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REVIEW

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Flavonoids derived from medicinal plants as a COVID-19 treatment

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 disease. Through its viral spike (S) protein, the virus enters and infects epithelial cells by utilizing angiotensin-converting enzyme 2 as a host cell's receptor protein. The COVID-19 pandemic had a profound impact on global public health and economies. Although various effective vaccinations and medications are now available to prevent and treat COVID-19, natural compounds derived from medicinal plants, particularly flavonoids, demonstrated therapeutic potential to treat COVID-19 disease. Flavonoids exhibit dual antiviral mechanisms: direct interference with viral invasion and inhibition of replication. Specifically, they target key viral molecules, particularly viral proteases, involved in infection. These compounds showcase significant immunomodulatory and anti-inflammatory properties, effectively inhibiting various inflammatory cytokines. Additionally, emerging evidence supports the potential of flavonoids to mitigate the progression of COVID-19 in individuals with obesity by positively influencing lipid metabolism. This review aims to elucidate the molecular structure of SARS-CoV-2 and the underlying mechanism of action of flavonoids on the virus. This study evaluates the potential anti-SARS-CoV-2 properties exhibited by flavonoid compounds, with a specific interest in their structure and mechanisms of action, as therapeutic applications for the prevention and treatment of COVID-19. Nevertheless, a significant portion of existing knowledge is based on theoretical frameworks and findings derived from in vitro investigations. Further research is required to better assess the effectiveness of flavonoids in combating SARS-CoV-2, with a particular emphasis on in vivo and clinical investigations.

KEYWORDS
ACE2, COVID-19, flavonoids, medicinal plants, S protein, SARS-CoV-2

1 | INTRODUCTION

The angiotensin-converting enzyme 2 (ACE2) protein is encoded by its corresponding gene. This protein is a member of the family of dipeptidyl carboxypeptidases known as angiotensin-converting

Mentor Sopjani and Francesca Falco contributed equally to this study, thus sharing the first authorship.

enzymes. This protein catalyzes the cleavage of angiotensin I into the vasodilator angiotensin 1–9 and angiotensin II into the vasoconstrictor angiotensin 1–7 (Donoghue et al., 2000; Li et al., 2020). It is known that ACE2 is expressed in a variety of human organs, and its organ- and cell-specific expression suggests that it may be involved in the regulation of numerous functions (Bernstein et al., 2005), including cardiovascular and renal functions. The ACE2 protein resides in the cell membrane and functions as a functional receptor for the spike (S) glycoprotein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the agent responsible for coronavirus disease 2019 (COVID-19). Coronaviruses are a virus group so called because of the crown-like shape of the spikes on the surface of its virion. The distribution of ACE2 gene expression is relatively widespread (Bernstein et al., 2005; Tipnis et al., 2000). The ACE2 enzyme is present in the cells of numerous organs, including the lungs, the heart, the intestine arteries, and the kidneys. The SARS-CoV-2 envelope S glycoprotein plays a crucial role in viral infection by identifying the host cell membrane receptor ACE2, allowing fusion, and facilitating viral entry through the cell membrane. The C-domain of SARS-CoV-2, which functions as a receptor-binding domain (RBD), is used to attach the virus to its receptor, ACE2. The extracellular N-terminal domain (peptidase domain [PD]) with the catalytic site of ACE2 serves as the direct binding site for the virus S glycoprotein.

1.1 | SARS-CoV-2 is a member of the beta coronaviruses and has a single-stranded RNA genome

CoVs are members of the family Coronaviridae, the biggest family in the order Nidovirales, the subfamily Orthocoronavirinae, class Pisoniviricetes, the phylum Pisuviricota, and the kingdom Orthornavirae. α-CoV (*alphacoronavirus*), β-CoV (*betacoronavirus*), γ-CoV (*gammacoronavirus*), and δ-CoV (*deltacoronavirus*) are the four genera that make up the subfamily Orthocoronavirinae, according to the International Committee on Taxonomy of Viruses (ICTV) (Lefkowitz et al., 2018). The α-CoV and β-CoV are found in mammals, but the γ-CoV and δ-CoV are not found in mammals but mostly in birds (Woo et al., 2010). According to reports, seven different CoV species—two from the α-CoV (HCoV-NL63 and HCoV-229E) and five others from the β-CoV genus—are easily capable of infecting humans. The betacoronavirus species that have been documented to infect people are HCoVHKU1, hCoV-OC43, SARS-CoV, and MERS-CoV. However, given the high prevalence and widespread distribution of CoVs in animals, their high genetic diversity, frequent recombination of their genomes, increasing human-animal interface activities, and the numerous cross-species infections that follow, not only SARS-CoV-2 but also new CoVs may potentially emerge periodically in humans (Herrera et al., 2020; Luk et al., 2019; Zhou et al., 2020).

The CoVs contain a remarkable genome, which is the biggest RNA virus genome ever identified. They have positive-sense single-stranded RNA genomes that range in size from 26 to 32 kilobases (kb) (Coleman & Frieman, 2014; Khailany et al., 2020). Genomic variety and flexibility that depend on several variables are features of the coronavirus genomes. The vast genome of CoVs makes it likely that randomly occurring gene changes may occur, which could increase or decrease the virulence of the virus during infection (Woo et al., 2009). The impact of CoV replication on mutation rates has been demonstrated to be significant. With an error rate of 1 in 103–104 nucleotides during genome replication, their RNA-dependent RNA polymerases (RdRp), also known as RNA replicases, have substantial mutation rates (Duffy et al., 2008; Rowe et al., 1997). The homologous RNA recombination mechanism between viral genomes can have an impact on the high mistake rates of CoVs since they use a template-switching process (Duffy et al., 2008; Rowe et al., 1997). The high diversity of CoV genomes is related to their various plasticities and diversity-generating mechanisms, and they may also have the potential for emerging new CoVs to threaten human life in the future.

1.2 | The SARS-CoV-2 molecular structure and virus entry into the host cell

The reported SARS-CoV-2 genome sequence (GenBank: MN908947, China, Wuhan-Hu-1 coronavirus) contains a total of 29,903 nucleotides, including both coding and noncoding RNA sequences (Herrera et al., 2020; Zhou et al., 2020). Nonstructural proteins encoded by gene fragments include but are not limited to, RNA-dependent RNA polymerase, papain-like protease, and 3-chymotrypsin-like protease (Dërmaku-Sopjani & Sopjani, 2021a, 2021b). The coronavirus phosphoprotein (N protein, a structural protein) binds to the CoV ssRNA genome. During virion formation, this nucleocapsid (or ribonucleoprotein, RNP) complex works with the viral envelope protein. The envelope (E) and membrane (M) structural proteins surround the nucleocapsid in a CoV particle (Alsaadi & Jones, 2019; Bianchi et al., 2020). The E and M proteins are pretty similar between coronaviruses. Sequence studies show that the SARS-CoV-2 E protein (reference genome, RefSeq code: YP_009724392) is the same as the genome sequences of the Pangolin CoV MP798 and the Bat CoV CoVZXC21, RaTG13, and CoVZC45 isolates. Still, the unique multiple sequence alignments have shown that there are several different mutation-induced SARS-CoV2 E and M protein variants that are different from each other. The M protein is important for the budding process of CoVs because it interacts with the nucleocapsid as well as the E, S, and M proteins themselves (Bosch et al., 2003).

The attachment of the virus to the host cell membrane during infection is mediated by the S protein and ACE2 proteins, respectively, which determine the host range (Figure 1). The human cell membrane contains numerous protein and lipid molecules (Sopjani et al., 2015, 2016, 2017, 2019, 2021, Sopjani & Dërmaku-Sopjani, 2016, Dërmaku-Sopjani & Sopjani, 2019), each of which conducts or participates in specific cellular processes. ACE2 is one of the transmembrane plasma membrane proteins (Dërmaku-Sopjani & Sopjani, 2021b). The S proteins are heavily glycosylated and cover the entire surface of the virus. The virus employs the spike glycoprotein trimer for recognition, binding to the host cell membrane entrance receptor ACE2, and subsequent cell membrane fusion. Upon binding of the

