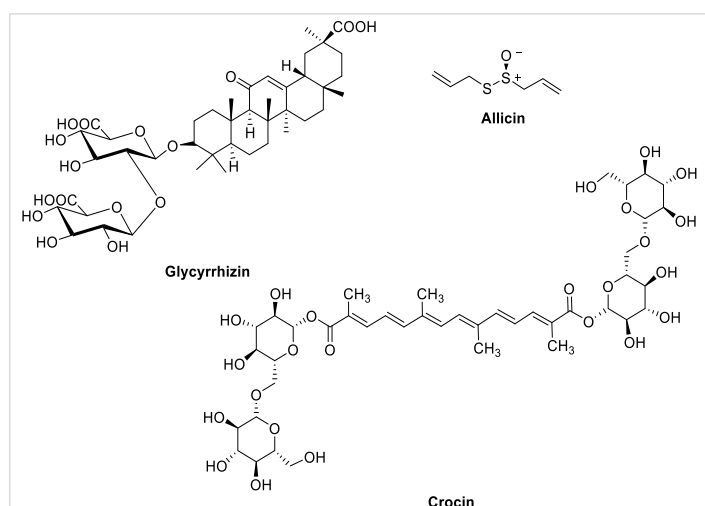
## 3. *Glycyrrhiza glabra* [Liquorice]

Liquorice has been used clinically for centuries in several therapeutic applications. The glycyrrhizin (Figure 3), bioactive substance extracted from liquorice plant, showed a clinical anti SARS-CoV activity by affecting the cellular signalling pathways like protein kinase C, casein kinase II, and nuclear factor in SARS-CoV [11].

## 4. *Scutellaria baicalensis* [Baikal skullcap]

The baicalin extracted from the herbs of *Scutellaria baicalensis* has been reported as potential inhibitor of SARS-CoV infection within only 48 hours [1]. Moreover, another study showed that baicalin inhibited the angiotensin-I converting enzyme (ACE) [18]. Recently, scientists have reported that baicalin (at concentration of 2.24 Mm) could potentially inhibit ACE2 by binding to ASN-149, ARG-273, HIS-374, HIS-378, HIS-505, and ALA-348 sites [1,17].

Natural compounds of Baikal skullcap (Figure 2), such as scutellarein has showed potent inhibition of SARS-CoV helicase by affecting the activity of ATPase [19]. Besides, the scutellarin compound was revealed as promising agent to prevent SARS-CoV-2 infection by inhibiting ACE2 [1].



**Figure 3:** Chemical structure of saponins (glycyrrhizin), organosulfur compounds (allicin), and carotenoids (crocin).

## 5. *Lycoris radiata* [Red spider lily]

Li, et al. [20] reported that the stem cortex of the *Lycoris radiata* herbs has potent antiviral activities against coronavirus (SARS-CoV) at a concentration of 15.7 nM. These results indicate that lycorine may be an alternative candidate to prevent or treat SARS-CoV-2 infection, since it shared similarity with the SARS virus (Table 1).

## 6. *Allium sativum* [Garlic]

The garlic is widely consumed due to its bioactive compounds richness. As show in figure 3, allicin is one of the most bioactive compounds with high activity against SARS-CoV-2 through the inhibition of 3-chymotrypsin-like cysteine protease [6].

## 7. *Isatis indigotica* [Woad]

The anti-SARS coronavirus activity was investigated by using *Isatis indigotica* root extract and plant-derived phenolic compounds. It showed that hesperetin from this plant inhibited the 3-chymotrypsin-like cysteine protease, which blocks the coronas virus [16].

## 8. *Houttuynia cordata* Thunb [Saururaceae]

The *Houttuynia cordata* (Saururaceae) is widely used in Chinese medicine to treat SARS disease. The saururaceae extract proved a varied inhibitory effect on SARS coronavirus 3-chymotrypsin-like cysteine protease and RNA-dependent RNA polymerase [21].

## 9. *Ligustrum lucidum* [Broad-leaf privet]

Phytochemicals isolated from *Ligustrum lucidum* fruits known by their richness of bioactive compounds. Of particular interest, specnuezhenide and neonuezhenide, which belong to secoiridiod glycosides class. These compounds have showed potent inhibitory activity against 3-chymotrypsin-like cysteine protease through binding to conventional hydrogen bonds, carbon hydrogen bonds, van der Waals force, and hydrophobic interaction [5].

## 10. *Zingiber officinale* [Ginger]

Ginger is frequently used in food and traditional medicine. Bioactive compounds from ginger, such as zingerol and gingerol (Figure 2), have shown an inhibition of 3-chymotrypsin-like cysteine protease in SARS-CoV-2 infection [6].

