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REVIEW

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Naringenin, a flavanone with antiviral and anti-inflammatory effects: A promising treatment strategy against COVID-19

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At the end of 2019, a novel flu-like coronavirus named COVID-19 (coronavirus disease 2019) was recognized by World Health Organization. No specific treatments exist for COVID-19 at this time. New evidence suggests that therapeutic options focusing on antiviral agents may alleviate COVID-19 symptoms as well as those that lead to the decrease in the inflammatory responses. Flavonoids, as phenolic compounds, have attracted considerable attention due to their various biological *properties*. In this review, the promising effects and possible mechanisms of action of naringenin, a citrus-derived flavonoid, against COVID-19 were discussed. We searched PubMed/Medline, Science direct, Scopus, and Google Scholar databases up to March 2020 using the definitive keywords. The evidence reviewed here indicates that naringenin might exert therapeutic effects against COVID-19 through the inhibition of COVID-19 main protease, 3-chymotrypsin-like protease (3CLpro), and reduction of angiotensin converting enzyme receptors activity. One of the other mechanisms by which naringenin might exert therapeutic effects against COVID-19 is, at least partly, by attenuating inflammatory responses. The antiviral activity of the flavanone naringenin against some viruses has also been reported. On the whole, the favorable effects of naringenin lead to a conclusion that naringenin may be a promising treatment strategy against COVID-19.

KEYWORDS

ACE2 receptors, antiviral effects, *coronavirus main protease*, COVID-19, naringenin

Abbreviations: 3CLpro, *3-chymotrypsin-like protease*; ACE2, angiotensin converting enzyme; ALT, alanine transaminase; AMPK, AMP-activated protein kinase; ApoB100, apolipoprotein B100; ARDS, acute respiratory distress syndrome; Asp187, aspartic acid; AST, aspartate transaminase; BHK-21, Baby hamster kidney-21; CAT, catalase; CHIKV, chikungunya virus; COVID-19, coronavirus disease 2019; CoVs, Coronaviruses; COX-2, cyclooxygenase-2; DENV, dengue virus; Glu, glutamic acid; GPx, glutathione peroxidase; GR, glutathione reductase; HBV, hepatitis B virus; HCV, hepatitis C virus; His, histidine; IFNγ, interferon γ; IL, interleukin; iNOS, inducible nitric oxide synthase; LEU, leucine; LOOH, lipid hydroperoxides; LYS, lysine; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MERS-CoV, Middle East respiratory syndrome coronavirus; NF-κB, nuclear factor kappa B; NOX2, NADPH oxidase-2; NSV, sindbis neurovirulent strain; PDB, protein data bank; PGE_2, prostaglandin E_2; PLpro, papain-like protease; PPARα, peroxisome proliferator-activated receptor α; PRO, proline; RAS, renin-angiotensin system; RBD, receptor binding domain; RNS, reactive nitrogen species; ROS, reactive oxygen species; SARS, severe acute respiratory syndrome; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; Thr, threonine; TLR4, toll like receptor 4; TNF-α, tumor necrosis factor-alpha; VLDL, very low-density lipoprotein; WHO, World Health Organization; ZIKV, Zika virus.

1 | INTRODUCTION

Coronaviruses (CoVs) are the well-known cause of severe respiratory, enteric, and systemic infections in both animals and humans (Malik et al., 2020). CoVs are the subfamily Orthocoronavirinae in the family of Coronaviridae, and this subfamily includes alpha-, beta-, gamma-, and delta-CoVs (Shereen, Khan, Kazmi, Bashir, & Siddique, 2020; Woo & Lau, 2019). At the end of 2019, a novel flu-like coronavirus named COVID-19 (coronavirus disease 2019) was recognized by World Health Organization (WHO) and there was an evidence of the sustained human-to-human transmission by close contacts (Peng et al., 2020). Nowadays, the global prevalence of COVID-19 has

reached pandemic proportions, which resulted in a great concern of public health worldwide (Sehn, 2020). Currently, no specific treatments exist for COVID-19 (Guo et al., 2020), and up to April 7, 2020, more than 1,279,000 cases of COVID-19 have been reported by WHO. Severe acute respiratory syndrome (SARS-CoV-2) has affected 211 countries worldwide (WHO, 2020). The acute respiratory distress syndrome (ARDS) is the most prevalent cause of death among the patients with COVID-19 that finally leads to multiple organ failure and sepsis (Wang, Zhao, Xu, & Gu, 2020). The groups who are at the highest risk of COVID-19 are older adults and subjects with major chronic diseases such as cancers, diabetes, and hypertension (The, 2020). The outbreak of SARS in 2002 in China's Guangdong province, and the prevalence of Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 in the Kingdom of Saudi Arabia have demonstrated the lethality of CoVs when they cross the species barrier and then infect humans (Schoeman & Fielding, 2019; Zhong et al., 2003).

