A critical evaluation of risk to reward ratio of quercetin supplementation for COVID-19 and associated comorbid conditions

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Abstract
The interim results of the large, multinational trials on coronavirus disease 2019 (COVID-19) using a combination of antiviral drugs appear to have little to no effect on the 28-day mortality or the in-hospital course. Therefore, there is a still vivid interest in finding alternate re-purposed drugs and nutrition supplements, which can halt or slow the disease severity. We review here the multiple preclinical studies, partially supported by clinical evidence showing the quercetin's possible therapeutic/prophylaxis efficacy against severe acute respiratory syndrome coronavirus (SARS-CoV) as well as comorbidities like chronic obstructive pulmonary disease (COPD), diabetes mellitus, obesity, coagulopathy, and hypertension. Currently, 14 interventional clinical trials are underway assessing the efficacy of quercetin along with other antiviral drugs/nutritional supplements as prophylaxis/treatment option against COVID-19. The present review is tempting to suggest that, based on circumstantial scientific evidence and preliminary clinical data, the flavonoid quercetin can ameliorate COVID-19 infection and symptoms acting in concert on two parallel and independent paths: inhibiting key factors responsible for SARS-CoV-2 infections and mitigating...
1 | INTRODUCTION

Quercetin (3, 3', 4', 5,7-pentahydroxyflavone; PubChem CID: 5280343) is a plant flavonol, a sub-group of the flavonoid class of phenolic compounds, that has been the subject of intense investigations because of its immunomodulatory and immune-boosting properties. Quercetin is one of the rare phytomedicine or food supplements approved by the US Food and Drug Administration (FDA) as GRAS (Generally Recognized As Safe) for use as an ingredient at levels up to 500 mg per serving. The main sources of quercetin are onions, grapes, berries, cherries, broccoli, citrus fruits, Chinese herbs (Bai, Wang, & Ren, 2014) and its plasma levels can fluctuate depending on the specific diet (Hollman et al., 1997).

Quercetin, like other flavonoids, possesses anti-allergic and antiinflammatory effects mediated through the inhibition of the cyclooxygenase and lipooxygenase pathways, ensuring decrement in the production of pro-inflammatory mediators (Bhaskar, Kumar, Krishnan, & Antony, 2013; H. P. Kim, Mani, Iversen, & Ziboh, 1998). In addition, it modifies the eicosanoid biosynthesis, checks platelet aggregation, promotes the relaxation of cardiovascular muscles, and helps in neuroprotection (Khan, Ullah, Aschner, Cheang, & Akkol, 2019).

Quercetin plays an important role in protection against several life-threatening diseases, such as cancer, coronary heart disease, atherosclerosis, hypercholesterolemia, rheumatic diseases, and infections by virtue of its antioxidant properties and the capacity to interfere with several signal pathways regulating cellular homeostasis (comprehensively reviewed in Batba et al., 2020; Cushnie & Lamb, 2005; R. V. Patel et al., 2018; Russo, Mupo, Spagnuolo, & Russo, 2010).

The antimicrobial activity of quercetin is known for more than 35 years, and has attracted quite a lot of research. Since then, considerable research has been done on investigating quercetin’s role and its mechanism of action as an antibacterial and antiviral agent (Brito, Lima, Cordeiro, & da Cruz Nizer, 2021; Cushnie & Lamb, 2005; Di Petrollo, Orrù, Fais, & Fantini, 2022). Subsequently, several independent in vitro studies have demonstrated that quercetin is capable of inhibiting the replication of various respiratory viruses, such as influenza virus (Mehrbd et al., 2018), parainfluenza and respiratory syncytial virus (Kaul, Middleton Jr, & Ogra, 1985), coronavirus (Debiaggi, Tateo, Pagani, Luini, & Romero, 1990), rhinovirus (Dimova et al., 2003), herpes simplex virus and adenovirus (Chiang, Chiang, Liu, & Lin, 2003), and severe acute respiratory syndrome (SARS) viruses (L. Chen et al., 2006; Derosa, Maffioli, D'Angelo, & Di Pierro, 2021; Russo, Moccia, Spagnuolo, Tedesco, & Russo, 2020; Saakre, Mathew, & Ravisankar, 2021; Yi et al., 2004).

Despite the broad therapeutic properties of quercetin, further high power randomized clinical trials are needed to firmly establish its clinical efficacy against COVID-19.

KEYWORDS
chronic obstructive pulmonary disease, coagulation, COVID-19, diabetes, hypertension, quercetin

2 | ANTI-SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2 (SARS-CoV-2) EFFECTS OF QUERCETIN

SARS-CoV is the causative pathogen of SARS that may seriously aggravate the host immune system. SARS-CoV-2 (comparatively large enveloped viruses with diameter of 60–140 nm) is a single-stranded, positive-sense RNA virus containing 29,891 nucleotides encoding 9,860 amino acids (V’kovski, Kratzel, Steiner, Stalder, & Thiel, 2021). During infection, 5 protein of SARS-CoV-2 binds with human ACE2 (Angiotensin-Converting Enzyme 2) protein, a component of renin-angiotensin-aldosterone system involved in regulation of blood pressure in humans (Yan et al., 2020). Besides acting as a viral receptor, ACE2 also plays an important role in the initiation of pulmonary hypertension-like complications in COVID-19 patients (Emami et al., 2021). It catalyzes the conversion of angiotensin II (Ang II) into angiotensin 1-7 (Ang1-7) and converts Des-Arg9- bradykinin (DABK) into an active peptide (Donoghue et al., 2000; Stec, Juncos, & Granger, 2016). Ang II and DABK can affect many physiologic processes by constricting blood vessels, promoting inflammation, neutrophil infiltration, and pulmonary fibrosis (Donoghue et al., 2000; Sodhi et al., 2018). Hence, ACE2 is
indirectly involved in antiinflammatory and anti-lung injury effects (Zhou et al., 2020).

In vitro and computational studies, or their combination (L. Chen et al., 2006; Ryu et al., 2010; Yi et al., 2004) showed promising evidence that quercetin could be effective against SARS virus infection and consequent clinical outcomes (reviewed in Savant, Srinivasan, & Kruthiventi, 2021). It is intriguing to note that ACE2 receptor, expressed in organs such as lung, kidney, heart, intestine, and endothelial cells (Ferrario et al., 2005), mediates the SARS-CoV-2 infection in humans. Quercetin can target ACE2 expression (ACE2 gene expression is required for SARS-CoV-2 entry into human cells) (Glinsky, 2020) by interfering with Spike-ACE2 binding and interacting with papain-like protease (PLpro) (Figure 1). The net result of quercetin action is a significant reduction of the SARS-CoV-2 potential infectivity (Huang et al., 2020a). PLpro is a crucial enzyme of CoV implicated in the viral spread and immune evasion mechanisms (Shin et al., 2020). Yi et al. (2004) developed HIV-luc/SARS pseudotyped virus and carried out in vitro virus entry inhibition assay using quercetin and another related flavonoid, luteolin. Both these flavonoids were effective in inhibiting the entry of SARS-CoV inside the host cell.