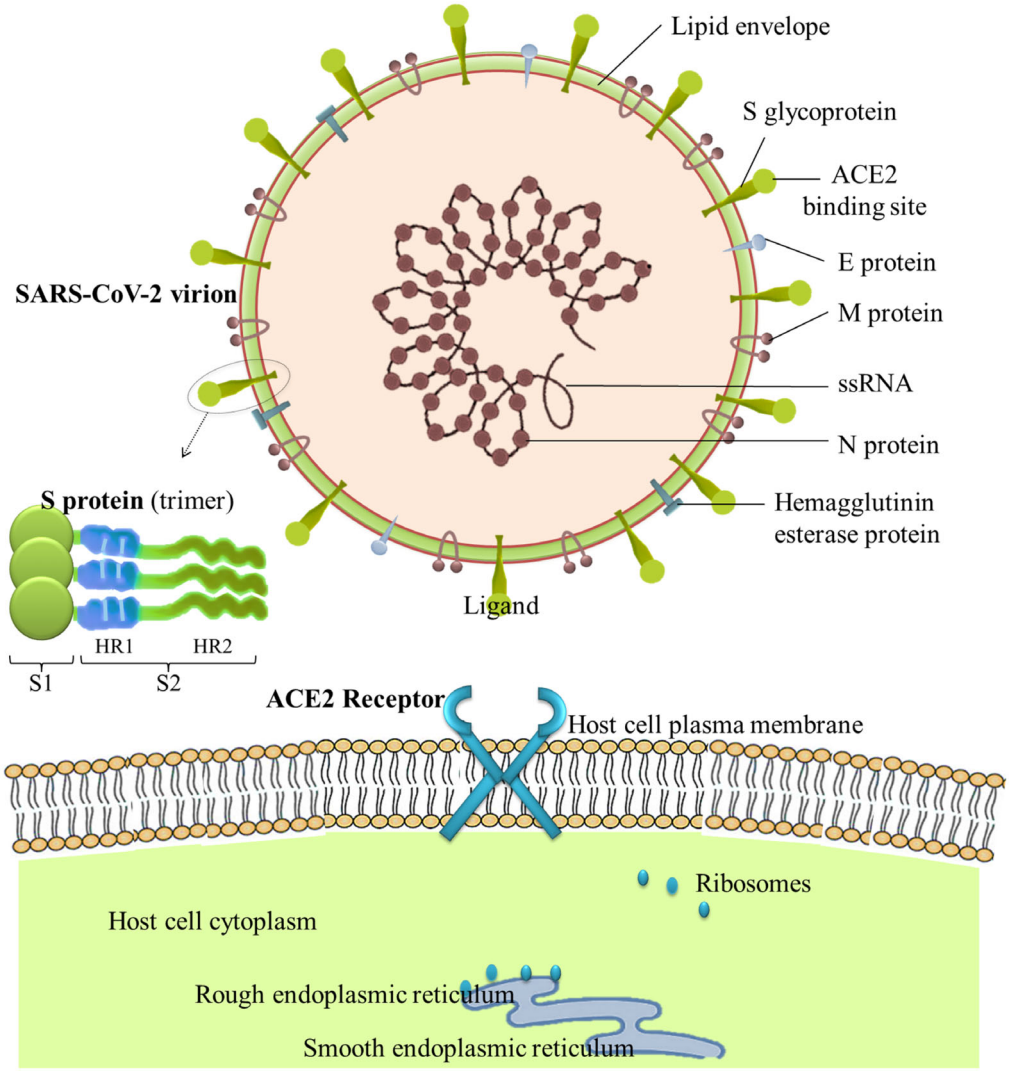


FIGURE 1 The structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and virus entry into the host cell using angiotensin-converting enzyme 2 (ACE2) (Dërmaku-Sopjani & Sopjani, 2021a). The lipid envelope of the SARS-CoV-2 virion is composed of four major structural proteins that play a vital function in virus assembly and infection. Spike/surface (S) glycoprotein, membrane (M) protein, nucleocapsid (N) protein, and a small envelope (E) protein are examples of structural proteins, as depicted in the figure. Additionally, numerous other accessory proteins exist. Protein S is required for viral fusion and host cell entry using the ACE2 receptor. Further details are available in the text.

virus S protein to the ACE2 receptor, the host plasma membrane protease TMPRSS2 activates the virus S protein, thereby facilitating viral entry into the cell (Dërmaku-Sopjani & Sopjani, 2021a, 2021b). Viral RNA is replicated, whereas the RNA genome is transcribed and translated into proteins. Along with RNA, viral proteins are synthesized, assembled, and packaged in the host cell before being released as viral particles through cell membrane branching, ready to infect surrounding target cells (Herrera et al., 2020; Zhou et al., 2020). As the S protein of SARS-CoV-2 is involved in multiple processes, including receptor recognition, viral attachment, and host cell entry, it may be the most essential target for drug therapies, such as therapeutic research and vaccines. Molecular characterization of S protein structure, as well as other proteins involved in the viral life cycle, is crucial.

1.3 | The S protein structure and function

During viral infection, SARS-CoV-2's surface S protein acts as a mediator between the infected cell's receptor and the virus's ability to bind to and fuse with the host cell membrane. It facilitates viral entrance into the host cell (Dërmaku-Sopjani & Sopjani, 2021a, 2021b). As presented in Figure 1, the S protein is a trimeric class I TM glycoprotein found in all known types of human coronaviruses (HCoVs) and many other viruses, including influenza (influenza hemagglutinin, HA), HIV (HIV glycoprotein 160, Env), Ebola (Ebola virus glycoprotein), and paramyxovirus (paramyxovirus F) (Weissenhorn et al., 1999).

Reportedly, the S protein of SARS-CoV-2 is 1273 amino acids long and 180–200 kilodaltons in size. It is comprised of multiple

elements, including an extra viral N-terminus, a membrane-spanning (or transmembrane) domain anchored in the viral envelope, and a short intraviral C-terminal part (or cytoplasm domain) (Dërmaku-Sopjani & Sopjani, 2021a, 2021b). The N-terminal signal peptide (1–13 amino acids) is followed by the S1 subunit (14–685 residues) and the S2 subunit (686–1273 residues) out of a total of 1273 amino acids. The S1 region is responsible for ACE2 receptor binding, and the S2 region is responsible for plasma fusion. Specifically, the S1 subunit is composed of two domains: an N-terminal domain (consisting of 14–305 residues) and an RBD (319–541 residues), while the S2 subunit comprises five parts: the fusion peptide (FP) (containing 788–806 residues), heptapeptide repeat sequence 1 (HR1) (912–984 residues), HR2 (1163–1213 residues), transmembrane domain (TMD) (1213–1237 residues), and cytoplasm domain (CD) (1237–1273 residues) (Xia et al., 2020), as it is presented in Figure 2. Even though the highly variable S1 subunit was initially investigated as an attractive target for antiviral therapy and vaccine development, the more conserved S2 domain may be a better target for therapies able to provide broad-spectrum protection against multiple emerging strains of SARS-CoV-2.

Using cryo-electron microscopy techniques at the atomic level, the structure of the SARS-CoV-2 S protein was determined to be a complex of three identical spike monomers (trimeric), with different conformations of the S1 RBD domain in open and closed states depending on its correlative functions. S protein trimers form a distinct, globular structure resembling a crown or halo that encircles the entire viral particle. The S1 and S2 subunits create the bulbous head and stem regions (Woo et al., 2009; Wra et al., 2020). Notably, the entire S protein, including the stalk, is covered with sugar-like molecules known as glycan chains, which disguise and camouflage their viral S proteins to avoid detection by the human immune system during entry (Watanabe et al., 2020).

The protective coating of this chain conceals the spikes from human-neutralizing antibodies, allowing the virus to escape the body. Prefusion and postfusion are two structurally distinct conformations of the S protein. S proteins are typically in prefusion conformation. Upon interaction with the plasma membrane of the host, the virus undergoes structural rearrangement, allowing SARS-CoV-2 to fuse with the plasma membrane of the host (Bosch et al., 2003; Yi et al., 2004).

1.4 | SARS-CoV-2 binding to the hACE2 host membrane receptor

The RBD of the S1 subunit protein binds to the human ACE2 receptor at the plasma membrane to initiate SARS-CoV-2 infection. ACE2 is a metallopeptidase that is also recognized as a SARS-CoV receptor (Donoghue et al., 2000). The binding of SARS-CoV to ACE2 mediates the formation of a trimer at the host cell membrane (Q. Wang, Zhang, et al., 2020). The virus RBD region of S1 binding to hACE2 promotes internalization, followed by the formation of an endosome in which the low pH environment triggers viral fusion in the host cell (Shang et al., 2020).

In humans, ACE2 mRNA appears to be widely distributed and present in almost all organs. The protein expression of ACE2 is primarily localized in cells of the lung and intestine, especially in alveolar epithelial type II cells and enterocytes of the human small intestine, but it is also present in cells of the heart and kidneys (Hamming et al., 2004). However, according to another study (Li et al., 2020), the small intestine, kidneys, thyroid, testes, heart, and adipose tissue all have high ACE2 expression levels, whereas the lungs, liver, bladder, colon, and adrenal gland all have medium ACE2 expression levels. The spleen, blood, bone marrow, arteries, brain, and muscles all express ACE2 at far lower levels than the rest of the body. The pathogenesis of COVID-19 is dependent on the entry route for the SARS-CoV-2 infection. Some patients infected with COVID-19 will likely have more severe symptoms than others. Therefore, as reported, the ACE2 expression and localization are linked to the progression of viral infection (Dërmaku-Sopjani & Sopjani, 2021a, 2021b).

In addition to host immunological responses to the virus, variations in ACE2 expression and ACE2 polymorphisms may account, at least in part, for the wide range of illness severity observed among people infected with this virus. It has been observed that SARS-CoV-2 infects primarily the respiratory system, with the severity of symptoms varying at least in part with the degree to which the epithelia lining the human airways are differentiated (Dërmaku-Sopjani & Sopjani, 2021a, 2021b; Jia et al., 2005).

The interaction between the ACE2 and S1 component proteins of the virus may be a relevant target in identifying potential medicines against SARS-CoV-2.

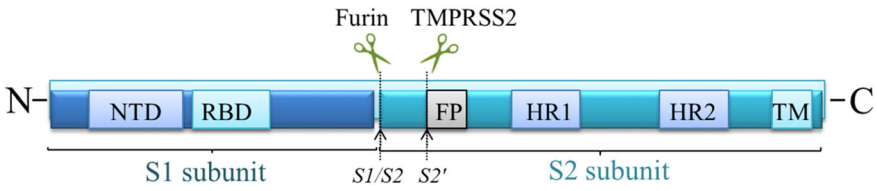


FIGURE 2 The structure of the S protein of the severe acute respiratory syndrome coronavirus 2. The arrows denote the cleavage sites of the human host cell enzymes furin (S1/S2) and TMPRSS2 (transmembrane protease, serine 2) (S2′) on the primary structure of the coronavirus spike (S) protein. The S protein is comprised of S1 and S2 subunits (regions). The S1 subunit contains an N-terminal domain (NTD) and a receptor-binding domain (RBD), while the S2 subunit contains a fusion peptide (FP), heptad repeats 1 (HR1) and 2 (HR2), and a transmembrane domain (TM).

2 | COVID-19 AND MEDICATION

The SARS-CoV-2 virus causes an infectious disease, COVID-19 (Dërmaku-Sopjani & Sopjani, 2021a, 2021b). Most infected patients develop mild to moderate respiratory illness and recover without special treatment. Nonetheless, some patients will become gravely ill and require medical care. People who are older or who have preexisting conditions such as cardiovascular disease, diabetes, chronic respiratory disease, or cancer are more likely to develop significant illnesses. Small liquid particles can disseminate the virus from an infected person's mouth or nose when they cough, sneeze, speak, sing, or breathe. These particles range in size from respiratory droplets to aerosols. Two to 14 days after exposure to the virus, symptoms may manifest. Anyone can experience moderate to severe symptoms, including fever, shortness of breath, coughing, fatigue, headaches, muscle or body aches, a runny nose, vomiting, a new loss of taste or smell, a sore throat, and diarrhea.