The most important reason for the high transmission rate of COVID-19 is genetic recombination event at S protein in the receptor binding domain (RBD) region of this virus (Ghaffari, Roshanravan, Tutunchi, Ostadrahimi, & Kafil, 2020; Zhu et al., 2020). SARS-CoV-2 RNA sequence has almost 30,000 bases in length (Xiao et al., 2020), and the analysis of whole-genome sequencing data has exhibited a strong similarity between SARS-CoV-2 and SARS-CoV in the RBD (Zhang & Holmes, 2020). SARS-CoV-2 RBD has a great binding affinity to the human angiotensin-converting enzyme 2 (ACE2) receptors, which are widely expressed in various cells belonged to kidney, lung, brain, and digestive tract. ACE2 can negatively modulate the renin-angiotensin system (RAS) through the degradation of angiotensin II, and can play a protective role against the progression of acute lung failure (Madjid, Safavi-Naeini, Solomon, & Vardeny, 2020). SARS-CoV-2 seems to infect host cells through ACE2 (Diaz, 2020). It is supposed that, the decreased ACE2 activity in host-cell membranes may reduce the ability of SARS-CoV-2 to enter cells (Letko, Marzi, & Munster, 2020). According to the current theory, the entrance of the virus into cells increases the inflammatory activity, which leads to serious damages, especially in the respiratory tract. Collectively, COVID-19 seems to be the fifth endemic CoV worldwide. Since an established vaccine or medication is yet to be discovered against this viral infection, preventive policies are very crucial at this time. New evidence suggests that therapeutic options focusing on antiviral agents may alleviate COVID-19 symptoms as well as those that lead to the decrease in the inflammatory responses (Monteleone & Ardizzone, 2020; Stebbing et al., 2020). Various important biological activities of flavonoids, as phenolic compounds, have been reported that include antiviral, anti-inflammatory, therapeutic, antibacterial, and other properties in nature (Tapas, Sakarkar, & Kakde, 2008). Among the naturally occurring flavonoids, naringenin, due to its potent biological roles, is one of the most important flavonoids (Den Hartogh & Tsiani, 2019). Therefore, in the present study, we aimed to discuss the promising effects and possible mechanisms of action of naringenin, which is a flavonoid with antiviral and anti-inflammatory activities, against COVID-19.

2 | METHODS

2.1 | Search strategy

We investigated four most popular search engines PubMed/Medline, Science direct, Scopus, and Google Scholar using the following keywords: "naringenin" or "naringenin7-sulfate" or "4′ 5 7-trihydro xyflavanone" in the title and "viral diseases" or "virus-related diseases" or "*infectious disease*" *or* "inflammatory lung diseases" or "lung injury" or "*inflammation*" or "COVID-19″ or "coronaviruses" in the title or abstract. Relevant studies published in the English language up to March 2020 were eligible. All articles evaluating the effects of naringenin on viral diseases, *infectious disease*, *and* inflammatory lung diseases were included. Studies with insufficient information were excluded from the review. To minimize the loss of studies, the reference lists of articles that were included were also reviewed to identify additional studies. The articles identified in the search were saved in an EndNote software file and sorted to remove duplicate reports. The remaining studies were examined for choosing eligible articles. Then, the full texts of the screened articles were critically analyzed for extraction of data.

2.2 | Results

In total, 103 potentially title/abstract were retrieved by the search strategy, of which 71 were considered after removal of duplicate articles. Of these, 58 articles were excluded because of not providing the inclusion criteria. Finally, 13 articles were included in the present study based on the research topic. Figure 1 presents the diagram for the search and selection process of the present review. Details of the selected studies are presented in Table 1.

3 | FLAVONOIDS AND COVID-19

Based on the available information, 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro), as CoV-encoded proteins, play crucial roles in CoV replication, and also exert essential roles in the inhibition of host innate immune responses (Baez-Santos, St John, & Mesecar, 2015). Therefore, targeting these proteases appears to be pivotal for the treatment of COVID-19 (Tahir Ul Qamar, Alqahtani, Alamri, & Chen, 2020). Recent data suggests that some metabolites from a group called flavonoids can inhibit the activity of these proteins. In fact, flavonoid compounds attach to the active site of proteins, and then inactivate them (Sawikowska, 2020). Moreover, flavonoids are a large class of plant pigments by having many subgroups including chalcones, flavones, flavonols, and isoflavones (Panche, Diwan, & Chandra, 2016). Flavonoids have been shown to have multiple functions including antioxidant activity, free radical scavenging capacity, hepatoprotective, anti-inflammatory, anticancer, and antibacterial effects, as well as the potential antiviral activities (Pietta, 2000). In this regard, Shimizu et al. (2017) demonstrated that