Quercetin as well as its derivatives (luteolin, quercetin-3-β-galactoside, and epigallocatechin gallate) were observed to inhibit the activity of SARS-CoV proteases. Ryu et al. (2010) in an in vitro study observed that both luteolin and quercetin inhibited the enzyme activity of chymotrypsin-like protease (3CLpro), also known as the main protease (Mpro) of SARS-CoV, which plays a pivotal role in viral replication and infection processes. However, their inhibitory activity was lower than amentoflavone, a flavonoid derived from Torreya nucifera plant (Ryu et al., 2010). Nguyen et al. (2012) observed that both quercetin and epigallocatechin gallate inhibited 3CLpro in vitro with an IC50 (50% inhibitory concentration) of 73 μM. A similar study by Park et al. (2017) revealed that quercetin inhibited SARS-CoV proteases (3CLpro [IC50 of 52.7 μM] and (PLpro [IC50 of 8.6 μM]) as well as the Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) protease (3CLpro [IC50 of 34.8 μM]) in vitro. More recently, the screening
of a chemical library consisting of about 150 compounds, identified quercetin as a potent inhibitor of SARS-CoV-2 3CLPro (Ki~7 μM, Abian et al., 2020). In a different study, quercetin-3-β-galactoside, a quercetin derivative, was identified as an inhibitor of SARS-CoV 3CLPro using mutagenesis studies, molecular docking, surface plasmon resonance, and fluorescence resonance energy transfer bioassays (L. Chen et al., 2006).

The effectiveness of quercetin not only against SARS-CoV, but also SARS-CoV-2 has been suggested in a thought-provoking prediction study showing that the hypothetical tripartite combination of vitamin-D, quercetin, and estradiol can be putative COVID-19 mitigation agents. The authors of this computational work used supercomputer SUMMIT drug-docking screen and Gene Set Enrichment Analyses of expression profiling experiments and found quercetin and the structurally similar flavonoid, luteolin, as one of the top-scoring candidate therapeutics that can serve as scaffolds for the development of possible SARS-CoV-2 infection inhibitors (Glinsky, 2020). This finding has been supported by in vitro evidence indicating that both luteolin and quercetin could impede the entry of the SARS virus into the cells (Yi et al., 2004).

Besides these actions, quercetin supplementation will also help to circumvent the zinc deficiency problem in COVID-19 infected/elderly subjects as it acts as a zinc ionophore (Dabbagh-Bazarbachi et al., 2014), thereby helping in increasing the labile intracellular zinc concentration (Figure 1). It is noteworthy to mention that zinc has been shown to inhibit RNA-dependent RNA polymerase (RdRp) activity of the SARS virus under in vitro conditions in a dose-dependent manner (reviewed in Read, Obeid, Ahlenstiel, & Ahlenstiel, 2019). However, the hypothesis that quercetin along with zinc supplementation can be beneficial for COVID-19 treatment/prophylaxis is not clinically tested yet.

In summary, accumulating evidence deriving from both computational and experimental studies suggests that quercetin, as other phenolic compounds, can act at multiple levels to inhibit or reduce the infectivity of coronaviruses including SARS-CoV and SARS-CoV-2 although only very recently the clinical efficacy of these treatments have been explored (Bemini & Velotti, 2021; Di Pierro, Derosa, et al., 2021; Di Pierro, Iqtadar, et al., 2021; Rondanelli et al., 2022; Shohan et al., 2022).

3 | ROLE OF QUERCETIN IN COMORBID CONDITIONS INCREASING THE SUSCEPTIBILITY TO COVID-19

Emerging data clearly states that aging as well as various other concomitant conditions, such as COPD, diabetes, obesity, cardiovascular disease (CVD), and hypertension enhance the disease severity and mortality among COVID-19 patients (A. K. Singh & Misra, 2020; B. Wang, Li, Lu, & Huang, 2020; Wu & McGoogan, 2020). In the following sub-sections, we will analyze the potential beneficial role of quercetin in these conditions following COVID-19 infection.

3.1 | Senotherapeutics Potential of Quercetin against COVID-19

Epidemiological data on the mortality rate of COVID-19 patients clearly demonstrate that the elderly population, especially in the presence of co-morbidities, has a greater risk of death than the rest of the younger population in different countries (Ioannidis, Axfors, & Contopoulos-Ioannidis, 2020). If the simplest explanation implies that old people are at risk for their “intrinsic” frailty due to the presence of co-morbidities, such as diabetes, hypertension, cancer, and cardiovascular pathologies, this medical evidence is still poorly explored from a biological point of view (Blagosklonny, 2020). The big scientific challenge is to understand why the aging process is strictly correlated to SARS-CoV-2 deleterious infection. A possible answer resides in the biological process known from the early ‘60 and targeted as one of the “hallmarks of aging and cancer” : senescence (Roy et al., 2020).

Cellular senescence, first reported in 1961 by Hayflick and Moorehead (1961) is a cell condition that involves an irreversible replicative arrest, sustained viability with resistance to apoptosis, and, frequently, increased metabolic and inflammatory activity known as SASP (Senescence Associated Secretory Phenotype). SASP includes a myriad of inflammatory, pro-apoptotic, insulin resistance inducing cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, transforming growth factor (TGF)-β family members, all contributing to fibrosis, stem cell and progenitor dysfunction, increased plasminogen activator inhibitor-1 (PAI) that can cause blood clotting and fibrosis (Kirkland & Tchkonia, 2017; Roy et al., 2020).

Mechanistically, there are multiple factors inducing a senescent state in cells. These intrinsic or environmental factors alter tissue homeostasis in physiological or pathological conditions: DNA damage, telomere shortening after every cell division, proteolytic stress due to an alteration in autophagy process, oncogene activation inducing replicative stress, reactive metabolites such as ROS, inflammatory cytokines, and pathogen-associated molecular patterns (PAMPs) (Roy et al., 2020; Zhou et al., 2020). The senescence-inducing factors activate downstream biochemical pathways involving cell cycle proteins, such as p16Ink4 and retinoblastoma protein (Rb), p53, and p21Cip1 in others (Kirkland & Tchkonia, 2020; Roy et al., 2020). Finally, after days or weeks, senescence leads to replicative arrest with altered expression of hundreds of genes, as well as epigenetic changes.