Although there are many effective vaccinations in use around the world, SARS-CoV-2 is not currently the target of any fully effective antiviral medications. The platforms used to develop SARS-CoV-2 vaccines include those based on nucleic acids (DNA or mRNA vaccines), proteins and subunit proteins, viral vector vaccines, immune cell treatment, and whole virus (attenuated and inactivated forms) vaccines (Flanagan et al., 2020). The viral S protein and the RBD region, respectively, are the primary research areas for SARS-CoV-2 vaccine development. SARS-CoV-2, like other well-known viruses, naturally mutates over time, and thousands of mutations have been documented since it first appeared in late 2019. The term "variant" refers to a modified virus. While the bulk of these changes have little to no effect on the virus's behavior, some of them may even improve the virus's ability to live and spread (Fontanet et al., 2021). Phytochemicals from medicinal plants are also used as potent medications against COVID-19. Therefore, more accurate molecular characterization of SARS-CoV-2 may aid in the development of COVID-19 therapeutic options such as vaccines and/or medications (Krasniqi et al., 2020).

This paper examines current developments in medication and the effectiveness of natural plant-based remedies against COVID-19, especially flavonoids-derived medications.

2.1 | Medicinal plants in COVID-19 medication

Several antiviral drugs are used to treat mild-to-moderate COVID-19 in patients who are more likely to develop a severe illness. These drugs are authorized or licensed globally. Antiviral drugs target the components of the virus to prevent it from replicating within the body, preventing serious illness and even death. The COVID-19 therapy recommendations are made available globally to help doctors choose the best course of action for their patients. COVID-19 can be treated through various drug combinations, as numerous recommendations have been made to address the condition in patients (Cheng et al., 2020; Donoghue et al., 2000; Flanagan et al., 2020; Fontanet et al., 2021).

A promising strategy for battling COVID-19 may involve investigating the herbs and herbal preparations used in conventional medicine and then bioassay-guided isolation of lead compounds from medicinal herbs. In several African nations, home remedies are used as an alternative treatment for COVID-19. In this regard, it has been reported that natural spices and medicinal plant leaves with antioxidant and anti-inflammatory properties are efficacious (Zhuang et al., 2009; Dërmaku-Sopjani & Sopjani, 2021b).

Numerous natural products have broad-spectrum antiviral activity, can inhibit numerous viral infections and replication steps, and have been used to treat SARS, MERS, influenza, and dengue viruses. There have been reports of many chemical structures of bioactive phytomolecules that are beneficial in the management of COVID-19-related complications (Panche et al., 2016; Rashidian et al., 2023; Rashidian, Mahboub, et al., 2022; Rashidian, Shahin, et al., 2022). Additionally, medicinal plant-derived immunomodulators inhibit the inflammatory effect responsible for the substantial morbidity and mortality associated with COVID-19 infection. Therefore, they are used in treating symptoms associated with COVID-19. Moreover, in some cases, the inhibition mechanism of medicinal plants and products against SARS-CoV-2 replication is revealed. However, more research and clinical studies are still needed to determine the safe and therapeutic levels for each natural compound, as phytochemicals may be toxic at certain concentrations (Krasniqi et al., 2020; Thaçi et al., 2022).

Numerous compounds can be extracted from medicinal plant products. Flavonoids are one of the most significant (Panche et al., 2016; Spagnuolo et al., 2018). Flavonoids are abundantly present in several plant species and exert a substantial impact on both the prophylaxis and therapeutic management of SARS-CoV-2. Flavonoids exhibited remarkable immunomodulatory and anti-inflammatory properties, including the inhibition of a variety of inflammatory cytokines. In addition, by promoting lipid metabolism, flavonoids were able to significantly reduce the severity of COVID-19 in obese patients (Mukherjee et al., 2022).

2.2 | Flavonoids in the treatment of COVID-19 disease

At the onset of the pandemic, as no specific (FDA-approved) drugs or vaccines were available for the treatment of COVID-19, there was an urgent need to develop candidate drugs or therapeutic molecules effective against COVID-19. For this reason, several natural metabolites, such as flavonoids (which comprise the polyphenol group), were identified and studied as potential drug candidates for the treatment of COVID-19. Polyphenols, secondary metabolites of plants, comprise a wide range of over 10,000 naturally occurring substances that have demonstrated significant pharmacological, biological, and physiological benefits for human health (K. B. Pandey & Rizvi, 2009). These benefits extend to the treatment of numerous chronic ailments like diabetes, cardiovascular disease, neurological disorders, and cancer. Traditional medicine has long employed polyphenols, using herbs such as thyme, oregano, rosemary, sage, mint, and basil to alleviate common

respiratory illnesses and colds. Several studies and clinical trials have established the efficacy of polyphenols in controlling several human pathogens, including SARS and MERS, which share similarities with COVID-19 (Khalil et al., 2020). Recent studies have shown that flavonoids have antiviral activity against some viruses, including SARS-CoV and MERS-CoV (Frabasile et al., 2017; Jucá et al., 2020; Kiat et al., 2006; L. Yang et al., 2017).

Flavonoids share a common basic structure consisting of three aromatic rings (rings A, B, and C), two of which are formed by six carbon atoms (rings A and B) and are linked to a three-carbon heterocycle (ring C). Based on the variation in the type of heterocycle involved, flavonoids may be divided into six subclasses: flavonols, flavones, flavanones, flavanols, anthocyanins, and isoflavones (Panche et al., 2016). Flavonoids from natural sources—more than 4000 compounds—have gained increased importance in research because of their versatile benefits. They are present in many foods of plant origin, including fruits, vegetables, herbs, and marine plants. Several flavonoids have been shown to have antioxidant, anti-inflammatory, and antiviral properties and have been extensively studied for their potential health benefits (Ballard & Junior, 2019; Ekalu & Habila, 2020; Rampogu et al., 2022; Rashidian et al., 2023; Rashidian, Mahboub, et al., 2022). Flavonoids are divided into six main subclasses according to their different heterocycle types: Flavonols, Flavanones, Flavanols, Flavones, Anthocyanins, and Isoflavones as reported in Figure 3.

Individual differences within each group result from the number and arrangement of hydroxyl groups and the degree of alkylation and/or glycosylation. Flavanols (e.g., quercetin and kaempferol) have a 3-hydroxy-pyran-4-one group on the C ring. Flavanones (e.g., naringenin and taxifolin) have an unsaturated carbon-carbon bond on the C ring. Flavanols (e.g., catechins) have neither the 3-hydroxyl group nor the 4-one structure in the C ring. Flavones (e.g., luteolin) lack a hydroxyl group in the 3-position of the C-ring. Anthocyanins (e.g., cyanidin) are characterized by the presence of an oxonium ion on the C-ring and are therefore strongly colored. In isoflavones (e.g., genistein), the B ring is attached to the C ring in the 3-position and not in the 2-position as in other flavonoids (K. B. Pandey & Rizvi, 2009). The recent COVID-19 pandemic has led to renewed interest in the potential role of flavonoids in the treatment of this disease. Based on existing knowledge, efforts directed toward the design of anti-COVID-19 drugs focus on preventing virus entry into host cells, inhibiting protein-virus-host interactions, and disrupting viral replication, with the goal of interrupting inflammatory responses induced by viral invasion. Therefore, therapies that can act on coronaviruses can be mainly divided into three categories: (i) blocking virus binding to human cell receptors or acting on host-specific receptors, thus preventing the virus from entering cells, that is, inhibiting virus entry; (ii) preventing the synthesis and replication of virus RNA; and (iii) reducing the virulence factor to restore innate immunity. Thus, in silico studies have explored the use of flavonoids as therapeutic candidates against COVID-19 by targeting S-protein cleavage, S-protein binding to cell surface receptors such as ACE2, and binding to viral proteases such as papain-like protease (PLpro), main proteinase (M^{pro}), also termed 3-

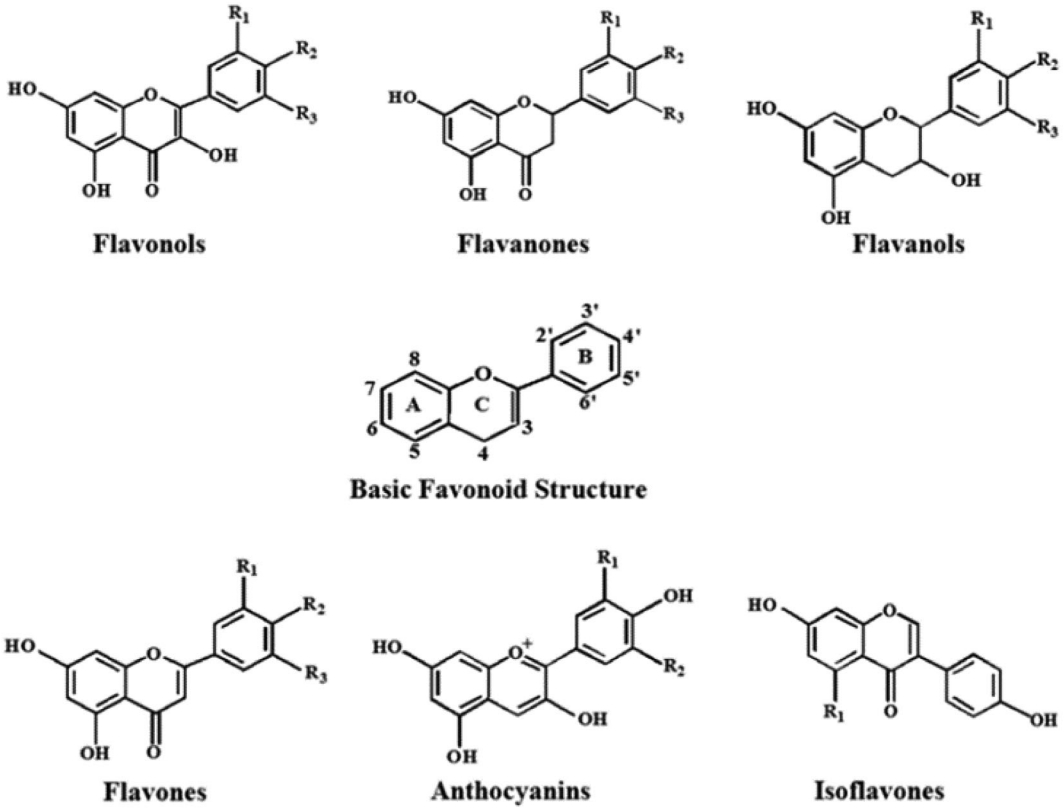


FIGURE 3 Chemical structures of flavonoid subclasses from the basic structure of the flavonoid in the center of the image.

chymotrypsin-like protease (3CL^{pro}), and RNA-dependent RNA polymerase (RdRp), as well as interfering with the nonstructural proteins (NSPs) of SARS-CoV-2 to hinder viral replication. M^{pro} is a key coronavirus protease that mediates viral replication and transcription. One of the first studies to evaluate flavonoids as antiviral agents for SARS-CoV-2 was performed in silico on the S-protein of SARS-CoV-2 (by AutoDock Vina). Considering that some of these have both anti-inflammatory and anti-viral properties, they showed a high binding affinity with the spike protein of SARS-CoV-2 compared with the standard drug dexamethasone used to treat critically ill patients (Table 1) (Jain et al., 2021).