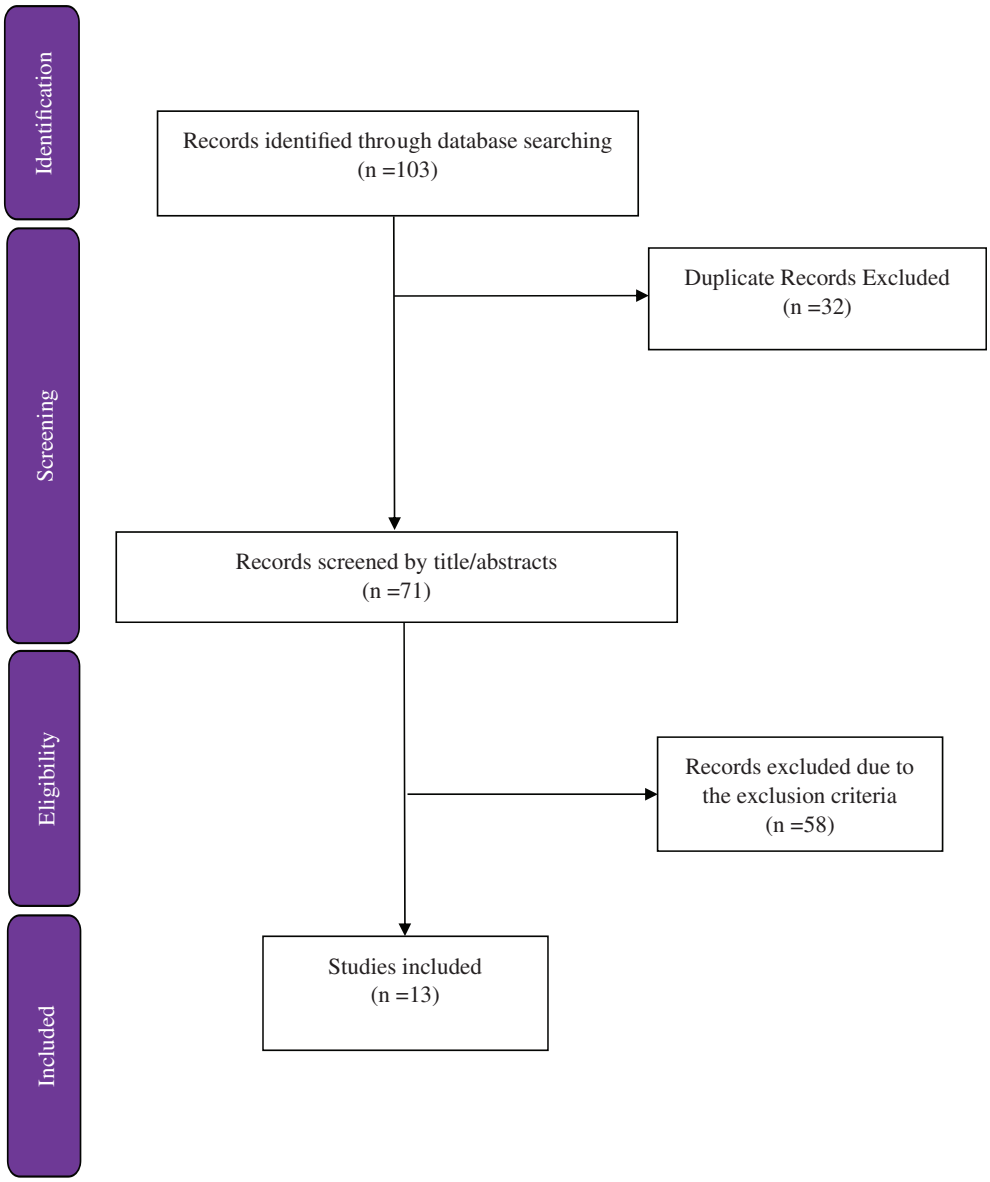

FIGURE 1 Flow diagram of the literature search and study selection process [Colour figure can be viewed at wileyonlinelibrary.com]

flavonoids could act against hepatitis C virus (HCV) infection by blocking the entry stage of HCV cycle. As a citrus flavonoid, naringenin could alleviate HCV infection by causing a reduction in apolipoprotein B100 (apoB100) secretion, which is required for HCV infection (Hernandez-Aquino & Muriel, 2018). Mechanistically, it is documented that the antiviral activity of some flavonoids against SARS-CoV-2 can be mediated through their ability in blocking 3CLpro (Jo, Kim, Shin, & Kim, 2020).