From a mechanistic point of view, a recent work demonstrated that, in a mouse model of SARS-CoV-2-related β-coronavirus, quercetin and Dasatinib targeted senescent cells and, acting on PAMP. Their combination significantly reduced mortality, cellular senescence, inflammatory markers, and increased antiviral antibodies (Camell et al., 2021).

Morphologically, senescent cells appear flattened and enlarged, express active β-galactosidase in lysosomes, and can appear at any point during life in vertebrates, even in 32 cell stage human blastocysts (Meuter et al., 2014). Typically, senescent cells accumulate in multiple tissues during the latter part of the lifespan, such as fibroblasts in the skin and adipocytes in adipose tissue. Senescent cells are also present in many “pathological” tissues such as in pulmonary...
fibrosis, endothelium membranes and cardiac cells in CVD, and adipose tissue in diabetes and obesity (Kirkland & Tchkonia, 2020).

Kirkland and Tchkonia proposed a “Unitary Theory of Fundamental Aging Processes” according to which “accelerating or targeting any one fundamental ageing process (e.g., cellular senescence) genetically or with drugs” should affect the entire aging mechanism (Kirkland & Tchkonia, 2017, 2020). This hypothesis suggests a strict correlation between the distribution of senescent cells in the organism and healthspan. Therefore, a delayed accumulation of p16INK4a-positive senescent cells in mice in which healthspan was extended by caloric restriction led to the idea that senescent cells could be eliminated by a selective drug or drug combinations called “senolytics” (Kirkland & Tchkonia, 2004). To develop the first senolytic drugs, the Kirkland group utilized a strategy based on RNAi screening and previous observation that senescent cells are resistant to apoptosis (E. Wang, 1995). This approach allowed the identification of different molecules called “senotherapeutics”: the BH3 mimetics ABT-263 (Navitoclax), the tyrosine kinase inhibitor Desatinib, and natural flavonoids such as quercetin and fisetin (Kirkland & Tchkonia, 2020; Russo et al., 2020). The latter have been included in clinical trials protocols (phase1-2) aimed to ameliorate age-related pathologies such as pulmonary fibrosis, osteoarthritis, and diabetic chronic kidney disease (Kirkland & Tchkonia, 2020).

It is worthwhile to mention that senescence and stem cell exhaustion are processes showing considerable overlaps being the latter involved in the decline of the tissue regenerative potential, a characteristic of aging (López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013). To what extent coronavirus infections induce senescence/exhaustion, or target previously senescent cells is not clearly defined. A recent pivotal article (S. Lee et al., 2021) reported that SARS-CoV-2 evoked cellular senescence as a primary stress response in infected cells. The authors also showed that senescent, such as navitoclax (BH3 mimetic) and a combination of Dasatinib plus quercetin selectively eliminated virus-induced senescent cells, mitigated COVID-19-reminiscent lung disease, and reduced inflammation in SARS-CoV-2-infected hamsters and mice.

In the specific case of elderly (comorbid) COVID-19 patients, selective elimination of infected “senescent” cells in the lung by quercetin alone or in association with BH3 mimetics or Dasatinib may be critical for the termination of viral infection without deleterious side effects. However, several unknown aspects of senescence-related to virus infection persist. Ten years ago, cellular senescence has been also described as an anti-viral mechanism. Indeed, the release of pro-inflammatory mediators and cell cycle arrest characterizing senescent cells are very similar to the features observed by many cells during an antiviral response (Reddel, 2010).

In the specific case of SARS-CoV-2 infection, many questions should be experimentally solved: are senescent cells a “favorite” target of coronavirus infection in the respiratory tissues due to the presence of cellular receptors, such as ACE2 or cluster of differentiation (CD)-26 (Sargiacomo, Sotgia, & Lisanti, 2020)? In fact, ACE2 is a known inhibitor of cell proliferation and the angiotensin system is upregulated in both premature and replicative senescence and quercetin is able to interact with this key cellular receptor. To reinforce this hypothesis, MERS-CoV cellular receptor CD26 (also called dipeptidyl-peptidase IV, DPP4), is known to be a bona fide cell surface marker of senescent cells (Sargiacomo et al., 2020).

On the opposite, could senescence be a mechanism that cells use to escape viral spreading through SASP? Alternatively, could SASP be a sort of hyperactivity due to immune-senescence resulting in the so-called cytokine storm? CD8+ cytotoxic lymphocyte senescence is associated with critical telomere shortening and induces a state of “hyper-function” with evasion of apoptosis, increased secretion of pro-inflammatory cytokines and loss of surface CD28, a co-stimulatory receptor necessary for the mobilization of targeted T-cell immune responses (Dock & Effros, 2011). The presence of this type of lymphocyte circulating in the blood of patients affected by COVID-19 could be useful in vivo marker to test the efficacy of senolytics in future clinical trials.

These questions remain unexplored in SARS-CoV-2 infection. Kirkland’s group observed that the senolytic flavonoid fisetin was able to reduce mortality in mice infected with mouse β coronavirus. If this unpublished study and the hypothesis that COVID-19 viral antigens exacerbate the SASP in human senescent cells will be confirmed (Kirkland & Tchkonia, 2020), it may represent strong scientific evidence to support the human clinical trials just approved by the FDA. These trials are based on natural flavonoids such as quercetin and fisetin in older hospitalized COVID-19 patients to prevent progression to cytokine storm and acute respiratory distress syndrome (ARDS). Hopefully, if positively concluded, these studies will demonstrate the efficacy of senotherapeutics based on natural molecules, such as quercetin or fisetin, to enrich the pharmacological arsenal of senolytic drugs (azithromycin) against SARS-CoV-2 and possibly other future coronaviruses variants (Malavolta, Giaconci, Brunetti, Provinciali, & Maggi, 2020). Indeed, the approach of senolytic drugs is not to attack a specific virus or to boost the immune system by specific targeting, rather it is aimed to improve health, including immune health, by targeting senescence, one of the hallmarks of aging biology. Of note, “the Geroscience approach is not specific to COVID-19, but once tried and proven, it would be effective against any future pandemics or epidemics” (Sierra, 2020).