In the present review, along with the structure and function of SARS-CoV-2 molecules, we have described some common flavonoids such as Quercetin, Catechins, Rutin, Kaempferol, Apigenin, Luteolin, Chrysin, Galangin, Eriodictyol, and Naringenin, which, according to many recent studies and reviews, have a good chance of providing immunity in the case of pandemic COVID-19, here shown in Table 2. Overall, natural metabolites represent a promising area of research for the development of new drugs against the pandemic COVID-19, and further studies in this area are likely to provide important insights and potentially life-saving treatments. The compounds presented here could be further investigated using in vitro and in vivo techniques to assess their potential efficacy against SARS-CoV-2, thus serving as a starting point for developing antiviral agents effective against COVID-19 (El-Missiry et al., 2021; Jain et al., 2021; Khalil et al., 2020).

Recent studies have highlighted several flavonoids as potential candidates for pharmaceutical trials in combating the SARS-CoV-2 virus responsible for the COVID-19 pandemic. International clinical trials have been initiated to explore the therapeutic prospects of traditional medicines, bioactive phytochemicals, and plant-based products due to the urgent need for effective treatments in the absence of established anti-COVID-19 drugs (S. Alam, Sarker, et al., 2021). Notably, ongoing research aims to assess the efficacy of certain flavonoids against COVID-19. For instance, bioactive flavonoids like isobavachalcone, herbacetin, and quercetin exhibit considerable promise as anti-coronavirus (anti-CoV) agents (Solnier & Fladerer, 2021; Tatar et al., 2022).

TABLE 1 Estimated binding affinity (kcal/mol) of the flavonoids with the severe acute respiratory syndrome coronavirus 2 protein (Jain et al., 2021).

Flavonoid	Binding energy value (kcal/mol)
Apigenin	−7.8
Chrysin	−8.1
Fisetin	−8.3
Galangin	−8.2
Hesperetin	−7.7
Luteolin	−8.0
Morin	−8.1
Naringin	−9.8
Quarcetin	−8.2
Rutin	−9.2
Standard (dexamethasone)	−7.9

Among these, quercetin stands out for its remarkable ability to suppress SARS-CoV-2 infection and modulate the immune system. Innovative delivery methods such as throat or nasal sprays are being explored to enhance quercetin's effectiveness in clinical trials (Alzaabi et al., 2021; Williamson & Kerimi, 2020). Budak et al. (2022) conducted valuable research isolating specific glycone-aglycone conjugated flavonoids, studying their impact on molecular concentrations and bioavailability. Utilizing in vitro and in vivo cytotoxicity experiments, the study investigated various flavonoids including quercetin, quercetin 3-sambubioside-3'-glucoside, luteolin, apigenin-7-4′ alloside, kaembpferol-7-O-glucoside, epicatechin-epigallocatechin-3-O-gallate, and hesperetin. The findings revealed that flavonoids exhibit strong binding affinity toward the spike protein and major protease of SARS-CoV-2, owing to their higher attraction to the virus. Additionally, the study underscores their anti-inflammatory and immune-modulating properties.

Shohan et al. (2022) investigated the therapeutic effects of quercetin (at a daily dosage of 1000 mg) alongside remdesivir or favipiravir in 60 severe COVID-19 patients. The intervention group displayed a significant correlation with earlier discharge and a reduction in inflammatory markers (ALP, q-CRP, LDH). Notably, while hemoglobin and respiratory rate increased, they remained within the normal range. However, despite indicating safety and efficacy, the results lack significance concerning mortality, intensive care unit (ICU) admission, and duration of ICU stay, necessitating further investigation.

Similarly, Rondanelli et al. (2022) explored the preventive potential of quercetin Phytosome® (at 250 mg twice daily) against symptomatic COVID-19 over 3 months. Among 120 subjects (60 in each group), only five tested positive for COVID-19, with one in the quercetin group and four in the placebo group. Both groups achieved complete clinical remission, but the quercetin group recovered faster. After 5 months, the COVID-free survival rate was 99.8% in the quercetin group and 96.5% in the placebo group, indicating a 14% higher protection factor in the supplement group. While these results are promising, additional studies are imperative to validate regular prophylactic use.

2.2.1 | Quercetin

Numerous plant foods, including scallions, apples, and tea, contain quercetin (QUE). It has been demonstrated to have potent antiviral, anti-inflammatory, and immunomodulatory effects, which may be advantageous for the treatment of COVID-19. QUE inhibits the replication of multiple respiratory viruses, including influenza virus, RSV, and HRV (Lopes et al., 2020). QUE is an effective agent against SARS and MERS due to its antimicrobial, antiviral, anti-inflammatory, antioxidant, and other advantageous properties (Gasmi et al., 2022). Due to its inhibition of multiple stages of the viral life cycle, QUE may have therapeutic potential against SARS-CoV-2. QUE inhibits viral replication by inhibiting the activity of the SARS virus; it inhibits viral entry,

TABLE 2 The main common flavonoids that show a good ability to provide immunity in the case of COVID-19.

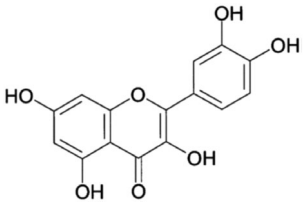
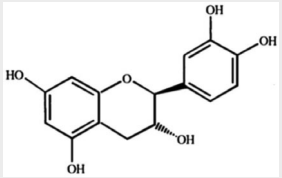
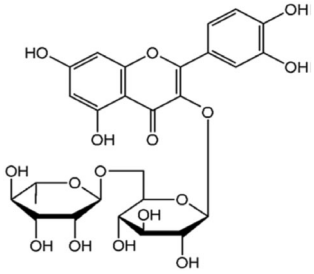
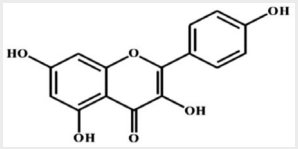
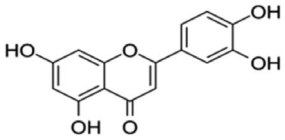
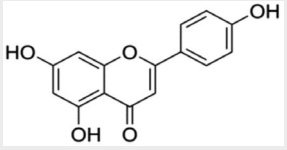
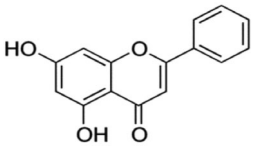
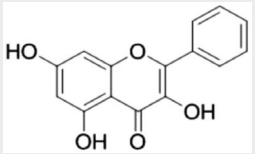
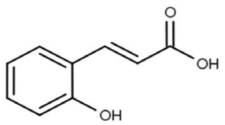
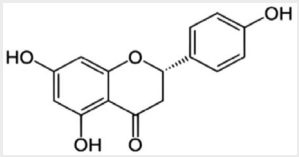
Flavonoids	Class	Formula	COVID-19 protein and protease targets	Reference
Quercetin	Flavonol		• $3CL^{pro}$ • PLpro • S-protein • ACE2 • RdRp	Gasmi et al. (2022), Huang et al. (2020)
Catechins	Flavonol		• PLpro • ACE2 • $3CL^{pro}$	Jang et al. (2021), C. Wu et al. (2020)
Rutin	Flavonol		• RdRp • ACE2 • $3CL^{pro}$ • PLpro	Chen et al. (2023), Mazik (2022), F. Rahman et al. (2021)
Kaempferol	Flavonol		• $3CL^{pro}$ • 5R84 protein	Shen and Yin (2021), Sun et al. (2023)
Apigenin	Flavone		• M^{pro}	Farhat et al. (2022), Matondo et al. (2022)
Luteolin	Flavone		• ACE2 • $M^{pro}/3CL^{pro}$ • PLpro	Shawan et al. (2022)
Chrysin	Flavone		• $3CL^{pro}$ • PLpro • ACE2	Guler et al. (2021), Hashem (2020), Shahbazi et al. (2022), C. Wu et al. (2020)
Galangin	Flavonol		• $M^{pro}/3CL^{pro}$ • ACE2	Bora et al. (2020), Kusomorini et al. (2023), Singh et al. (2022)
Eriodictyol	Flavonon		• $3CL^{pro}$	Y. J. Lin et al. (2012)

TABLE 2 (Continued)

Flavonoids	Class	Formula	COVID-19 protein and protease targets	Reference
Naringenin	Flavonon		• S-Protein • TMPRSS2 • ACE2 • RdRp • TPCs • M^{pro}/$3CL^{pro}$ • Nsp5 • P450 cytochrome	Agrawal et al. (2022), Clementi et al. (2022), Madeswaran et al. (2021), Tutunchi et al. (2020)

Abbreviations: $3CL^{pro}$, 3-chymotrypsin-like protease; ACE2, angiotensin-converting enzyme 2; M^{pro}, main proteinase; NSPs, nonstructural proteins; PLpro, papain-like protease; RdRp, RNA-dependent RNA polymerase; S-Protein, spike protein; TMPRSS2, transmembrane serine protease 2.

absorption, and penetration in the SARS-CoV virus, which may be partially explained by the ability of quercetin and its derivatives to inhibit $3CL^{pro}$ and PLpro (Gasmi et al., 2022). Docking studies of QUE on $3CL^{pro}$ and other important targets suggested that it bound well to each target, with a binding energy of 5.6 kcal/mol to $3CL^{pro}$. Surprisingly, Que binds well to S-protein, ACE2, RdRp, and PLpro, indicating excellent potential against SARS-CoV-2 (Huang et al., 2020).

