
**REVIEW ARTICLE**

# Are Plant-derived Flavonoids the Emerging Anti-coronavirus Agents?

Firdous Sayeed Mohammad<sup>1\*</sup>, Mohsina F. Patwekar<sup>2</sup>, Faheem I. Patwekar<sup>3</sup>,  
Hunashal Sarah Priya Basawaraja<sup>2</sup>

<sup>1</sup>Department of Pharmacology, Calcutta Institute of Pharmaceutical Technology and AHS, Uluberia, Howrah 711316, West Bengal, India

<sup>2</sup>Department of Pharmacology, Luqman College of Pharmacy, Gulbarga 585102, Karnataka, India

<sup>3</sup>Department of Pharmacognosy, Luqman College of Pharmacy, Gulbarga 585102, Karnataka, India

\***Corresponding Author:** Prof. Firdous Sayeed Mohammad, **Email:** firdous.oncology@gmail.com, **Tel:** +918116427040

**Received:** March 8, 2022; **Accepted:** April 19, 2022; **Published:** April 29, 2022 **DOI:** 10.36922/itps.v4i2.42

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## Abstract:

The current outbreak of coronavirus disease 2019 (COVID-19), which is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has negatively impacted the global health and economy. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) shares many similarities with SARS-CoV and Middle East respiratory syndrome-related coronavirus. Within the past 20 years, these three highly pathogenic and deadly viruses have caused serious global infections and mortalities. It has been identified that the 3C-like protease (3CLpro) enzyme in coronaviruses can be a major therapeutic target for combating these serious infections. Therefore, flavonoids are believed to hold high potential in eliminating the viruses and infections. Flavonoids are polyphenolic secondary metabolites found in plants and have been demonstrated for their notable benefits for health. The antiviral activity of flavonoids has been reported in recent studies. Flavonoids, such as apigenin, quercetin, luteolin, amentoflavone, epigallocatechin gallate, gallic acid, and kaempferol, are known to be able to fight against coronaviruses by reducing the 3CLpro activity, according to the docking studies. Besides, we also found that several flavonoids have the potential to suppress the inflammatory cytokines, which are generally expressed in the lungs of coronavirus-infected individuals. However, the studies utilizing 3CLpro using various scaffolds of flavonoids need to be performed for better understanding on the antiviral potential of flavonoid derivatives against 3CLpro.

**Keywords:** COVID-19, SARS, MERS, 3C-like protease, Flavonoids

## 1. Introduction

An outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that causes coronavirus disease 2019 (COVID-19) has caused serious health threats and economic burden worldwide. At present, researchers are testing on a variety of possible treatments for COVID-19 [1]. However, it is very important to

identify the symptoms of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome-related coronavirus (MERS-CoV) that include cough, high fever (body temperature greater than 38°C), chills, convulsions, migraines, wooziness, lymphocytopenia, and dynamic radiographic changes of the chest [2]. The severe condition of severe acute respiratory syndrome (SARS) will lead to acute infectious

pneumonia that may cause death in people more than 60 years old [3].

Due to the rapid spread of COVID-19 through human-to-human transmission, the cases are still on the rise. Furthermore, Middle East respiratory syndrome (MERS) caused by MERS-CoV raised terror of conceivable reoccurrence of SARS or related hazardous diseases [4,5]. Since there is no powerful treatment for these viral diseases, developing anti-coronavirus drugs against future outbreaks are very imperative.

Numerous plants have been recognized for possessing antiviral activity; however, not many of them have been utilized to treat viral diseases clinically [6]. *In vivo* and *in vitro* testing has been used to investigate the antiviral activity of medicinal plants. A group of Canadian researchers has demonstrated antiviral properties of some widely available flavonoid-rich fruits, such as grape, apple, and strawberry, as well as other organic product juices against herpes simplex infection, coxsackievirus B5, poliovirus I, and echovirus [7]. Hence, in this context, this review consolidates the recent reports on targeting coronaviruses using flavonoids.

## 2. 3C-like protease (3CLpro)

In the genome of coronaviruses, there are two overlapped open reading frames (ORF), namely, ORF1a and ORF1b, which encode two polyproteins, that is, pp1a and pp1ab. 3CLpro and a papain-like protease degrade these polyproteins, yielding 16 non-structural proteins. These protease enzymes are crucial for the replication of coronaviruses; therefore, they could serve as potential therapeutic targets for drug development against coronaviruses [8].