4 | NARINGENIN

Among flavonoids, naringenin with the chemical name of 4′ 5 7-trihydroxyflavanone, is considered as one of the most important flavonoids, mainly a flavanone, due to its potential biological activities such as antioxidant, anti-inflammatory, and antiviral properties (Den Hartogh & Tsiani, 2019). Naringenin is the aglycone of naringin, known as the bitter component of citrus fruits (Ameer, Weintraub, Johnson, Yost, & Rouseff, 1996). This flavanone is widely distributed in a variety of fruits and vegetables such as grapefruit, lemon, oranges, bergamot, and tomatoes; and thus, its consumption from the diet can be relatively high (Manchope, Casagrande, & Verri Jr., 2017). To date, oral bioavailability rate of naringenin is almost 5.81% and its absorption occurs through both passive diffusion and active transport in gastrointestinal tract (Kanaze, Bounartzi, Georgarakis, & Niopas, 2007). Moreover, Xu et al. (2009) demonstrated that the absorption rate of naringenin was 47, 42, and 39% in deudenum, terminal illeum, and jejunum, respectively. After absorption, naringenin binds to albumin and is then distributed in the highly perfused organs such as the liver, cerebrum, kidney, spleen, and heart (Erlund, Meririnne, Alfthan, & Aro, 2001). Finally, metabolites of naringenin can be excreted through biliary and urinary pathways (Barreca et al., 2017). Due to having several beneficial health effects, naringenin can be used in different pharmaceutical formulations to improve human health (Salehi et al., 2019). However, because of its

TABLE 1 Summary of studies evaluating antiviral and anti-inflammatory effects of naringenin

Articles	Type of study	Reference	Samples	Study design	Main results
Viral-related articles	In vitro	Paredes, Alzuru, Mendez, & Rodriguez-Ortega, 2003	BHK-21 were infected with NSV	Administration of naringenin: 25 μg/ml	Inhibition of viral replication up to 80%
	In vitro, In vivo	Nahmias et al., 2008	Huh7.5.1human hepatoma cell line were infected with HCV; male mice were infected with HCV	Administration of naringenin: 200, 1,000, and 5,000 μM	Silencing apoB100 messenger RNA, a 70% reduction in the secretion of both apoB100 and HCV, a 80% reduction in HCV secretion in infected cells, a decrease in TG levels following injection
	In vitro	Goldwasser et al., 2011	Huh7.5.1 human hepatoma cell line infected with HCV	Administration of naringenin: 200 μM	A dose-dependent inhibition of HCV production without affecting intracellular levels of the viral RNA or protein, inhibition of the assembly of intracellular infectious viral particles, a rapid 1.4 log reduction in HCV similar to 1,000 U of interferon
	In vitro	Zandi et al., 2011	Vero cells infected with DENV-2	Administration of Naringenin: 50 μg/ml	A decrease in the DENV-2 RNA level by 50% with naringenin compared to the non-treated virus inoculum
	In vitro	Ahmadi et al., 2016	BHK-21 were infected with CHIKV; Vero cells were infected with CHIKV	Administration of naringenin: Up to 500 μM	Reduction of the CHIKV intracellular replication efficiency and downregulation of the production of viral proteins involved in replication
	In vitro	Frabasile et al., 2017	Huh7.5 cells were infected with DENV; primary human monocytes were infected with DENV	Administration of naringenin: 250 μM	Inhibition of DENV replication with an efficiency similar to IFN-α 2A and ribavirin, a reduction in the number of DENV-infected cells
	In vitro	Cataneo et al., 2019	Human A549 cells were infected with ZIKV; primary human monocyte-derived dendritic cells were infected by ZIKV	Administration of naringenin: 15.6, 31.25, 62.5 and 125 μM	Inhibition of viral replication or assembly of viral particles
	Human	Goncalves et al., 2017	43 adult patients with chronic HCV	Supplementation with 500 ml/day orange juice containing 2.7 mg naringenin	Protection against harmful effects of HCV by an increase in antioxidant capacity and a decrease in inflammation
	Quantitative analysis	Alam, Parvez, Arbab, & Al-Dosari, 2017	*Guiera senegalensis*	Sensitive RP-/NP-HPTLC methods	Exhibiting anti-HBV activity of *Guiera senegalensis* including naringenin
Inflammation-related articles	In vivo	Fouad, Albuali, & Jresat, 2016	Induced-lung injury rats	Administration of naringenin: 50, 100 mg/kg	Attenuating the production of inflammatory cytokines, pulmonary edema, neutrophil recruitment, myeloperoxidase activity, and reduction of oxidative/nitrosative stress markers
	In vivo	Ali et al., 2017	Rats with lung damage	Administration of naringenin: 100 mg/kg	Downregulation of the expression of NF-κB and COX2

TABLE 1 (Continued)

Articles	Type of study	Reference	Samples	Study design	Main results
COVID-19 related articles	Molecular docking analysis	Cheng et al., 2020	Citrus fruit flavonoids including naringenin	Docking analysis	Reduction of ACE2 receptor activity through the binding of naringenin to ACE2 with binding site proline, leucine, and lysine
	Molecular docking analysis	Khaerunnisa, Kurniawan, Awaluddin, Suhartati, & Soetjipto, 2020	6 LU7 and native ligands including naringenin	Docking analysis	Inhibition of COVID-19 main protease through the interaction of naringenin with amino acids histidine, glutamic acid, aspartic acid, and threonine in the CoV main protease active site