2.2.2 | Catechins

Catechins (CATs) are mostly found in plants such as tea leaves, beans, black grapes, cherries, and cocoa and have a variety of physiological effects. Green tea extract is recognized as a rich dietary source of catechins, containing significant amounts of (-)-epicatechin (EC), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC), and (-)-epigallocatechin-3-gallate (EGCG) (Diniz et al., 2021). These CATs have been reported to have health-promoting and health-improving effects on various diseases. In addition, the antioxidant effect, prevention of liver damage, cholesterol-lowering effect, and anti-obesity effect have been confirmed by in vivo animal studies and clinical trials (Kim & Heo, 2022). For instance, EGCG performed well as a potential therapeutic agent for symptomatic and asymptomatic SARS-CoV-2 infections (Chourasia et al., 2021). In a recent virtual ligand screening study, it was suggested that at least one catechin, EGCG, likely targets PLpro, compromising the coronavirus replication process and host infection (C. Wu et al., 2020). Furthermore, the inhibition of SARS-CoV-2 3CL protease and coronavirus replication by EGCG has recently been demonstrated in vitro (Jang et al., 2021), and a recent study reported that green tea EGCG effectively blocked infection by SARS-CoV-2 and novel variants by inhibiting binding to the ACE2 receptor (Jang et al., 2021). Thus, the identification of catechin as a novel multi-targeted agent may provide the structural basis for the design strategy of potential drug molecules targeting SARS-CoV-2 in the therapy of COVID-19 (Mishra et al., 2021).

2.2.3 | Rutin

Rutin (RUT) is found in numerous fruits and vegetables, including apples, figs, cranberries, and citrus fruits, as well as buckwheat and several medicinal plants. RUT has demonstrated a variety of beneficial activities, such as antioxidant, anti-inflammatory, cytoprotective, vasoprotective, anti-carcinogenic, neuroprotective, cardioprotective, anti-asthmatic, antimycobacterial, antifungal, antidiabetic, antiallergic, analgesic, and antiviral (Ganeshpurkar & Saluja, 2017; Panche et al., 2016). Y. J. Lin et al. (2012) described the antiviral effects of rutin on the 3C protease of enterovirus A71 (EV-A71) in a study. In a separate study, rutin's antiviral activity against herpes simplex virus type 1 was observed in vitro (Boligon et al., 2013). Multiple computational studies, including docking and molecular dynamics simulations, have identified RUT as a potential inhibitor of the principal SARS-CoV-2 protease (Chen et al., 2023). RUT may also inhibit human ACE2 and viral $3CL^{pro}$, in addition to other viral and host cell targets (F. Rahman et al., 2021). Moreover, rutin has been identified as a potential inhibitor of SARS-CoV-2-bound PLpro (Al-Zahrani, 2020). So, according to an in silico study, RUT has potent antioxidant and anti-inflammatory properties that may be advantageous in the treatment of COVID-19 (Mazik, 2022). In conjunction with its high solubility and low lipophilicity, RUT showed promise as a drug targeting COVID-19 (Rashidian, Mahboub, et al., 2022; Rashidian, Shahin, et al., 2022).

2.2.4 | Kaempferol

Kaempferol (KAE) is found in grapes, broccoli, and yellow fruits. Anticancer, antimicrobial, neuroprotective, antioxidant, antiallergic, and cardioprotective properties have been reported (Singhal et al., 2021). Kaempferol may play an important role in the prevention and treatment of COVID-19, according to studies (Khalil et al., 2020; Sun et al., 2023). It has been reported that the traditional Chinese herbal remedy Lianhua Qingwen contains essential components such as KAE, which demonstrate a high binding affinity with $3CL^{pro}$ of SARS-CoV-2, and that these components may modulate the inflammatory response of patients with severe COVID-19 (Shen & Yin, 2021). Sun et al. (2023) have recently discovered, through bioinformatics analysis and pharmacological effects on endotoxin-induced cytokine storms, that KAE offers potential targets for combating COVID-19. In their study, they confirmed that kaempferol suppresses the activation of the MAPK/NF-B pathway in LPS-stimulated macrophages and inhibits the secretion of inflammatory factors; they also demonstrated that

kaempferol inhibits endotoxin-induced cytokine storm, thereby ameliorating inflammatory pathology and enhancing mouse survival. Molecular docking analysis revealed that kaempferol can bind the SARS-CoV-2 protein 5R84 and form a hydrogen bond with the residues, whose free binding energy is less than that of the original ligand (Sun et al., 2023).

2.2.5 | Apigenin

Apigenin (API) is present in numerous fruits and vegetables, such as parsley, celery, onions, citrus, oranges, and chamomile (Farhat et al., 2022; Shukla & Gupta, 2010). API has the potential to be used in cancer prevention and therapy due to its effectiveness in inhibiting cell proliferation in numerous human cancer cell lines, such as leukemia, thyroid, skin, prostate, colon, and breast cancer cells (Meng et al., 2017; Y. Zhu et al., 2013, 2015; H. Zhu et al., 2016). Recent in silico studies have demonstrated that API and its analogues can inhibit the replication of SARS-CoV-2, confirming the potential of apigenin 7-glucoside-4′-p-coumarate to inhibit M^{pro} SARS-CoV-2 with the highest binding energy (Ashaari et al., 2018). At API (−7.52 kcal/mol), compounds with a high docking score were identified as hits. Their pharmacokinetic profile demonstrated that they have an excellent pharmacological and safe therapeutic profile. Its anti-inflammatory properties in relation to the excessive production of pro-inflammatory cytokines in the most severe form of COVID-19 were highlighted in a molecular docking (Autodock tool) study based on the score of interaction with the main SARS-CoV-2 protease (Xie et al., 2022).

2.2.6 | Luteolin

Luteolin (LUT) is abundant in herbs like parsley, peppermint, oregano, and thyme, as well as in vegetables such as celery seed, sweet bell peppers, carrots, and broccoli; seasonings like cardamom and anise; and flowers like *Reseda luteola* and Chrysanthemums. By partially absorbing UVA and UVB radiation, LUT plays an essential role in plant defense, for example, against UV radiation. Consequently, LUT can reduce the negative photobiological effects on the skin by functioning as the first line of defense. In addition, the antioxidant and anti-inflammatory effects of LUT on keratinocytes, fibroblasts, and numerous immune cells (such as macrophages, mast cells, neutrophils, dendritic cells, and T cells) have been described (Kempuraj et al., 2022). LUT is capable of inhibiting proinflammatory mediators and regulating multiple signaling pathways (Gendrisch et al., 2022). COVID-19 is associated with significant respiratory issues as well as a long-lasting COVID syndrome characterized primarily by cognitive dysfunction and fatigue. The symptoms of the long-COVID syndrome, particularly brain fog, are comparable to those of patients undergoing or having undergone chemotherapy for cancer (chemofog or chemobrain), as well as those of patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) or mast cell activation syndrome (MCAS). Currently, the pathogenesis of brain fog in these disorders is unknown, but it may be related to neuroinflammation caused by mast cells, which are stimulated by pathogenic and stressful stimuli to release mediators that activate microglia and cause inflammation in the hypothalamus. Recent research indicates that a phytosomal formulation of LUT may inhibit these processes (Theoharides & Kempuraj, 2023). Indeed, LUT penetrates the brain and inhibits both microglia and mast cells, thereby reducing neuroinflammation and cognitive dysfunction (Ashaari et al., 2018; Kwon, 2017; Theoharides et al., 2015), as well as Alzheimer's disease (Di Stadio et al., 2022). Olfactory dysfunction after SARS-CoV-2 infection is attributed to neuroinflammatory processes in the olfactory bulb and central nervous system; therefore, targeting neuroinflammation is a potential strategy for promoting recovery from chronic olfactory dysfunction after COVID-19 infection. In conjunction with olfactory training, LUT has been combined with palmitoylethanolamide (PEA-LUT) to treat olfactory dysfunction caused by COVID-19. In patients with olfactory disorders following COVID-19, the combination of PEA-LUT and olfactory training resulted in greater olfactory recovery than olfactory training alone (Xie et al., 2022). In addition, Xie and coworkers investigated the pharmacological mechanism of LUT against COVID-19/asthma comorbidity and presented results from system pharmacology and bioinformatics analyses. Using system pharmacology and bioinformatics analysis, the researchers evaluated the physicochemical properties and biological activities of luteolin. Additionally, they assessed the binding activities, targets, biological functions, and mechanisms of luteolin against COVID-19 and asthma comorbidity. In addition, they discovered that LUT may possess optimal physicochemical properties and bioactivity, and molecular docking analysis confirmed that luteolin exhibited effective binding activities in COVID-19/asthma comorbidity. Furthermore, a protein-protein interaction network containing 538 prevalent drug-disease targets and 264 hub targets was built. The main six hub targets of LUT against the COVID-19/asthma comorbidity were then determined to be TP53, AKT1, ALB, IL-6, TNF, and VEGFA (Xie et al., 2022). The antiviral activity of LUT has also been demonstrated by an in silico approach to molecular modeling against M^{pro}/$3CL^{pro}$, PLpro, and ACE2 of COVID-19, reporting a good score of binding energy, respectively −8.2 kcal/mol for M^{pro}/$3CL^{pro}$, −7.1 kcal/mol for PLpro (6WX4), and −10.1 kcal/mol for ACE2 (1R4L) (Shawan et al., 2022).