In conclusion, the evidence reported in this section demonstrates that targeting senescent cells using senolytic drugs significantly reduced mortality, cellular senescence, and inflammatory markers and increased antiviral antibodies following infection by SARS-CoV-2 and other viruses.

### 3.2 Anti-COPD effects of quercetin

COPD is a highly diffuse disease whose morbidity and mortality cause a general social and economic worry, considering that WHO reported a global number of COPD cases in 2016 of about 251 million, with an estimation of 3.17 million deaths in 2015 (equal to about 5% of the overall deaths in the world) (Goncalves et al., 2018; D. Singh et al., 2019). Since 2006, it was predicted that COPD in 2030 would
represent the fourth cause of death after ischemic heart disease, cerebrovascular disease (stroke), and HIV/AIDS (Mathers & Loncar, 2006). COPD can be considered a multifactor disease with tobacco smoking (active and passive) and air pollution exposure representing the strongest risk factors (Lange, Ahmed, Lahmar, Martinez, & Bourdin, 2021). At cellular level, COPD is associated with changes in the airway epithelium of both progenitors and differentiated cells. Following smoke exposure, the reprogramming and proliferation of basal cells cause aberrant differentiation leading to exhaustion of progenitors cells, an increase of squamous cell numbers, and production of pro-inflammatory cytokines and other molecular mediators responsible for the emphysematous destruction of the alveolar structure (Lange et al., 2021).

Following the recent COVID-19 pandemic, clinical observations indicate that a proportion of patients can develop pneumonia and acute severe respiratory failure associated with higher mortality (Zhou et al., 2020). In this scenario, COPD patients have been identified as a high-risk sub-group who need to remain protected from viral transmission (Higham, Mathioudakis, Vestbo, & Singh, 2020). In fact, the observations that COPD patients show an increased pulmonary expression of the SARS-CoV-2 receptor, ACE2, (Smith et al., 2020) and their features of endothelial cell dysfunction and increased coagulopathy (Vaidyula, Criner, Grabianowski, & Rao, 2009), provide molecular and physio-pathological explanations of the increased susceptibility of COPD patients to COVID-19 infection and associated morbidity (Higham et al., 2020).

Early in 2003, it was reported that resveratrol inhibited cytokine release in alveolar macrophages isolated from COPD patients (Culpitt et al., 2003). Since then, the role of polyphenols in COPD has been largely studied and proceeded in parallel with the “antioxidant hypothesis” in the therapeutic and preventive approach to COPD treatment (Rahman, 2006; Rahman & Adcock, 2006). In those years, it was suggested that dietary polyphenols could ameliorate COPD conditions by multiple mechanisms relaying on inhibiting nuclear factor kappa B (NF-κB) activation, histone acetylation, the release of pro-inflammatory cytokine (Rahman, 2006; Rahman & Adcock, 2006). Although this initial enthusiasm has not been fully supported by intervention studies and currently no nutritional recommendations for COPD management have been formally published, the role of polyphenols in maintaining lung function and preventing respiratory diseases remain of great interest (Scoditti, Massaro, Garbarino, & Toraldo, 2019).

Quercetin is among the polyphenols identified as being potentially effective against COPD (Figure 2). Originally, it was observed that this flavonol and its derivatives inhibited the phosphodiesterase (PDE)-4, the PDE isoenzyme present in airway tissues and immune cells with relevant functions to the pathogenesis of asthma. This suggested the potential effectiveness of quercetin also in the therapy of COPD alone or in association with other PDE4 inhibitors (Chan et al., 2008). However, it must be underlined that the inhibitory activity was assayed on enzymes purified from guinea pig tissues and no in vivo treatment with quercetin or its derivatives was performed. This initial observation was confirmed later by a study designed to assess the capacity of quercetin to induce bronchoconstriction by preventing the PDE4-dependent degradation of cyclic adenosine monophosphate (cAMP) in myograph studies using ex vivo A/J mouse tracheas (Townsend & Emala Sr, 2013). In the same study, the authors reported that nebulization of quercetin (100 μM) induced bronchorelaxant effects when administered acutely before the methacholine challenge (Townsend & Emala Sr, 2013).

Several works confirmed the bronchodilator capacity of quercetin on human airway smooth muscle (ASM) in obstructive lung diseases such as asthma and COPD. As an example, quercetin, at micromolar concentrations (50–100 μM), reduced current mediated by L-type voltage-dependent Ca^{2+} channels (LVDCCs) in single ASM cells isolated from BALB/c mouse tracheal smooth muscle and lowered precontraction induced by acetylcholine chloride (ACH) in human bronchial ASM strips (Luo et al., 2018). At comparable concentrations, quercetin reduced reactive oxygen species (ROS) and nitric oxide (NO) production in J774A.1 alveolar macrophage exposed to cigarette smoke extract. The same antioxidant effect of quercetin (10 mg/kg-day) was supposed in C57BL/6 mice exposed to cigarette smoke (da Silva Araújo et al., 2020). Administration of 0.5 mg of quercetin daily for 10 days in elastase/lipopolysaccharide (LPS)-exposed mice, which mimic the typical features of COPD resulted in reduced emphysema, lung inflammation, goblet cell metaplasia, and expression of pro-inflammatory cytokines, all markers of progressive COPD (Ganesan et al., 2010).

The preclinical evidence that quercetin could be effective in COPD and other obstructive lung diseases has been recently corroborated by a randomized, double-blind, placebo-controlled phase I clinical trial on 10 eligible subjects with COPD. Here, a dose-escalation administration of quercetin (500, 1,000, or 2,000 mg/day for 1 week) was well tolerated with no serious adverse events or significant changes in lung functions (forced expiratory volume in 1 s and forced vital capacity) and blood parameters (white blood cells, platelets and fasting glucose) (Han, Barreto, Martinez, Comstock, & Sajjan, 2020). Unfortunately, due to the limited number of subjects in each arm, statistical significance was not performed in this study.

In conclusion, although to our knowledge no studies have been published on quercetin in COPD patients affected by COVID-19, it is of interest that in C57BL/6 mice, where a mild COPD-like lung disease was induced, infection by rhinovirus (RV) increased inflammatory scores (peribronchial and perivascular inflammation, alveolar inflammation, and emphysema). These effects were reduced or abolished by quercetin supplementation (0.1% quercetin in the diet) 10 days prior to RV infection (Farazuddin et al., 2018). This result is even more important considering that RV infection exaggerates respiratory illness in COPD patients making the disease more severe and prolonged (Mallia et al., 2011).