Abbreviations: ACE2, angiotensin-converting enzyme 2; apoB100, apolipoprotein B100; BHK-21, baby hamster cells 21 clone 15; CHIKV, chikungunya virus; DENV, *dengue* virus; HBV, hepatitis B virus; HCV, hepatitis C virus; IFN-α 2A, interferon-alpha 2A; NSV, sindbis neurovirulent strain; PR-/NP-HPTLC, reverse phase−/normal phase-high performance; TG, triglyceride; Vero cells, african green monkey kidney cells; ZIKV, zika virus.

limited bioavailability, some formulations like naringenin-loaded nanoparticles have been developed to resolve the limited bioavailability of naringenin (Zobeiri et al., 2018). In 1996, the first study was conducted on the toxicity of naringenin. In a model system of the isolated rat liver nuclei, naringenin induced a concentration-dependent peroxidation of nuclear membrane lipids along with DNA strand breaks (Sahu & Gray, 1997). In addition, naringenin can be oxidized to generate naringenin phenoxyl radicals (Galati, Moridani, Chan, & O'Brien, 2001) and it also exhibited a medium lethal dose LD(50) > 5,000 mg/kg (Ortiz-Andrade et al., 2008). However, due to the relatively low bioavailability and the rapid metabolism and elimination of most of the flavonoids like naringenin, no side effects have been reported by consuming them (Clark, Zahradka, & Taylor, 2015). In this regard, a pharmacokinetic study exhibited no undesirable or adverse effects after the oral administration of naringenin in the human subjects (Kanaze et al., 2007). Similarly, no side effects were observed in a clinical study that assessed the efficacy and safety of polyphenolic citrus dry extract including naringenin among the healthy overweight subjects (Dallas et al., 2014). However, due to the lack of adequate studies performed on the safety and toxicity of naringenin, this flavanone should be cautiously used in clinical settings (Hernandez-Aquino & Muriel, 2018).

4.1 | Antiviral effect of naringenin

Flavonoids have been reported to have some biological activities against several types of viruses (Cataneo et al., 2019). The antiviral activity of the flavanone naringenin against some viruses such as HCV, Chikungunya virus (CHIKV), Dengue virus (DENV), and Zika virus (ZIKV) has been tested. Also, it was demonstrated that HCV production by human hepatocytes is dependent on the expression of apoB100 and the assembly of very low-density lipoprotein (VLDL) (Huang, Sun et al., 2007). Administration of 200 μM naringenin to the Huh7.5.1 human hepatoma cell infected by HCV, led to the inhibition of apoB100-dependent HCV secretion. In addition, it was reported that naringenin resulted in silencing of the apoB mRNA in the infected cells and also caused a 70% reduction in the release of both apoB100 and HCV (Nahmias et al., 2008). In another study, naringenin administration inhibited HCV secretion with no effect on intracellular viral RNA or on protein levels. The assembly of infectious virus particles was also blocked by naringenin. Moreover, by activating peroxisome proliferator-activated receptor α (PPARα), naringenin led to a reduction in VLDL production, which is necessary for secretion of HCV particles (Goldwasser et al., 2011). HCV infection leads to oxidative stress due to the stimulation of cell metabolism, with a decrease in the activity of antioxidant enzymes and an increase in the activity of liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST) (Goncalves et al., 2017). Goncalves et al. (Goncalves et al., 2017) demonstrated that intake of 2.7 mg naringenin in the patients with hepatitis C results in a great reduction in lipid profile and liver enzyme AST. Therefore, naringenin can improve HCV infection, and in a dose-dependent manner, its administration can inhibit the post entry stages of CHIKV replication activity by downregulating the production of the viral proteins involved in replication. Prevention of CHIKV intracellular replication in CHIKV infected hamster kidney cells was caused by the administration of 6.818 μM naringenin (Ahmadi et al., 2016). Additionally, naringenin (250 μM) showed a direct virucidal activity against DENV type-2 (DENV-2) infection, while it did not inhibit viral replication (Zandi et al., 2011). However, in another study, naringenin administration to infected Huh7.5 cells could inhibit all of the DENV serotypes replication (Frabasile et al., 2017). In a study by Cataneo et al. (2019) ZIKV infection in human A549 cells was inhibited by naringenin administration in a concentration-dependent manner. The antiviral activity of naringenin was also found when the primary human monocyte-derived dendritic cells were treated after infection. Accordingly, this finding suggests that naringenin can inhibit viral replication or assembly of viral particles. In addition, an interaction between the protease domain of the NS2B-NS3 protein of ZIKV and naringenin can explain the anti-ZIKV activity of naringenin (Cataneo et al., 2019). Also it was shown that, in baby hamster cells 21 clone

15 (BHK-21), administration of 25 μg/ml naringenin blocked sindbis neurovirulent strain (NSV) replication up to 80% (Paredes et al., 2003). As an antiviral biomarker in *Guiera senegalensis*, a traditional medicinal plant, naringenin administration (0.14 μg/mg) could inhibit hepatitis B virus (HBV) life cycle either by targeting viral envelopes or by reverse-transcriptases (Alam et al., 2017). The summary of the studies demonstrating antiviral effects of naringenin is presented in Table 1.