2.2.7 | Chrysin

Chrysin (CHR) is a hydroxylated flavonoid belonging to the flavone family. It is found in honey, propolis, and citrus, among other foods (Stompor-Gorący et al., 2022). Due to its biological and therapeutic activities, including antioxidant, anti-inflammatory, hepatoprotective, and neuroprotective properties, CHR has demonstrated tremendous potential in the treatment of a variety of diseases (Talebi et al., 2022; Moghadam et al., 2020). In recent years, researchers have also investigated the antitumor activity of chrysin, which is regarded as a promising agent for the prevention of numerous diseases, including cancer (Angelopoulou et al., 2020), diabetes, and neurodegenerative diseases

such as Alzheimer's and Parkinson's disease (Hashem, 2020). Following an in silico (molecular docking—Glide Docking, Schrödinger Maestro software) assessment of the potential effects of natural chemical phenolic honey compounds against SARS-COV-2, Hashem discovered that caffeic acid phenethyl ester (CAPE), galangin, and chrysin have a high potential to inhibit the viral $3CL^{pro}$ enzyme and thereby prevent viral replication (Hashem, 2020; Ul Qamar et al., 2020). Another computational analysis suggested the potential inhibitory effect of chrysin, not only against $3CL^{pro}$ but also against the second SARS-CoV-2 protease, PLpro (Talebi et al., 2022). Anyway, in an in silico (molecular docking—AutoDock 4.2 program) compared study on flavonoids presents in propolis able to bind to ACE2 receptors, although chrysine was the most abundant compounds in ethanolic propolis exracts, it don't expressed the best inhibition potentials among the studied molecules, unlike instead of rutin that showed with high binding energy (−8.04 kcal/mol) (Guler et al., 2021). While in a more recent study Chrysin presents high conformation stability with ACE2 during 120 ns of Molecular Dynamics simulation (MM/PBSA method); Chrysin, in fact, sufficiently interacted with ACE2 (through Ala348 and Arg393 and Arg93) and blocked the Spike binding pocket of ACE2 and for this reason could be a potential inhibitor against the binding of SARS-CoV-2 to ACE2 receptor, which is considered early stage of infection (Shahbazi et al., 2022).

2.2.8 | Galangin

Galangin (GAL), the bioactive component of galangal and honey, is one of the lesser-known flavonoids but is of considerable medical interest due to its antiviral, antibacterial (Cushnie et al., 2003), and anticancer activities. Recent reviews (Rampogu et al., 2022; Singh et al., 2021; Singh et al., 2022) demonstrate that galangal is a promising anticancer agent based on its effects on numerous cancers (e.g., breast, ovarian, colon, renal, laryngeal, and cervical) and their targets.

In 2020, an in silico investigation of some natural flavonoids as potential agents against COVID-19 was conducted by Bora et al. (2020). GAL demonstrated an excellent inhibitory profile against SARS-CoV-2 M^{pro} compared to the control, hydroxychloroquine. Among the four flavonoids examined (quercetin, luteolin, naringenin, and GAL), it exhibited the highest number of interactions with the greatest number of amino acid residues; in fact, molecular docking of the natural flavonoids to the active site of the SARS-CoV-2 main protease resulted in negative binding values of −8.007, −8.106, −7.68, and −8.066 for quercetin.

Another in silico study conducted in 2022 revealed that natural antioxidants, including sesamin, ellagic acid, capsaicin, and epicatechin, along with GAL, exhibited significant binding to the catalytic site of the M^{pro} enzyme. They interacted with high efficiency with the principal active site residue, Cys145, and thus appear to have remarkable potential as drug candidates for treating COVID-19 (A. K. Pandey & Verma, 2022).

As part of an ongoing study, a series of computational approaches were applied to investigate GAL as a potential molecular mechanism against COVID-19 with mucormycosis infection to determine its functional role and underlying mechanism of action. Protein–protein interactions were constructed for 57 common gene targets associated with coinfection. Treatment with GAL showed that it can inhibit several cytokines, including TNF-α, TGF-β1, and the release of IL-6, which reduces inflammation and tissue injury through IL-17, HIF-1α, TGF-β, and cytokine-mediated signaling pathways. The major transcription factor (TF) E2F1 and the miRNA hsa-miR-16-5p were identified by analyzing the gene regulatory network and serve as diagnostic biomarkers. GLA could be considered a potential therapeutic agent for the treatment of COVID-19 and mucormycosis (Hasan et al., 2023). A further in silico analysis of GLA as a competitor of SARS-CoV-2 spike protein showed that this molecule, as an inhibitor of Sars-CoV-2, is able to bind to ACE2 with a stable interaction. In addition, the authors conclude that GLA, like the other molecules studied, that is, catachin and hesperidin, is safe for consumption, as evidenced by the fulfillment of the requirements of the Lipinski pharmacological tests (Kusomorini et al., 2023).

2.2.9 | Eriodictyol

Eriodictyol (ERI) is extensively distributed in a variety of citrus fruits, particularly lemon, vegetables, and medicinal plants, and it plays a significant role in the health, nutrition, and pharmaceutical industries (Pérez-Gregorio et al., 2014; Somerset & Johannot, 2008). Mehmood et al. (2022) report that citrus species contain the maximum concentrations of ERI, particularly in peel and pulp.

Consumption of ERI-rich natural fruits and vegetables can play an important function in the human body. It is anticipated that ERI will shed light on molecular and cellular pathways. ERI appears to be correlated with its ability to regulate a multitude of cascades of cell-signaling pathways. Numerous studies, as summarized by Mehmood et al. in their review, have demonstrated that ERI has multiple pharmacological and therapeutic effects, including antioxidant, anticancer, neuroprotection, anti-obesity, cardioprotection, anti-inflammation, hepatoprotection, antidiabetic, and other effects. In addition, many other pharmacological properties have been demonstrated and reported in the scientific literature, such as cardiovascular protection, skin protection, mouth, eye, and skin dryness, as well as central nervous system effects, immunomodulatory effects, neuroprotective effects, analgesic activity, antipyretic activity, and antinociceptive activities (Deng et al., 2020; Talebi et al., 2022).

In addition, ERIs are considered a nutraceutical or functional food ingredient with potent antioxidant potential, making them an essential dietary nutrition component (Miyake et al., 1998). ERI was considered one of the bioactive constituents of Yinqiao powder against COVID-19, along with hesperetin, ERI, luteolin, quercetin, and naringenin, because of its high affinity with $3CL^{pro}$. According to traditional Chinese medicine, Yinqiao powder was recently regarded as a COVID-19 treatment agent based on network pharmacology (H. Lin et al., 2022). Furthermore, ERI can inhibit the release of inflammatory mediators mediated by neuro-COVID-associated mast cell activation and inflammatory mediators released by activated microglia. Neuro-COVID is a

prevalent manifestation in patients with long-term COVID and may be at least partially caused by the activation of brain mast cells and microglia, which results in perivascular inflammation, disruption of neuronal connectivity, and impairment of neuronal signal transmission (Theoharides & Kempuraj, 2023). In the absence of approved medications, a combination of certain natural compounds, such as ERI, could help reduce these processes and their associated symptoms. In fact, a new and innovative dietary supplement (ViralProtek®) combines ERI with oleuropein from olive leaves and sulforaphane from broccoli to obtain coronavirus inhibitory properties, reduce the severity of the disease, or treat neuro-COVID (Theoharides & Kempuraj, 2023).

2.2.10 | Naringenin

Naringenin (NAR) is primarily found in citrus fruits, such as grapefruits, and other fruits, such as tomatoes and cherries, in addition to consumables derived from medicinal plants (Arafah et al., 2020; Bhia et al., 2022). It possesses diverse biological activities and has been demonstrated to be a potential therapeutic agent for the treatment of numerous diseases (Patel et al., 2018). In vitro studies have shown that NAR can inhibit acute and chronic inflammatory responses in various cell types, in particular downregulating the expression of several inflammatory markers such as Toll-Like Receptor 4 (TLR4), TNF-α, IL-1β, IL-6, iNOS, and COX-2 by attenuating the NF-κB pathway and activating AMP-activated protein kinase (AMPK), which has been associated with the regulation and/or inhibition of several pro-inflammatory signaling pathways (Agrawal et al., 2022).

Given the impressive anti-inflammatory activity of NAR in vitro, several studies have tested the efficacy of naringenin in animal models and demonstrated the therapeutic potential of NAR as cardioprotective, expectorant, eye-protective, and so on (Du et al., 2009; L. Jin et al., 2017; Motallebi et al., 2022; Qin et al., 2011; Zeng et al., 2018). The mechanism of action of NAR has not been fully elucidated (Salehi et al., 2019), but recent mechanistic studies have shown that NAR suppresses inflammatory cytokine production via both transcriptional and posttranscriptional mechanisms. Surprisingly, NAR not only inhibits mRNA expression of cytokines but also promotes lysosome-dependent degradation of cytokine proteins. This unique property of NAR contrasts sharply with some widely studied natural products, such as apigenin and curcumin, which regulate cytokine production essentially at the transcriptional level. NAR could therefore be a starting point for the development of new anti-inflammatory agents.

On the other hand, the hydrophobic and crystalline nature of NAR is mainly responsible for its low water solubility, low oral bioavailability, and instability, which hinder its efficient medicinal use. To overcome these physicochemical problems, nano-drug delivery systems have been used for formulation (Ji et al., 2016; Saka & Chella, 2022; Wadhwa et al., 2022; Muralidharan & Shanmugam, 2022). These nanocarriers protect the encapsulated molecule from lysis and pH changes, improve its solubility, and enable sustained drug delivery to target cells, mainly due to their surface modification. For these reasons, various nanocarriers, including polymeric nanoparticles (such as chitosan-based nanocarriers), lipid-based nanoparticles, micelles, nanoemulsions, liquid crystalline nanoparticles, solid dispersions, and cyclodextrin inclusion complexes, have been developed for the encapsulation of naringenin to enhance its bioavailability.