## 11. *Salvia miltiorrhiza* [Chinese sage herb]

*Salvia miltiorrhiza* knows as Chinese sage herb, is widely used in Chinese traditional medicine. Lithospermic acid B is one of the polyhydroxy phenolic acid compounds isolated from this herb. This bioactive substance has been reported as a potential candidate to inhibit the 3-chymotrypsin-like cysteine protease in SARS-CoV-2 [5].

**Table 1:** Sources and bioactivity of phytochemical compounds and *in silico* its target sites on SARS-CoV-2.

Phytochemical compounds	Plants source	Bioeffects	Target sites <i>in silico</i> SARS-CoV-2 (Inhibition)	References
Hesperetin	<i>Isatis indigotica Citrus sp</i>	Antioxidant, Anti-inflammatory, Anti-HSV type 1, Anti- poliovirus type 1, Anti-parainfluenza virus type 3, and influenza	3-chymotrypsin-like cysteine protease	[31,32]
Bananin	<i>Banana</i>	Inhibition of viral replication	ATPase inhibitor of the SARS-CoV-2 helicase.	[33]
Naringin	<i>Citrus sp</i>	Anti-rotavirus infection, Anti-inflammatory, Anti-carcinogenic	ACE2 protein, Interfere in levels of TNF- $\alpha$ , IL-1 $\beta$ , IL-10, IFN $\gamma$	[17,31,32,34]
Baicalin	<i>Scutellaria baicalensis</i>	Anti-HSV type 1 and 2 Anti-adenoviruses	ACE2 protein	[1,17,35]
Quercetin-3-O-rutinoside	<i>Citrus sp</i>	Antiviral, Anti-inflammatory, Antioxidant	3-chymotrypsin-like cysteine protease	[5,36]
Neodiosmin	<i>Citrus sp</i>	Not reported		[5]
Oleuropein, Apigenin-7-glucoside	<i>Olea europaea</i>	Antiviral, Anti-atherogenic, Anti-inflammatory, Antioxidant, Anti-leukemia	3-chymotrypsin-like cysteine protease	[6,37,38]
Crocin	<i>Crocus Sativus</i>	Anti-HSV and Anti-HIV	COVID-19 spike protein	[25,26]
Allicin	<i>Allium sativum</i>	Antioxidant, Antiviral, Hypolipidemic	3-chymotrypsin-like cysteine protease	[6,39]
Scutellarein, Scutellarin	<i>Scutellaria baicalensis</i>	Antioxidant, Anti-inflammatory, Antiviral	Helicase protein, ACE2 protein	[1,40]
Zingerol, Gingerol	<i>Zingiber officinale</i>	Anti-inflammatory, immunomodulatory properties, Antioxidant	3-chymotrypsin-like cysteine protease	[6,41]
Kaempferol	<i>Spinacia oleracea, Brassica oleracea, Anethum graveolens, Brassica rapa, Sauropus androgynus</i>	Inhibit transcription with RNA polymerase II, Antioxidant	3-chymotrypsin-like cysteine protease	[6,42]

## 12. *Torreya nucifera* [Japanese torreyia]

*Torreya nucifera* is an ancient tree used for decades in traditional Asian medicine. The ethanol extract of *T. nucifera* leaves exhibited good activity against SARS coronavirus. Three bioflavonoids from *T. nucifera* (apigenin, luteolin, and quercetin) have demonstrated a potential inhibitory activity of 3-chymotrypsin-like cysteine protease [22].

## 13. *Cupressus sempervirens* L [Cypress]

The hydro-ethanolic extract from fresh cones of cypress (*Cupressus sempervirens* L) has been tested against Corona VR-740. The study revealed a massive amount of bioactive molecules in cypress extract, such as catechin, epicatechin, tannins of proanthocyanidin, and flavonoids that inhibited the coronavirus activity within 60 min [23].

## 14. *Laurus nobilis* [Bay tree]

The essential oil of *Laurus nobilis* berries was also found to be potent against corona viruses. The presence of  $\beta$ -ocimene and 1.8-cineole in sweet bay berries oil gave an interesting anti SARS-CoV activity [24].