4.2 | Antioxidant and anti-inflammatory activities of naringenin

The antioxidant activity of naringenin is attributed to hydroxyl substituents (OH) in its structure. These hydroxyl groups have high reactivity against reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Hernandez-Aquino & Muriel, 2018; Zaidun, Thent, & Latiff, 2018). Naringenin exerts its antioxidant activity by scavenging of free radicals, and by preventing lipid peroxidation-mediated oxidative DNA damage in a dose-dependent manner (Cavia-Saiz et al., 2010; Da Pozzo et al., 2017; Rashmi, Bojan Magesh, Mohanram Ramkumar, Suryanarayanan, & Venkata SubbaRao, 2018). In an experimental study, naringenin treatment was reported to decrease the levels of thiobarbituric acid reactive substances (TBARS), conjugated dienes, and lipid hydroperoxides (LOOH) (Chtourou et al., 2015). Furthermore, it could promote the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR) (Cavia-Saiz et al., 2010).

In addition to playing an antioxidant role, naringenin has been reported to exert a potent anti-inflammatory activity through the inhibition of nuclear factor kappa B (NF-κB) signaling pathway (Jayaraman, Jesudoss, Menon, & Namasivayam, 2012). NF-κB stimulates the expression of several important inflammatory proteins such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), cyclooxygenase-2 (COX-2), interleukin-1 (IL-1), and inducible nitric oxide synthase (iNOS) (Hernandez-Aquino & Muriel, 2018). Also, the results obtained from in vitro studies and in vivo animal models indicate that naringenin can downregulate the expression of several inflammatory markers such as toll like receptor 4 (TLR4), TNF-α, IL-1β, IL-6, iNOS, and COX-2 through the attenuation of the NF-κB pathway and the activation of the AMP-activated protein kinase (AMPK), which is associated with the inhibition of multiple pro-inflammatory signaling pathways (Yoshida et al., 2010; Zobeiri et al., 2018).

5 | ADVANTAGES OF NARINGENIN COMPARED TO OTHER IMPORTANT NATURAL ANTI-INFLAMMATORY AGENTS

Curcumin has been shown to regulate many transcription factors, cytokines, adhesion molecules, and enzymes associated with inflammation. In this regard, numerous studies have revealed the potential role of curcumin in the prevention and treatment of various pro-inflammatory diseases (Moballegh Nasery et al., 2020). Zerumbone, which is isolated from the tropical plant *Zingiber zerumbet* Smith, has been reported to have anti-inflammatory effects by inhibiting iNOS, COX-2 expressions, and prostaglandin E_2 (PGE_2) production (Prasannan et al., 2012). Thymoquinone is considered as the main active component in *Nigella sativa* that has been found to exert anti-inflammatory activities by reducing the expression of iNOS protein (Siveen, Ahn et al., 2014; Siveen, Mustafa et al., 2014). The NF-κB inhibition activity of honokiol, as a phenolic compound (Rajendran et al., 2012); escin, as the main active ingredient of *Aesculus hippocastanum* seed extract (Tan et al., 2010); pinitol, which is isolated from *Abies pindrow* leaves (Sethi, Ahn, Sung, & Aggarwal, 2008); and tocotrienols, which are the members of vitamin E family (Siveen, Ahn et al., 2014; Siveen, Mustafa et al., 2014), have also been reported.

Due to the dose-related side effects of curcumin and thymoquinone at the dosages of 12 g/day (Hewlings & Kalman, 2017) and 2–3 g/day (Goyal et al., 2017), respectively, the use of some novel agents like naringenin with no undesirable side effects, can be considered. In comparison to naringenin, zerumbone has shown antimicrobial effects against fungi and bacteria as well as some anti-inflammatory activities (Nagaraj, Shridhar, Nirguna Babu, & Gowrishankar, 2012). However, antiviral effects of zerumbone have not been reported yet. Although escin, pinitol, and tocotrienols exhibit anti-inflammatory and antiviral activities, the beneficial biological effects of naringenin on human health appear to be more extensive (Michelini, Alche, & Bueno, 2018; Mileva & Galabov, 2018; Sethi et al., 2008). In fact, flavonoid compounds have received much attention due to having many types of pharmacological activities including antioxidative, anti-inflammatory, anti-mutagenic, antimicrobial, hepatoprotective, and anti-carcinogenic effects (Panche et al., 2016). To the best of our knowledge, all the natural agents with the above-mentioned anti-inflammatory activities, except curcumin and thymoquinone, showed no inhibitory effect on COVID-19 main protease. However, naringenin is capable of inhibiting the enzymatic activity of CoV 3CLpro (Khaerunnisa et al., 2020).