### 3.3 Anti-diabetic and anti-glucose effects of quercetin

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (American Diabetes Association, 2010). The global prevalence of
diabetes is very high as there were nearly 415 million people were affected with diabetes in 2015 (Zimmet, 2017). Diabetes patients have an enhanced incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease along with hypertension and abnormalities of lipoprotein metabolism. If uncontrolled, diabetes may lead to stupor, coma, and even death (Craig, Hattersley, & Donaghue, 2009; Galtier, 2010). Prevailing data from existing literature suggest that diabetes itself is not a risk factor for COVID-19; however, it may augment the disease severity in critically ill patients as compared to non-diabetic patients (Pugliese, Vitale, Resi, & Orsi, 2020). As ACE2 receptors are also expressed by pancreatic beta cells (Hamming et al., 2004), SARS-CoV-2, by interfering with glucose metabolism, may create more complications in diabetes patients, or even lead to the onset of new diabetes in infected subjects (Rubino et al., 2020). Conversely, complications associated with diabetes involving diabetic ketoacidosis and hyperosmolarity may result in an enhanced risk of COVID-19 severity (Chee, Ng, & Yeoh, 2020). In diabetic persons, enhanced ROS and oxidative stress lower insulin secretion and augment hyperglycemia, which in turn resulting pancreatic β-cell death (H. Patel, Chen, Das, & Kavdia, 2013). Studies in COVID-19 patients have established that various comorbidities including obesity, hypertension as well as CVD, and chronic kidney disease (CKD) are more common in diabetes patients than in non-diabetes ones (Yan et al., 2020b; Zhu et al., 2020b).

Several animal studies reported the ability of quercetin to improve glycemic control in both type-1 as well as type-2 diabetes (Arias, Macarulla, Aguirre, Martínez-Castaño, & Portillo, 2014). Quercetin reduces the level of blood glucose mostly via its antioxidant action or by modulating hepatic gene expressions (J. Y. Jung, Lim, Moon, Kim, & Kwon, 2011), and obstructing the action of the α-glucosidase enzyme in vitro (J. H. Kim et al., 2011). Dai et al. (2013) observed that quercetin reduced the blood sugar significantly by stimulating AMP-activated protein kinase (AMPK; a crucial manager of entire body-energy homeostasis) mediated glucose uptake by skeletal muscles and enhanced Glucose transporter type 4 (GLUT4) expression.
Hamilton et al. (2018) also reported similar effects of quercetin, which triggered the uptake of glucose in C2C12 skeletal muscles in vitro through a mechanism involving AMPK. In mice, quercetin, by activating the AMPK complex, increases the intracellular levels of AMP or AMP-ATP ratio, reduces oxidative destruction, and enhances the uptake of glucose (Antonioli et al., 2016). Quercetin enhances glucose uptake by interfering with glucose transport and insulin-receptor signaling (Dhanya, Arya, Nisha, & Jayamurthy, 2017). In fructose-streptozotocin (STZ)-nicotinamide-induced diabetic rats, quercetin counteracted the negative effects of oxidative stress, inflammation, and apoptosis in the heart (Roslan, Nelli Giribabu, Karim, & Salleh, 2017). In the same rat model, the treatment with quercetin and resveratrol preserved the action of hepatic glucose metabolic enzymes as well as the structure of pancreatic β-cells (Yang & Kang, 2018). Another study reported that the dietary consumption of quercetin decreases the possibility of type-2 diabetes (Song, Manson, Buring, Sesso, & Liu, 2005). Diet-induced insulin resistance can be reduced by long-term dietary intake of quercetin, and it also upregulates peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC1α) in skeletal muscles to improve mitochondrial function (Henagan, Lenard, Gettys, & Stewart, 2014) to support insulin action. According to this observation, the meta-analysis of Bule, Abdurahman, Nikfar, Abdollahi, and Amini (2019) indicated that quercetin was able to reduce the serum glucose level at doses ranging between 10 and 50 mg/kg.

In conclusion, the evidence gleaned in this section exhibits that quercetin lowers blood glucose levels by different mechanisms. However, no studies have been published on the effect of quercetin in diabetic patients affected by COVID-19.

3.4 | Anti-obesity effects of quercetin

Obesity along with overweight presents a major public health challenge affecting nearly a third of the world’s population (Hruby & Hu, 2015). It is a complex, multifactorial disease involving the unnecessary accumulation of adipose tissue. A higher level of infectious disease watchfulness is needed for such subjects because there is always a possibility of the development of various risk factors, such as diabetes mellitus, CVD, hypertension, and dyslipidemia (Panuganti, Nguyen, & Kshirsagar, 2020). Patients with severe obesity as well as those with weight-related comorbidities, such as CVD, diabetes, kidney, and liver ailments are at higher risk of COVID-19 infection (A. K. Singh & Misra, 2020). Manifestations caused by these comorbidities may result in an improper immune response against the virus and may reduce patient response to general COVID-19 therapy.
(Dietz & Santos-Burgoa, 2020; Sattar, McNees, & McMurray, 2020). Besides innate immunity, obesity also affects the adaptive immune responses as observed against the influenza virus (Green & Beck, 2017). Obesity also potentiates many factors including the development of cardiorespiratory and cardiovascular disorders as well as adverse cardio-renal consequences (Sattar et al., 2020). All these observations confirm the seriousness and adverse impacts of obesity in COVID-19 patients.

Oxidative stress plays an important role in the initiation and progression of obesity (Karam, Chavez-Moreno, Koh, Akar, & Akar, 2017). Quercetin is involved in the regulation of hepatic gene expression and lipid metabolism (C. H. Jung, Cho, Ahn, Jeon, & Ha, 2013). It induces the breakdown of adipocyte lipid in a dose- and time-dependent way by enhancing the levels of cyclic adenosine monophosphate and hormone-sensitive lipase action. It can also decrease the gene expression of main adipogenic factors peroxisome proliferator-activated receptor γ (PPAR-γ) and CCAAT/enhancer binding protein α to prevent the formation of adipocytes (Ahn, Lee, Kim, Park, & Ha, 2008). A recent study demonstrated that quercetin and one of its acetylated derivatives were able to induce chromatin remodeling at the SRE regulatory region of c/EBPα and PPARα and reduce in rats body weight and adipocyte size determined by HFD (high-fat diet) (Nettore et al., 2019). In addition, by regulating the extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinases (JNK) pathways, quercetin induces apoptosis in mature fat cells (S. Chen, Jiang, Wu, & Fang, 2016). In vitro studies also showed the potential role of quercetin in inhibiting foam cell formation (Cao et al., 2019; Sun et al., 2015). Furthermore, quercetin prevented obesity by enhanced expression of uncoupling protein 1 (UCP1) in adipose tissues, along with up-regulation of AMPK activation (H. Choi, Kim, & Yu, 2018) (Figure 4).