A number of studies have demonstrated the effects of flavonoids on 3CLpro of coronaviruses. Binding of flavonoids inhibits the activity of this protease enzyme (**Figure 1**). Many well-known flavonoids could inhibit 3CLpro by binding with S1 or S2 pocket of 3CLpro. Interactions of flavonoids with 3CLpro showed top-grade structures (as per glide score) of some flavonoids, as recapitulated in **Table 1**. Rhoifolin showed the highest glide score, which indicates a good affinity of this molecule to 3CLpro. Kaempferol and morin are two close analogs that show almost similar glide score [9].

## 3. Flavonoids as anti-coronavirus agents

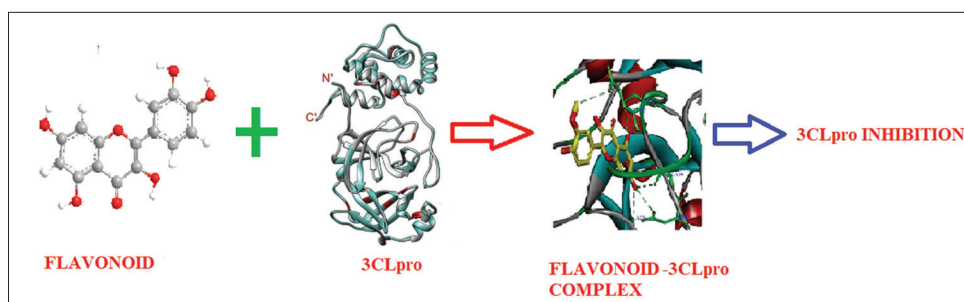
As a group of naturally occurring phenolic structures, flavonoids are widely present in plants. These naturally occurring chemicals are notable for their valuable benefits for health. Docking studies of flavonoids against the various targets/enzymes have demonstrated its inhibitory potential against many disease conditions [10,11]. The suppression of 3CLpro is thought to be the direct trigger of antiviral action of some flavonoids against coronaviruses. The 3CLpro is fundamental for SARS-CoV replication and is a promising target of drugs [12].

In 2010, Ryu *et al.* demonstrated the inhibitory effect of bioflavonoids isolated from *Torreya nucifera* on SARS-CoVs 3CLpro [13]. Amentoflavone showed the most profound inhibitory effect against SARS-CoV 3CLpro. Another three flavonoids, namely, quercetin, apigenin, and luteolin, have also been found to possess inhibitory activity against SARS-CoV 3CLpro [13]. Besides, quercetin, epigallocatechin gallate, and gallic acid have been found to impart inhibition of 3CLpro with an estimated  $IC_{50}$  of 73, 73 and 47  $\mu$ M, respectively [12].

In a previous study, an extract of *Isatis indigotica* roots, five major compounds of the roots, and seven phenolic compounds were examined for anti-SARS-CoV 3CLpro activity using cell-free and cell-based cleavage assays. It was observed that sinigrin was effective in blocking the cleavage processing of the 3CLpro in the cell-based assay. Only two phenolic compounds aloe-emodin and hesperetin were found to show dose-dependent inhibition of cleavage activity of the 3CLpro in the cell-based assay [14].

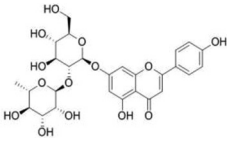
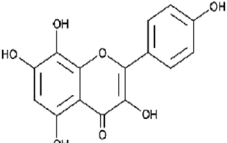
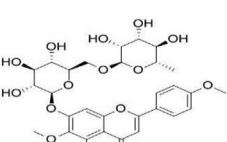
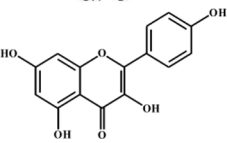
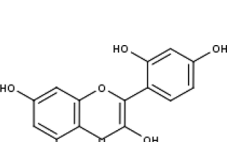
The peel of citrus fruits is rich in flavonoids and recently has been studied against coronaviruses based on the fact that hesperetin could act as a strong inhibitor of SARS-CoV 3CLpro. Moreover, molecular docking was carried out to anticipate the coupling of citrus flavonoids to angiotensin-converting enzyme 2 (ACE2), which is a receptor used by the coronaviruses to gain entry into the host cells, and the researchers obtained positive results in this regard [15].