6 | PROTECTIVE EFFECTS AND POSSIBLE MECHANISMS OF ACTION OF NARINGENIN AGAINST COVID-19

A recent study suggests that some flavonoids such as naringenin, kaempferol, quercetin, and apigenin are the most recommended compounds that may act as the potential inhibitors of SARS-CoV-2 main protease (Khaerunnisa et al., 2020). These agents share a pharmacophore similar to nelfinavir (Dabeek & Marra, 2019; Salehi et al., 2019). Nelfinavir is a protease inhibitor used in patients infected by the human immunodeficiency virus (HIV) (Yamamoto et al., 2004). Because proteases play essential roles in viral replication of different types of viruses, they may be considered as potential pharmacological targets for preventing CoV replication (Chang, Kim, Lovell, Rathnayake, & Groutas, 2019; Xin Liu & Wang, 2020). The COVID-19 main protease, Protein Data Bank (PDB) ID 6 LU7, is pivotal for the proteolytic maturation of CoV (Xin Liu & Wang, 2020). SARS-CoV-2 main protease or 3CLpro contains two chains, which make a

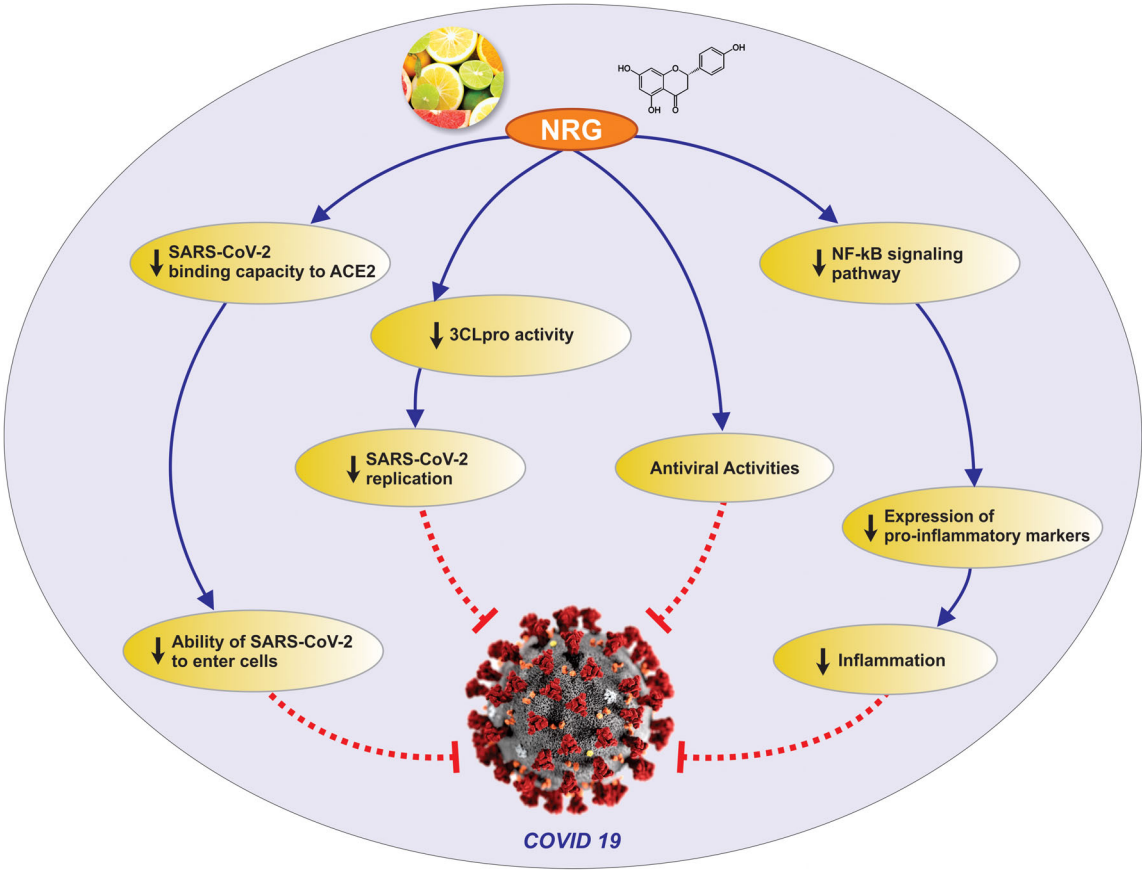

FIGURE 2 Possible mechanisms for the actions of naringenin against COVID-19. ACE2, angiotensin-converting enzyme 2; NRG, naringenin; NF-κB, nuclear factor kappa B; 3CLpro, 3-Chymotrypsin-like protease; SARS, Severe acute respiratory syndrome [Colour figure can be viewed at wileyonlinelibrary.com]

homodimer (Berman et al., 2002). The molecular docking analysis study demonstrated that naringenin binds to 3CLpro chains as a ligand and blocks its activity. The binding energy obtained from docking 6 LU7 with naringenin was −7.99 kcal/mol, which was associated with the number of H-bonds formed with 6 LU7. Naringenin H-bonds interact with amino acids histidine (His164), glutamic acid (Glu166), aspartic acid (Asp187), threonine (Thr190) in the CoV main protease active site. Altogether, due to the lower binding energy of naringenin and the presence of H-bonds, the affinity of naringenin bonds is high and this flavanone is capable of inhibiting the enzymatic activity of CoV 3CLpro (Khaerunnisa et al., 2020).