Numerous studies have evaluated NAR's antiviral and anti-inflammatory properties (Tutunchi et al., 2020). In silico molecular docking investigations of certain commercially available flavonoids as effective antiviral agents against the spike glycoproteins of SARS-CoV-2 revealed that NAR exhibited exceptional SARS-CoV-2 inhibiting properties with remarkable docking scores and orientation. Several receptor–ligand interaction studies have shown that NAR binds effectively with several targets of the virus, including S-Protein, Transmembrane Serine Protease 2 (TMPRSS2), ACE2, RdRp, targeting two-pore channels (TPCs), M^{pro}, and Nsp5, as well as with the host, cytochrome P450. Therefore, NAR was presented to the scientific community for further investigational confirmation to develop a potent SARS-CoV-2 inhibitor for the treatment of COVID-19 (Alberca et al., 2020; Clementi et al., 2022; Madeswaran et al., 2021; Cataneo et al., 2019).

3 | MARINE PLANT FLAVONOIDS IN COVID-19 DISEASE

A significant portion of the human diet consists of plants and animals derived from marine biodiversity. Seaweed is known to produce a diversity of compounds, and some of these compounds have been demonstrated to have biological activity and potential medicinal value. Significant progress has been made in the discovery of metabolites with biological activity in seaweed. Marine macroalgae, or algae, are one of nature's most vital biologically active resources because they contain a multitude of bioactive compounds (Zhao et al., 2018). Algae are the earliest members of the plant kingdom, with hundreds of millions of tons of reserves in the world's oceans that are used for both human and animal health. There is currently a developing interest in using algae as a raw material for numerous natural products. The structural diversity of polyphenols, which are abundantly found in algae, is fascinating. As potent modulators of biochemical processes associated with chronic diseases, phlorotannins, which are exclusive to brown algae, are invaluable among algal polyphenols. Flavonoids in algae have been less researched than other polyphenol classes. Both flavonoids and phlorotannins have a diverse range of structural configurations. The growing interest in seaweeds in the biomedical field is primarily attributable to the bioactive compounds they contain, which have great potential as anti-inflammatory, antimicrobial, antiviral, and antitumor medications (Blunden, 1993; Smit, 2004). Several kinds of compounds have been identified in mangroves (*Sonneratiaceae*), including flavonoids, aromatic compounds, steroids, triterpenoids, and alkaloids (Tian et al., 2009) These compounds have demonstrated antioxidant (Sadhu et al., 2006) and cytotoxic (C. Wu et al., 2020) properties.

Marine plants, also known as seaweeds or marine macroalgae, are a diverse group of organisms that inhabit marine environments and have attracted attention as a possible source of pharmaceuticals for

treating a variety of diseases, including SARS-CoV-2 (M. A. Alam, Parra-Saldivar, et al., 2021; Kalasariya et al., 2022). The unique chemical compositions of these plants, which may include flavonoids, may have therapeutic properties.

In recent years, extracts or single compounds of marine plants have been tested for the prevention or treatment of viral diseases. The antiviral activity of the polyphenolic complex associated with seagrasses, such as *Thalassodendron ciliatum* or the Zosteraceae family (Hamdy et al., 2012; Hawas & Abou El-Kassem, 2017; Krylova et al., 2018; Mohammed et al., 2014), and also from mangroves, such as *Sonneratia hainanensis*, *Sonneratia paracaseolaris*, and *Xylocarpus moluccensis* (Gong et al., 2017; Liu et al., 2012; Riccio et al., 2020), was studied (Gentile et al., 2020). Several classes of compounds, such as phlorotannins, flavonoids, and pseudo peptides, from the marine plant were tested with molecular docking approaches as inhibitors of SARS-CoV-2 M^{pro}. Using the Marine Natural Product (MNP) library and Pharmacophore filter were screened in search of new potential SARS-CoV-2 M^{pro} inhibitors. Seventeen potential SARS-CoV-2 M^{pro} inhibitors have been identified among the natural substances of marine origin (Fayed et al., 2021).

In 2021, Singh et al. compiled a review of studies that investigated the therapeutic potential of bioactive compounds from marine sources against COVID-19. Prior to that time, no significant information regarding flavonoids from marine vegetation had been published (Shen & Yin, 2021). Fayed et al. (2021) published a study in the same year on the repurposing of marine bioactive compounds to target SARS-CoV-2. This latter investigation involved an in silico search for marine bioactive agents recognized for their antiviral properties, followed by a structure-based evaluation against co-crystallized SARS-CoV-2 proteins. Molecular docking of marine bioactive compounds against SARS-CoV-2's main proteases (PDB ID: 6lu7 and 6y2f), spike glycoprotein (PDB ID: 6vsb), and RNA polymerase (PDB ID: 6 m71) was conducted. In addition, a ligand-based strategy employing rapid overlapping chemical structures (ROCS) was utilized to determine if these marine compounds maintained their relevance and drug ability for the reported medications. In multiple aspects of virtual screening, compounds containing the flavonoid core, acyl indole, and pyrrole carboxamide alkaloids performed the best, as indicated by the examined marine database. Among all target proteins, sulfated flavonoid glycosides of thalassoilin (A–B) demonstrated the highest binding and similarity results (Fayed et al., 2021).

4 | THE MECHANISMS OF ACTION OF FLAVONOIDS IN COMBATING COVID-19 DISEASE

Computational research by Alzaabi et al. (2021) has suggested that flavonoids may exert inhibitory activity against SARS-CoV-2, binding primarily to crucial viral targets essential for virus entry and replication. Understanding the structural features of SARS-CoV-2 is fundamental to unraveling the action mechanisms of flavonoids. According to computational research (Alzaabi et al., 2022), flavonoids may exhibit possible inhibitory activity against SARS-CoV-2 and primarily bind to critical viral targets necessary for the virus's entrance and/or replication activities. Understanding the mechanisms of action of flavonoids, we should explain what the main structural action features of the SARS-CoV-2 or 2019 nCOV are. According to Mahmoud et al. (2020), SARS-CoV-2 contains four essential proteins, including three embedding proteins in a lipid bilayer membrane: M, S, E, and N proteins that coat the single-stranded positive-sense viral RNA (Y. Jin et al., 2020). According to research conducted by Boopathi et al. (2022) on the mechanism of action for SARS-CoV-2, the M protein is the most prevalent protein that is thought to serve as a central organizer for coronavirus assembly, and the N protein is crucial for virus transcription and translation. However, additional information on the E protein was provided by Gupta et al. (2021), and it appears that the aforementioned protein is essential for virus assembly. The receptor used by SARS-CoV-2 to enter human cells is ACE2 (Samavati & Uhal, 2020). Indeed, ACE2 is now getting more attention as a result since it could be a target for antiviral treatments. ACE2 comes in two different forms: the first version, known as sACE2, is soluble and enters the bloodstream (Batlle et al., 2020), whereas the second version is found in transmembrane cells on full-length mACE2, which represents the receptor site for the S proteins of SARS-CoV-2. S protein recognizes the host receptor protein ACE2 on the cell membrane after cleavage and activation by two host serine proteases: transmembrane protease serine 2, TMPRSS2, and FURIN (S. B. Wu et al., 2009). Once membrane fusion occurs, viral RNA replication begins, which proceeds quickly toward cell death with successive pro-inflammatory cytokines. Thus, TLRs detect the viral RNA, known as PAMPs (pathogen-associated molecular patterns), and this sets off a series of events that culminate in the activation of the nuclear transcription factor that culminates in the production of type I interferons (IFNs), which primarily include numerous subtypes of IFN-α and a single IFN-β, as well as proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) (Boopathi et al., 2022).

As previously mentioned, flavonoids are phenolic phytochemicals that are among the natural products that potentially have an antiviral effect against the SARS-COV-2 virus. They are "pleiotropic" substances, which means that their functional groups can interact with various cellular targets and block multiple pathways, and their capacity to work in synergy with conventional medications has also been extensively proven (Chen et al., 2004). Furthermore, the hydroxyl functional groups or flavonoids' fundamental skeleton of 15 carbons, made by two phenyls (rings A and B) and one heterocyclic (ring C), commonly known as the (C6–C3–C6) structure, appears to represent their normal chemical structure, which makes these chemicals capable of preventing coronavirus infection. Since all this began, it has been crucial to investigate these natural compounds against SARS-CoV-2 (Chaari, 2020). Studies on the antiviral mechanisms of flavonoids (Russo et al., 2020), which looked at their efficiency with different viruses, including coronaviruses, indicate that flavonoids may have a good chance against SARS-CoV-2. Flavonoids' antiviral activity can be divided into two categories: direct antiviral effects, where the flavonoid directly affects the virus, and indirect effects, where the

flavonoid strengthens the host's defenses against viral infection. Until now, more than 69 flavonoids with inhibitory activities against specific SARS-CoV-2 targets have been identified, most of which belong to the classes of flavonols and flavones (Alzaabi et al., 2022). The major targets of the anti-SARS-cov-2 strategy were $3CL^{pro}$, also known M^{pro}, and PL^{pro}, and disruption of the connection between S-ACE2 (Pillaiyar et al., 2016). Moreover, H. Yang et al. (2003) had already identified that M^{pro} was necessarily required for the replication of SARS-CoV, which was confirmed by Ul Qamar et al. (2020) who showed that M^{pro} of SARS-CoV-2 and SARS-CoV are very similar, so they have established them as promising drug and vaccine targets in the areas of therapeutic research against COVID-19 or SARS-CoV-2 (Alzaabi et al., 2022). Indeed, according to Razali et al. (2022), $3CL^{pro}$/M^{pro} and papain-like proteases are involved in the processing of two large polyproteins (pp1a [4405 amino acids] and pp1ab [7096 amino acids]). The big polyprotein 1ab (replicase 1ab, 790 kDa) has no less than 11 cleavage sites where the M^{pro}/$3CL^{pro}$ is active; the recognition sequence at most of these sites is Leu-Gln (Ser, Ala, Gly) (which also indicates the cleavage site).