A team of researchers used a flavonoid database to find potential antagonistic flavonoids against



**Figure 1.** Inhibition of 3CLpro through complexation with flavonoid. Flavonoids bind to S1 or S2 pocket and inhibit the activity of 3CLpro.

**Table 1.** Glide gscores of some flavonoids from the fit docking study

S. No.	Flavonoids	Structure	Glide gscore
1.	Rhoifolin		-9.56
2.	Herbacetin		-9.26
3.	Pectolinarin		-8.05
4.	Kaempferol		-8.52
5.	Morin		-8.93

SARS-CoV 3CLpro and they discovered that herbacetin, rhoifolin, and pectolinarin effectively blocked SARS-CoV 3CLpro's enzymatic activity, which has been validated using a tryptophan-based fluorescence approach. An induced-fit docking study has proven that flavonoids have higher affinity to S1, S2, and S3 sites of the target [9].

A protein coded by the ORF3a in SARS-CoV is involved in the formation of a cation-specific channel, which may be expressed in the infected cell. This cation-specific channel is responsible

for virus release and thus, the inhibition of this channel could be a source for the development of novel antiviral agents. Based on this hypothesis, flavonols kaempferol, kaempferol glycosides, and acylated kaempferol glucoside derivatives have been studied to evaluate their potency to block the 3a channel using *Xenopus* oocytes. It was found that kaempferol glycosides are the potential candidates for targeting the 3a channel proteins of coronaviruses [16].

Based on the above-mentioned literature, flavonoids such as apigenin, quercetin, luteolin, amentoflavone, epigallocatechin, gallic acid, and kaempferol have been reported to block the proteolytic activity of SARS-CoV 3CLpro. Therefore, it is presumed that flavonoids may suppress the activity of coronaviruses through the inhibition of SARS-CoV 3CLpro. Despite that, a thorough investigation on numerous flavonoid scaffolds is required. Recently, an assay was conducted on different flavonoids to find the best scaffold in a bid to inhibit the proteolytic function of SARS-CoV 3CLpro. Among them, herbacetin, rhoifolin, and pectolinarin were found to show potent anti-SARS-CoV 3CLpro activity [9].

Targeting the ACE2 receptor is a well-known treatment approach. Both SARS-CoV and SARS-CoV-2 demonstrated good capacity to interact to mammalian ACE2 receptor due to the high degree of similarity of the receptor-binding domain of S protein. The binding affinity of several flavonoids to ACE2 and/or S protein has been investigated in molecular docking study. Hesperetin, myricetin, linebacker, and caflanone have been demonstrated to have high interaction affinity for S protein, helicase, and ACE2 receptor, and can, therefore, prevent virus entry into the cells [17]. A study found that naringenin binds to ACE2 receptor with

a minimal binding energy, suggesting a strong binding affinity for ACE2 [15]. In comparison to abacavir and hydroxychloroquine, baicalin flavonoid has superior binding selectivity to S protein, according to the molecular simulation. Baicalin has also been linked to antiviral efficacy in the treatment of various viral illnesses [18].

Human transmembrane serine protease 2 (TMPRSS2) is required for viral initiation through S protein degradation [19]. The results of an *in silico* analysis revealed that neohesperidin, myricitrin, quercitrin, naringin, and icariin have a significant interaction potential with TMPRSS2 [20]. Silybin also has a strong affinity for TMPRSS2, which is needed for viral entry, and chrysin may have an exceptional binding interaction for the main protease of SARS-CoV, MERS-CoV, and SARS-CoV-2, according to a thorough simulation study. Chrysin is also found to prevent ACE2 from interacting with the S protein of SARS-CoV-2 [21].

At an  $IC_{50}$  of 73 M, quercetin showed substantial inhibitory activities against SARS-CoV main protease expressed in *Pichia pastoris* [12]. Administration of quercetin coupled with Vitamin C has been demonstrated to engender immunomodulatory properties. Both quercetin and Vitamin C have a synergistic impact that can be used to prevent disease in high-risk people [22]. Likewise, flavonoids such as herbacetin, rhoifolin, and pectolinarin can effectively inhibit the enzymatic activities of SARS-CoV main protease [9]. By assessing fractionation-based anti-papain protease function of the methanolic extract of *Paulownia tomentosa* fruits, researchers have discovered that several geranylated flavonoid derivatives possess potent inhibitory impact on SARS-CoV papain protease [23].