As it was mentioned earlier, it has also been indicated that CoVs use the ACE2 receptors to enter the host cells; thus, compounds that can reduce the ACE2 activity may be useful in the treatment of the patients with COVID-19 (Letko et al., 2020; Lu et al., 2020). A recent study has investigated the immunoregulatory effects of citrus flavonoids as well as their impacts on ACE2 activity. The binding affinity of these compounds to ACE2 was assessed by molecular docking. The interaction between naringenin and ACE2 was also examined by binding energy. The docking findings demonstrate that naringenin is able to bind to ACE2 with docking energy of −6.05 kcal/mol, with binding site proline (PRO-146), leucine (LEU-143), and lysine (LYS-131). On the whole, the findings of the recent study showed that the energy required for the binding between naringenin and ACE2 was low, so it could easily bind to ACE2. The authors concluded that naringenin might be a promising treatment strategy for COVID-19 (Cheng et al., 2020).

An emerging evidence demonstrates that the patients infected with SARS-CoV-2 have high levels of cytokines including TNF-α, IL-1β, IL-10, interferon γ (IFNγ), and monocyte chemoattractant protein-1 (MCP-1). These findings indicate that the cytokine storm contributes to disease severity (Huang, Wang et al., 2020). To date, corticosteroids may be beneficial if utilized at the early acute stages of infection (Russell, Moss, Rigg, & Van Hemelrijck, 2020). Therefore, the use of anti-inflammatory agents may be considered as a promising treatment approach to relieve COVID-19 symptoms (Stebbing et al., 2020). As it was mentioned earlier, naringenin exhibits a potent anti-inflammatory activity and can be recognized as an option to decrease cytokine levels of inflammatory markers including TNF-α, IL-1β, IL-10, and IFNγ in the patients with COVID-19 (Cheng et al., 2020). Also, a protective effect of naringenin against lipopolysaccharide-induced acute lung injury was reported in rats. Naringenin at two doses (50 and 100 mg/kg/day), significantly attenuated the production of inflammatory cytokines, pulmonary edema, neutrophil recruitment, myeloperoxidase activity, and

decreased the markers of oxidative/nitrosative stress in lungs of LPS-challenged rats (Fouad et al., 2016). Moreover, administration of 100 mg/kg naringenin to rats with lung damage led to the down regulation of the expressions of NF-κB and COX2 (Ali et al., 2017). Fan, Pan, Zhu, and Zhang (2017) also found that administration of 5–20 mg/kg naringenin to Wistar rats with arthritic inflammation resulted in a decrease in TNF-α and NF-κB mRNA levels. Furthermore, an in vivo study demonstrated a reduction in NF-κB, TNF-α, IL-6, and IL-1β after naringenin administration (Hua et al., 2016). Besides, in the mice treated with 10 mg/kg naringenin, inflammatory markers including TNF-α, IL-6, TLR4, iNOS, COX2, NADPH oxidase-2 (NOX2), NF-κB, and mitogen-activated protein kinase (MAPK) were suppressed (X. Liu et al., 2016). A post-translational inhibition of TNF-α and IL-6 was also observed in an in vitro study that assessed the effects of naringenin on murine macrophage cell line RAW264.7 (Jin, Zeng, Zhang, Zhang, & Liang, 2017). In addition, mRNA and protein expression levels of TNF-α, IL-6, and IL-1β were attenuated by naringenin administration in female mice with hypertrophic scars (Shan et al., 2017). Collectively, a large amount of evidence supports the notion that naringenin represents a potential therapeutic agent to control the inflammation-related diseases. Therefore, one of the other mechanisms by which naringenin might exert therapeutic effects against COVID-19 is, at least partly, by attenuating inflammatory responses. The summary of the possible mechanisms for the protective effects of naringenin against COVID-19 is presented in Figure 2.

7 | CONCLUSIONS

In conclusion, the evidence reviewed here indicates that naringenin might exert therapeutic effects against COVID-19 through the inhibition of COVID-19 main protease, 3CLpro, and reduction of ACE2 receptors activity. One of the other mechanisms by which naringenin might exert therapeutic effects against COVID-19 is, at least partly, by attenuating inflammatory responses. The antiviral activity of the flavanone naringenin has also been reported against some viruses. On the whole, the favorable effects of naringenin lead to a conclusion that naringenin may be considered as a promising treatment strategy against COVID-19. However, the beneficial effects of naringenin still need to be confirmed in clinical trials.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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