## 15. *Crocus Sativus* L [Saffron crocus]

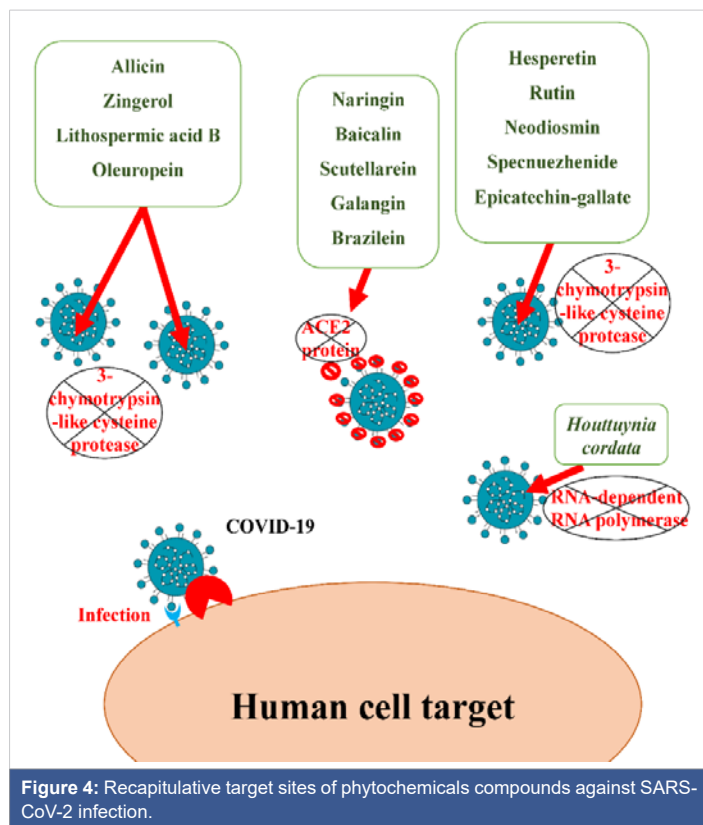
The flower of saffron crocus contains considerable amount of natural bioactive compounds like crocin, which is known as anti-HSV (Herpes simplex virus) and anti-HIV (human immunodeficiency viruses) agents (Table 1) [25,26]. A recent study revealed that crocin demonstrated good interaction with the receptor of SARS-CoV-2, similar to chloroquine [25].

## 16. Phytochemical compounds as Anti- SARS-CoV-2

Various phytochemical compounds proved to be promising in preventing and treating SARS-CoV-2 infection, are cited as follow: Amaranthin of (*Amaranthus tricolor*), Demethoxycurcumin of (*Curcuma longa* and *Curcuma xanthorrhiza*), Kaempferol of (*Spinacia oleracea*), Licoleafol of (*Glycyrrhiza uralensis*), Myricitrin, Myricetin 3-O-beta-D-glucopyranoside, 3,5,7,3',4',5'- hexahydroxy flavanone-3-O-beta- D-glucopyranoside of (*Myrica cerifera*), Methylrosmarinat, Calceolarioside B of (*Fraxinus Sieboldiana*), 5,7,3',4'-Tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone of (*Psoralethamnus arborescens*), (2S)-Eriodictyol 7-O-(6''-Ogalloyl)-beta-D-glucopyranoside and Epicatechin-gallate of (Green tea). These phytochemicals have found to be active against 3-chymotrypsin-like cysteine protease in SARS-CoV-2 [4,6]. In addition, Brazilein and Galangin extracted from *Caesalpinia sappan* and *Alpinia galanga*, respectively inhibited the ACE2 protein (Figure 4) [13]. Hence, we assumed that the compounds of flavonoid derivatives appear to be the most effective natural agents in inhibiting COVID-19 infection. As quercetin and its derivate found to be effective in blocking of SARS-CoV helicase activity by inhibiting the duplex DNA-unwinding activity, the ACE2 protein, and the 3-chymotrypsin-like cysteine protease activity. Similarly, luteolin, psoralidin, neobavaisoflavone, catechin, tomentin and its derivate could be served as a potential drug with the papain-like protease activity and acting as proteolytic agent against viral infections [27]. Therefore, the quercetin, catechin, genistein, and taxifolin molecules are acting as inducers of metallothioneins, especially Zn-ionophores, which showed potential antiviral properties and promising for the SARS-CoV-2 treatment [28].

Moreover, from a biological and pharmacological point of view, it is very important to note the vital activity of the





avarol molecule extracted from marine sponge *Dysidea avara Schmidt* in some pharmacological effects such as HIV-like infections [29]. The derivatives of this molecule can also inhibit acetyl cholinesterase activity and could be a promising in neurodegenerative disorders such as Alzheimer's disease [30].

## Conclusion

The current review summarized the principal medicinal plants and their phytochemicals compounds that have been screened *in silico* as promising preventive and curative candidate against SARS-CoV-2 infection. While, flavonoids showed the most potent activity. The main target sites of these compounds are the inhibition of 3-chymotrypsin-like cysteine protease, ACE2 protein, and viral replication. Overall, it is necessary to conduct further investigations to verify the *in vivo* potentiality of these phytochemicals compounds on SARS-CoV-2 infection. As well as, the interest should be taken on the use of bio-nanomaterials to benefit from the precise and high effect of the bioactive molecule.

## Author contributions

SH, NJ, and RH were responsible for the writing of the manuscript. AL corrected the manuscript. AC designed, corrected, and approved the manuscript.

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