In HFD fed mice, quercetin reduced the macrophage infiltration as well as the levels of proinflammatory mediators in adipose tissues (Dong et al., 2014). Moreover, in a study on healthy male smokers, the supplementation of quercetin dihydrate capsule (100 mg/day for 10 weeks) decreased the levels of total cholesterol and LDL-cholesterol in serum compared to the placebo control group (K. H. Lee et al., 2011). Quercetin (150 mg/day) reduced the waist size and triacylglycerol concentration in overweight-obese subjects (Pfeuffer et al., 2013). A randomized, double-blind, placebo-controlled study demonstrated that supplementation of quercetin (100 mg/day) for 12 weeks to obese subjects significantly decreased the total body fat and reduced the body mass index (BMI) (J. S. Lee, Cha, Lee, & Yim, 2016).

In conclusion, quercetin exhibits pleiotropic beneficial effects against obesity in preclinical models. To date, no studies have been published on the effect of quercetin in obese individuals affected by COVID-19.

3.5 Anti-thrombin and anti-fibrinogen effects of quercetin

Hemostasis is a highly regulated, orchestrated localized physiological process that checks to bleed at the injury site by the formation of a clot (Gale, 2011). Any kind of aberration in hemostasis may result in extensive thrombosis associated with microvascular injury in affected organs including the lungs (Ackermann et al., 2020) and even severe intravascular coagulation (Tang, Li, Wang, & Sun, 2020). Hypercoagulability is one of the common manifestations of COVID-19 which is associated with disease severity (G. Chen et al., 2020). Elevated levels of plasmin, due to diabetes and other comorbidities, support the virus binding to ACE2 as well as entry into the cells as plasmin cleaves the S protein of SARS-CoV-2. Furthermore, the breakdown of fibrin by plasmin leads to the usual elevation of D-dimer and other fibrin degradation products (J. Zhao, Matalon, & Matthay, 2020). Besides, elevated levels of D-dimer, cutaneous changes in extremities of several patients are indication of thrombotic microangiopathy (P. P. Liu, Biet, Smyth, & Li, 2020). Intravascular coagulation and thrombosis in large vessels were associated with multiple organ failure (Porfidia & Pola, 2020; Zhu et al., 2020a). It is worth noting that thrombosis is primarily related to inflammatory markers, but not as coagulation parameters (Al-Samkari et al., 2020).

The antiplatelet property of quercetin is largely proven by the observation that it inhibited the aggregation of platelets (Figure 5) upon in vitro treatment as well as ex vivo supplementation (Hubbard, Wolffram, Lovegrove, & Gibbins, 2004; Oh, Endale, Park, Cho, & Rhee, 2012). Quercetin at a concentration of 100 μM or higher showed an anti-clotting effect by prolongation of thrombin (an active plasma coagulation factor II) time (Mozzicafreddo, Cuccioloni, Eleuteri, Fioretti, & Angeletti, 2004). Quercetin and isoquercetin (quercetin-3-O-β-D-glucoside) exhibit antithrombotic and antiocoagulant effects by inhibiting the enzymatic action of thrombin and factor Xa (J. H. Choi, Kim, & Kim, 2016). Isoquercetin, when administered orally, inhibited the activity of protein disulfide isomerase, an enzyme required for thrombus formation, in plasma and reduced the platelet-dependent thrombin production mainly by obstructing the platelet factor Va production (Stopa et al., 2017). Bijak et al. (2014) suggested that the molecular structures of natural flavonoids, cyanidin, and quercetin, can be used as pharmacophores to design and synthesize more suitable anticoagulants due to their strong efficacy in inhibiting thrombin. Besides quercetin, a potential antithrombotic role is also suggested for its two metabolites, isorhamnetin, and tamarixetin, which exhibit antiplatelet activity as evident by the study of Stainer et al. (2019).

In conclusion, based on the scientific literature available it can be concluded that there is scant clinical data to support the role of quercetin as an anti-thrombin and anti-fibrinogen agent.

3.6 Anti-hypertensive effects of quercetin

Hypertension or high blood pressure is defined as the presence of a chronic rise in systemic arterial pressure above a certain threshold value (Oparil et al., 2018). Nearly 45% of the world’s adult population is at risk, particularly the people with an age above 60 years. Although most cases of hypertension are asymptomatic, some may show symptoms of chest pain, pulmonary edema, hypertensive encephalopathy or stroke, and shortness of breath (Vallelonga et al., 2020). As
observed in previous coronavirus epidemics, such as SARS and MERS, hypertensive patients are at high risk of enhanced mortality with COVID-19 than non-hypertensive patients (Nadar, Tayebjee, Stowasser, & Byrd, 2020; Pormohammad et al., 2020). Hypertension was observed to be the most predominant comorbidity with a prevalence of nearly 23.4% in severe cases of COVID-19 (Guan et al., 2020; Huang et al., 2020b). Liang et al. (2020) revealed that hypertension acts as a risk element for pathogenesis and mortality in patients with COVID-19. Factors, like CVD and old age, aggravate the death rate in hypertensive patients compared to those without hypertension (Leiva Sisnieguez, Espeche, & Salazar, 2020). Furthermore, data obtained from various clinical studies have revealed that imbalanced as well as elevated levels of certain cytokines, such as IL-6, IL-7, TNF-α results in hypertension and disease severity in COVID-19 patients (Drummond, Vinh, Guzik, & Sobe, 2019; Huang et al., 2020b). In such subjects, the enhanced inflammatory response may cause vasoconstriction and cell damage in the lung (Dhaun & Webb, 2019; Zhang et al., 2020).