It has been found that hesperetin and naringenin reduce the transcription of tumor necrosis factor (TNF)- $\alpha$  in murine adipocytes in an *in vitro* investigation. This leads to the inhibition of the nuclear factor kappa B (NF- $\kappa$ B) pathway, which, in turn, suppresses the production of interleukin (IL)-6 [24]. Hesperetin boosts the transcription of peroxisome proliferator-activated receptor gamma in animals after acute lung damage and suppresses NF- $\kappa$ B pathway, resulting in a considerable decrease in the supply of inflammatory cytokines, such as IL-6, IL-1 $\beta$ , and TNF- $\alpha$  [25]. Hesperetin

pre-treatment of murine lungs with acute injury resulted in a protection against pulmonary inflammatory responses, as well as a reduction in TNF- $\alpha$  and IL-6 levels [26].

Fisetin has been found to have anti-inflammatory and immunomodulatory properties. Fisetin pre-treatment of IL-1 $\beta$ -stimulated human lung epithelial cells resulted in cyclooxygenase 2 (COX-2) inhibition and decreases in IL-6, IL-8, TNF- $\alpha$ , chemokine (c-c motif) ligand 5, and prostaglandin E2. Fisetin inhibits the phosphorylation of proteins in the extracellular signal-regulated kinase or ERK1/2 pathway and decreased expression of the NF- $\kappa$ B pathway, resulting in a considerable decrease in intercellular adhesion molecule 1 production, which is important for monocyte adhesion [27].

Naringenin has been demonstrated to have immunomodulatory properties, which help lower the intensity of systemic inflammation [28]. In an animal study where rats were exposed to benzo[ $\alpha$ ]pyrene, naringenin elicited beneficial effect by decreasing pro-inflammatory mediators through NF- $\kappa$ B repression, which led to a reduction in COX-2 transcription and restoration of normal histological characteristics in the rats' lungs [29]. Additional investigation also found that naringenin reduced the transcription of NF- $\kappa$ B, inducible nitric oxide synthase, and TNF- $\alpha$  in the lungs of rodents with sepsis [30]. Furthermore, naringenin drastically decreased the generation of inflammatory cytokines, pulmonary edema, IL-6, and myeloperoxidase activity [30]. The current treatments could reduce the length of sickness but are unable to improve life expectancies [31]. Therefore, further research into naringenin as an immunomodulatory drug in SARS-CoV-2 infection is needed.

Overall, the suppression of NF- $\kappa$ B and reduced levels of pro-inflammatory cytokines by the above-mentioned flavonoids can bring about beneficial effects to the coronavirus-infected patients by reducing the lung inflammation. Although hesperetin, naringenin, and fisetin have not been clinically proven for their anti-coronavirus properties, the aforementioned *in vitro*, *in vivo*, and *in silico* studies have provides some insights into the potential of flavonoids in counteracting inflammation in the coronavirus infections.

#### 4. Prospects and challenges

Numerous studies have been conducted to examine the anti-viral and anti-inflammation activities of flavonoids. Despite the lack of clinical studies in this regard, flavonoids may play a complementary role in reducing inflammation and giving symptomatic relief in combination with the anti-coronavirus regimen. In addition, flavonoids are known for their high levels of antioxidants. Thus, flavonoids hold promise in being complementary medicine or supplements to infected individuals who take anti-coronavirus treatments. Nevertheless, caution should be practiced in the dosing of flavonoids since its effects are dose-dependent and its application should depend on the severity of infection. One of the major challenges of using flavonoids to treat coronavirus infections or other diseases is that they undergo auto-oxidation easily; this explains why flavonoids are relatively unstable and their beneficial effects cannot be fully maximized under normal conditions. Thus, flavonoids should be appropriately formulated to minimize auto-oxidation.

#### 5. Conclusion

Flavonoids are naturally occurring compounds with diverse structure biological activities. These compounds may counteract against and block SARS-CoV 3CLpro. For this reason, in addition to biochemical assays, more *in silico* studies should be performed to predict and screen for other flavonoid derivatives that could act against SARS-CoV 3CLpro. Aside from the ability to block SARS-CoV 3CLpro, flavonoids also possess anti-inflammatory activity by decreasing the activity of NF- $\kappa$ B pathway and the expression of inflammatory cytokines. Hence, flavonoids could be a group of emerging compounds that have anti-coronavirus and anti-inflammation potential.

#### Conflict of interest

The authors have declared that there is no conflict of interest.

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