To understand something much more about the action mechanism, an interesting work was that of Rashidian, Mahboub, et al. (2022) and Rashidian, Shahin, et al. (2022), where they reported the x-ray structures of the unliganded SARS-CoV-2 M^{pro} and its complex with an α-ketoamide inhibitor. This α-ketoamide was derived from a previously designed inhibitor but was modified to hide the amide bond within a pyridone ring to prevent cell cleavage by cellular proteases. Highlighting that in the inhibited SARS-CoV-2 M^{pro}, the inhibitor binds to the shallow substrate-binding site at the surface of each protomer, between domains I and II (Figure 4), through the nucleophilic attack of the catalytic Cys^{145} onto the α-keto group of the inhibitor, forming a thiohemiacetal with a general structure of a thiohemiacetal being R1-C(SH)(R2)-H, and a reversible reaction.

Another study (Khaerunnisa et al., 2020) has investigated some secondary metabolites among these, kaempferol and quercetin, using molecular docking on 6LU7 (the main protease (M^{pro}) found in COVID-19) and obtained binding energies of −9.41 and −8.58 kcal/mol of SARS-CoV-2 with a binding energy of −8.58 kcal/mol. Moreover, they reported that the main M^{pro} amino acids Thr24, Thr26, and Asn119 are also predicted to play roles in drug interactions and the native ligand structure. Moreover, according to recent studies (Adem et al., 2020; Khaerunnisa et al., 2020), it seems clear that Hesperidin also binds to SARS-CoV-2 M^{pro}, where the receptor-binding domain of spike glycoprotein S (RBD-S) and the peptidase domain of ACE2 limit the growth of SARS-CoV-2. Recent studies showed that Nelfinavir and Lopinavir also have a binding affinity for M^{pro}. Furthermore, another important study, based on those carried out by Bora et al. (2020) found that six flavonoids were presumed to be potential inhibitors of the COVID-19 3CL proteinase. Among these inhibitors, rutin (docking score: −9.16 kcal/mol and AUC: 0.990) was the most potent inhibitor compared with others. Indeed, it seems that rutin has the capability to form hydrogen bonds involving Cys145, Asn142, Gly143, and Thr190. Recently, other flavonoids have been identified as novel natural product inhibitors of 3CL protease in vitro (Bora et al., 2020)

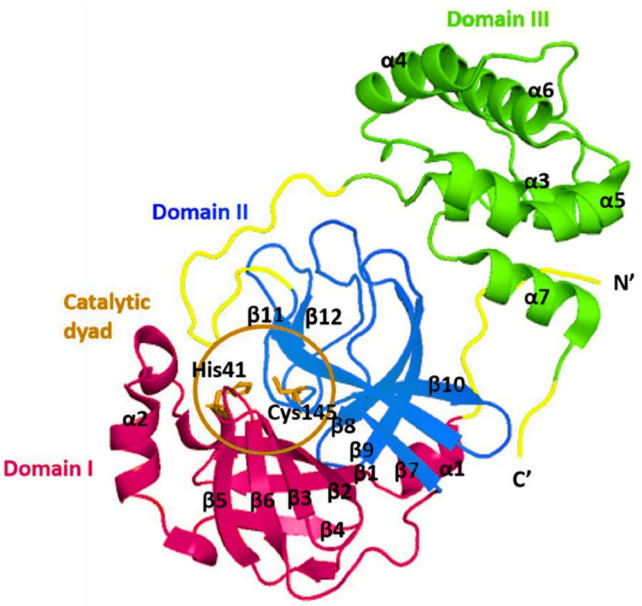


FIGURE 4 Domain organization of the monomeric structure of the severe acute respiratory syndrome coronavirus 2. $3CL^{pro}$ Domain I (residues 8–101) is colored in red, domain II (residues 102–184) is colored in blue, and domain III (residues 201–303) is colored in yellow. The catalytic dyad (His14 and Cys145) of $3CL^{pro}$ is shown as a stick (indicated by circles).

and the flavonoids could be potential anti-COVID-19 inhibitors (Y. Jin et al., 2020).

Furthermore, studies on the antiviral activity of flavonoids reveal their ability to interfere with various viral enzymes, including RNA polymerase, DNA polymerase, and reverse transcriptase, making them potential alternatives in the treatment of viral infections (L. Wang, Song, et al., 2020). Additionally, flavonoids such as baicalin, flavan-3-o1, and quercetin have been reported to inhibit the activity of viral neuraminidase, HIV-1 proteinase, and HIV-1 activation, respectively (Hour et al., 2013). The antiviral synergism observed between flavonoids, as well as their ability to reduce inflammatory responses, underscores their potential as agents that protect host cells from viral damage. The multifaceted action of flavonoids, targeting both viral and host factors, positions them as promising candidates for the development of new antiviral drugs against COVID-19.

5 | HERBAL MEDICINE AND CLINICAL PRACTICE

Clinical practice studies examining the efficacy of herbal medicine against SARS-CoV-2 are scarce. In a recent systematic review and meta-analysis, the authors conducted a comprehensive search of databases to identify pertinent studies that evaluated the efficacy of Chinese herbal medicines (CHM) in the treatment of COVID-19, specifically the roles of the herbal medicine in the immune response parameters (Shi et al., 2022) as well as in the gastrointestinal

symptoms and liver injury (Shi et al., 2021), which are common in patients with COVID-19. The researchers conducted an analysis of data obtained from a total of 3145 individuals across 30 eligible trials and subsequently compared these findings with those associated with standard regular care (Shi et al., 2022). Consequently, oral CHM was employed as a supplementary medication, leading to enhancements in specific immune response parameters, including lymphocyte counts, $CD4^+$ (white blood cell types that fight infection), $CD4^+/CD8^+$, and $CD3^+$, and reduced TNF-α. In addition, when compared to standard treatment alone, it resulted in a shorter duration of clinical symptom remission and a lower likelihood of all-cause mortality. Hence, the utilization of herbal medicine may be suggested as a supplementary kind of immunotherapy to facilitate disease modification and alleviate symptoms in the treatment of COVID-19. Gastrointestinal symptoms and liver damage are frequent among COVID-19 patients. Patients with COVID-19 have been increasingly treated with the herbal remedy; however, its clinical efficacy in relation to liver functions and gastrointestinal symptoms in COVID-19, in comparison to conventional pharmacotherapy, remains inadequately investigated. In comparison to standard pharmacotherapy alone, herbal medicine plus standard pharmacotherapy for COVID-19 was more effective at alleviating symptoms and reducing the time required for the viral assay to become positive, according to a review article that analyzed 48 trials involving 4704 participants (Shi et al., 2021). Thus, apparently herbal medicine as a supplementary treatment for COVID-19 may improve most gastrointestinal symptoms and liver function. However, additional rigorously conducted trials are required to validate the potential efficacy of herbal remedies.

6 | CONCLUSIONS AND FUTURE PERSPECTIVES

The rapid spread of COVID-19 has shown that the development of effective vaccines and medicines targeting SARS-CoV-2 is essential. Reducing the number of deaths caused by the spread of viruses is still a global priority. In the early stages of the pandemic, the primary public health policy was to limit the spread of the virus by encouraging people to maintain a safe distance from each other, use face masks, wash their hands often, and disinfect their surroundings. Vaccines against COVID-19 that are highly effective are currently widely used to maintain the infection and limit deaths to a minimum. Despite this, efforts are underway to develop new vaccine, with COVID-19 cases being reported. There have been several reports of different sorts of virus mutations, which could at least restrict the effectiveness of some vaccines. It is important to highlight that there are several approved pharmaceutical antiviral medications for treating SARS-CoV-2, such as Paxlovid, Molnupiravir, Remdesivir, and VV116, but their effects are limited. Therefore, medications derived from herbal medicine, such as flavonoids, demonstrate notable immunomodulatory and anti-inflammatory properties, suggesting their potential utility in the treatment or alleviation of symptoms associated with COVID-19. The molecular mechanism by which SARS-CoV-2 enters host cells is becoming increasingly well-understood. In this regard, flavonoids have been shown to be effective in both the prevention and treatment of SARS-CoV-2. Several in vivo and in vitro studies have revealed that flavonoids are effective against SARS-CoV-2. They can prevent the virus by blocking major viral targets such as the ACE2 receptor, TMPRSS2, M^{pro}, RdRp, S protein RBD, and other targets. Furthermore, flavonoids suppress SARS-CoV-2-induced inflammation by inhibiting the synthesis and release of proinflammatory factors during the inflammatory response (Alzaabi et al., 2021; M. M. Rahman et al., 2023). Simultaneously, flavonoids alleviate some of COVID-19's clinical symptoms. Over 69 flavonoids have been identified as having inhibitory effects on specific SARS-CoV-2 targets. The potential for adverse reactions to antiviral flavonoids should be considered and addressed. Therefore, their optimization may be needed to protect patients from their potentially adverse effects and to find the most effective medicine against COVID-19. Noteworthy, few in vivo and clinical studies have been conducted to examine the impact of flavonoids on the virus and disease, respectively, despite the abundance of in vitro and theoretical research on flavonoid effects. Thus, additional applied experimental research is required to further study the safety and effectiveness of flavonoid-based medications. Furthermore, there is a limit to the bioavailability of the ingested chemicals; therefore, it is important to address the issue of how to increase their bioavailability, either by selecting the best mode of administration or by formulating the medication (Namiot et al., 2023; Rauf et al., 2022). Flavonoids can surely exhibit direct or indirect anti-SARS-CoV-2 effects, even though there are still some issues to be addressed. Therefore, flavonoids may represent a promising class of anti-SARS-CoV-2 drugs. More research on the therapeutic potential of flavonoids and the creation of flavonoid-based pharmaceuticals is required.

AUTHOR CONTRIBUTIONS

Mentor Sopjani: Data curation; writing – original draft. **Francesca Falco:** Data curation; writing – original draft. **Federica Impellitteri:** Investigation; visualization; writing – review and editing. **Valeria Guarrasi:** Writing – review and editing. **Xuan Nguyen Thi:** Writing – review and editing. **Miribane Dërmaku-Sopjani:** Supervision; validation. **Caterina Faggio:** Supervision; validation.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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