Various experimental studies and clinical trials demonstrated that quercetin can exert anti-hypertensive effects through different mechanisms. Duarte et al. (2001) observed that quercetin reduced oxidative stress in spontaneously hypertensive rat models, mimicking hypertension in humans. In a similar study on spontaneously hypertensive rats, quercetin decreased blood pressure and reinstated

**FIGURE 4** Anti-adipogenesis activity of quercetin. Quercetin exerts a suppressive effect on fat accumulation by activating HSL which converts TGs to FFAs. Moreover, it also stimulates the expression of UCP1 to increase energy expenditure, an important player in the anti-obesity phenomenon. Furthermore, quercetin also restricts pre-adipocyte differentiation, adipogenesis, and inflammation by inhibiting MAPK mediated signaling and its downstream factors like PPARγ and CREB. Quercetin opposes the anti-apoptotic effect of ERK1/2 signaling to promote apoptosis in mature adipocytes and thereby displays its anti-obesity potential. Furthermore, quercetin also increases cholesterol efflux from macrophages to prevent foam cell formation via activation of the PPARγ-ABCA1 pathway and thereby lowers the risk of atherosclerosis. ABCA1, ATP-binding cassette transporter A1; AC, adenylyl cyclase; Bcl-2, B-cell lymphoma 2; cAMP, cyclic adenosine monophosphate; CREB, CCAAT/enhancer-binding protein; DG, diglycerides; ERK, extracellular-signal-regulated kinase; FFAs, free fatty acids; HSL, hormone-sensitive lipase; IR, insulin receptor; LEP-R, leptin receptor; MAPK, mitogen-activated protein kinase; MEK, ERK kinase; MG, monoglycerides; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-α; PKA, protein kinase A; PPARγ, peroxisome proliferator-activated receptor γ; TGs, triglycerides; UCP1, uncoupling protein 1.
endothelial dysfunction (Galindo et al., 2012). Häckl, Cuttle, Dovichi, Lima-Landman, and Nicolau (2002) observed that quercetin reduced the blood pressure induced by intravenous infusion of angiotensin I in Wistar rats and reduced the ACE activity by 31% as compared to baseline. The anti-ACE activity could be due to the presence of the catechol group in the B-ring of flavonoids, which may exert a charge–charge interaction with the Zn$^{2+}$ ion in the ACE active site (Guerrero et al., 2012).

Mackraj, Govender, and Ramesar (2008) suggested that quercetin lowers blood pressure through mechanisms, such as down-regulation of the angiotensin-I receptor in the kidney, enhanced urine volume, and augmented urinary sodium excretion. Serban et al. (2016) in their meta-analysis observed that other possible mechanisms by which quercetin exhibits anti-hypertensive properties include improvement in vascular function (Yamamoto & Oue, 2006), enhancing the endothelial nitric oxide (NO) synthase activity, and reduction of NADPH oxidase activity (Sanchez et al., 2006), decreasing endothelin-1 expression (Nicholson, Tucker, & Brameld, 2008) and maintaining the balance between circulating endothelin-1 and NO (Sanchez et al., 2006). Among the several polyphenols tested, quercetin and its metabolites were the most effective in inhibiting recombinant human (rh) ACE2 in vitro (P. P. Liu et al., 2020).

In conclusion, there is robust data to support the anti-hypertensive effects of quercetin. More clinical studies are needed to investigate the effect of dietary polyphenol intake on ACE2 as well as on blood pressure in healthy as well as COVID-19 patients.

4 | CHALLENGES POSED BY PHARMACOKINETICS OF QUERCETIN

Possible applicative outcomes of natural bioactive compounds, such as quercetin, on health, are limited by their low bioavailability after oral administration. Multiple studies have shown that quercetin and its methylated derivatives with an intact flavonol structure (isorhamnetin, tamarixetin) are present only in the conjugated form, mainly glucuronide and sulfate conjugates, and not as free aglycones (Egert et al., 2008). Rich, Buchweitz, Winterbone, Kroon, and Wilde (2017) reported poor oral bioavailability of quercetin after a single oral dose due to macronutrient absorption. Quercetin and its derivatives are transformed into various metabolites such as the smaller phenolics by intestinal enzymes and bacteria (D. H. Kim, Kim, Park, & Han, 1999). Quercetin is also metabolized in the liver into methyl, glucuronide, and sulfate metabolites, which circulate in plasma (Lotito, Zhang, Yang, Crozier, & Frei, 2011), and hence the
concentration of quercetin metabolites was observed to be lower in the liver than that of blood plasma (Manach et al., 1999).

Low bioavailability of the unmodified quercetin as compared to its metabolites in the systemic circulation, suggests extensive first-pass metabolism by gut and/or liver (Ader, Weissmann, & Wolffram, 2000; Oliveira, Watson, & Grant, 2002). Elevated concentration of conjugated quercetin in the bile through biliary excretion (Bravo, 1998; Y. Liu, Liu, Dai, Xun, & Hu, 2003) may result in elevated plasma metabolite concentrations (X. Chen, Yin, Zuo, & Chow, 2005). Hollman, de Vries, van Leeuwen, Mengers, and Katan (1995) detected that in ileostomized but healthy volunteers, 24% of quercetin was absorbed after consumption of quercetin aglycone (100 mg/day). Intake of quercetin along with vitamin C, folate, and additional flavonoids improved its bioavailability (Harwood et al., 2007; Manach, Mazur, & Scalbert, 2005). Elimination of quercetin from the human body is quite slow with a testified half-life of 11 to 28 hr, and an average terminal half-life of 3.5 hr (Manach et al., 2005).

Quercetin and its derivatives remain unaffected by gastric juice in the stomach, are hydrolyzed by beta-glucosidases to the aglycone form and are absorbed in the upper region of the small intestinal (Crespy et al., 1999). According to Dabeek and Marra (2019), the structure of sugar moieties had a significant impact on the absorption of these compounds. Sodium-dependent glucose transporter (SGLT 1) transports the quercetin glucosides actively into enterocytes (Williamson, Kay, & Crozier, 2018).

Quercetin bioavailability is also affected by the presence of other food components such as lipids, proteins, and carbohydrates in the intestine (H. Zhang et al., 2014). Interestingly, a typical Western-type diet of humans contains enough dietary fat to facilitate the absorption of quercetin (Lesser, Cermak, & Wolffram, 2004). Being a lipophilic compound, absorption of quercetin aglycone across the intestinal membranes is higher than its glycosidic forms since it takes place by simple diffusion (Nemeth & Piskula, 2007). Enhanced bioavailability and assimilation of quercetin if consumed with a fatty diet is probably due to its inclusion into lipid micelles (Guo et al., 2013).

In conclusion, the metabolism of quercetin, its biotransformation, bioavailability, and tissue distribution have been largely studied. It remains to be determined how the low circulating concentrations of quercetin aglycone can explain its biological effects. It is desirable that the low bioavailability of quercetin can be bypassed or ameliorated by innovative drug delivery systems (e.g., nanoparticles, lipid nanoparticles, liposomes, micelles, carbon nanotubes, etc.), a field constantly growing that is beyond the scope of the present work.

5  |  USE OF QUERCETIN IN CLINICAL TRIALS AGAINST COVID-19

Experimental and preclinical studies along with prospective masked randomized clinical trials will likely be relevant to answering quercetin effectiveness/mechanisms against SARS-CoV-2 related questions. In fact, currently (as of January 9, 2022) 14 interventional clinical trials are underway for evaluation of quercetin efficacy as prophylaxis and treatment option against COVID-19 as drug/by supplementing diet (Table 1, source: https://clinicaltrials.gov/). Among these, six studies have been completed and eight are ongoing, but in the large part of the former, the results are still awaited. However, one study, namely NCT04578158, (Table 1) was published and reported that quercetin phytosomes (quercetin formulated with sunflower lecithin, which increases its absorption rate up to 20 times compared to pure quercetin), if used in the early stage of COVID-19 infection (in combination with conventional anti-COVID-19 therapies), improved the early symptoms and helped in preventing the severity of COVID-19 (Di Pierro, Derosa, et al., 2021). Six other interventional, randomized trials are investigating the potential benefits of quercetin alone or quercetin phytosome in SARS-CoV-2 infected subjects (NCT04578158, NCT04377789, NCT04861298, NCT04853199, NCT04851821, NCT05037240; Table 1). The rationale behind several of these trials is the hypothesis that quercetin may reinforce the natural immune system making it more competent to counteract the progression of COVID-19 in the early stage of infection. On the other hand, the administration of *Psidium guajava* extract (2 capsules three times daily) has been suggested to shorten the duration of COVID-19 seroconversion in mild and symptomless cases (NCT04810728, Table 1).

The combined effects of quercetin plus zinc, vitamin C, and bromelain are under investigation in COVID-19 patients (NCT04468139; Table 1), while its capacity in improving the efficacy and safety of hydroxychloroquine for the prevention and treatment of COVID-19 infection is also ongoing (NCT04590274; Table 1). Furthermore, an RCT is exploring the efficacy and safety of quercetin derivate, isorquercetin (IQC-950AN) in combination with standard care or masitinib in confirmed moderate and severe COVID-19 patients (NCT04536090 and NCT04622865; Table 1). In fact, isoquercetin prevents the activity of disulfide isomerase (PDI) which is directly involved in the formation of the clots and also reduces D-dimer, an interpreter of SARS-CoV-2 infection mediated thrombosis severity. The implementation of masitinib, a tyrosine kinase inhibitor, may hamper the production of the “cytokine storm” by blocking mast cells and macrophages activity. Another comparative RCT is evaluating the efficacy and safety of NASAFYTOL® containing quercetin along with curcumin and vitamin D on hospitalized COVID-19 patients (NCT04844658; Table 1). NASAFYTOL® is designed to augment the bioavailability of the bioactive components in humans and it is also under investigation in patients with early COVID-19 symptoms to prove its capacity to ameliorate viral clearance (NCT05080003; Table 1).

In conclusion, a wide array of quercetin's therapeutic properties has prompted various clinical trials to study its effect in COVID-19. Overall, these clinical trials are rigorously trying to investigate the prophylactic and therapeutic index of quercetin during COVID-19 infection.

6  |  CONCLUSIONS AND FUTURE PERSPECTIVES

The current COVID-19 pandemic, hit mankind hard with a stuporous jolt, infecting more than 304 million people including 5.4 million
| #  | Clinical trial ID code | Intervention/drug(s)                                                                 | Types of intervention/allocation                                                                 | No. of subjects/age/sex                  | Phase |
|----|------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------------|-------|
| 1  | NCT04578158            | - Drug: Standard COVID-19 care<br>- Dietary supplement: 400 mg of oral quercetin Phytosome/day | Treatment/randomized/parallel assignment/open label study to assess the adjuvant benefits of quercetin phytosome in patients with COVID-19 | 152/18 years and older/all sex          | 3     |
| 2  | NCT04377789            | - Prophylaxis: 500 mg/day in non-COVID-19 (intervention group 1).<br>- Treatment: 1000 mg/day in COVID-19 cases (intervention group 2) | Prevention/randomized/parallel assignment/open label study to assess the effects of quercetin on prophylaxis and treatment of COVID-19 | 447/18 years and older/all sex          | NA    |
| 3  | NCT04861298            | - Drug: Standard of care for COVID-19 as per the hospital guidelines<br>- Dietary supplement: Quercetin phytosome 600 mg/day for the 1st week; 400 mg/day 2nd week | Treatment/randomized/parallel assignment/open label to investigate the benefits of dietary supplementation of quercetin in patients with early COVID-19 symptoms | 142/18 years to 65/all sex              | NA    |
| 4  | NCT04468139            | - Drug: Quercetin (500 mg/day), zinc (50 mg/day), vitamin C (1,000 mg/day)<br>- Dietary supplement: Bromelain (500 mg/day) | Treatment/single group assignment/open label to study the effects of a mixed therapy (zinc, quercetin, bromelain and vitamin C) in patients infected with COVID-19 | 60/18 years and older/all sex           | 4     |
| 5  | NCT04853199            | - Drug: Quercetin versus placebo (no information available on quercetin dose)       | Treatment/randomized/parallel assignment with triple masking to assess the efficacy of quercetin treatment in COVID-19 patients | 200/18 years and older/all sex          | Early |
| 6  | NCT04622865            | - Drug: Masitinib<br>- Drug: Isoquercetin (no information available on isoquercetin dose) | Treatment/randomized/parallel assignment with triple masking to assess the effects of masitinib combined with isoquercetin in hospitalized patients with moderate and severe COVID-19 | 200/18 years and older/all sex          | 2     |
| 7  | NCT04810728            | - Drug: Extract Psidii guava (no information available on quercetin dose)<br>- Combination product: Standard therapy | Treatment/randomized/parallel assignment with double masking to assess the efficacy of Psidii guava’s extract for COVID-19 | 90/13 to 59 years (child, adult/all sex) | 3     |
| 8  | NCT04590274            | - Drugs: Hydroxychloroquine and azithromycin<br>- Dietary supplement: Vitamins and minerals (no information available on quercetin dose) | Prevention/single group Assignment/open label to study the safety and efficacy of hydroxychloroquine for the treatment and prevention COVID-19 | 5,000/child, adult, older adult/all sex | 1     |
| 9  | NCT04536090            | - Drug: Isoquercetin (IQC-950AN; no information available on isoquercetin dose) | Treatment/randomized/parallel assignment/with single masking to study the effect of isoquercetin (IQC-950AN) in the treatment of COVID-19 | 150/18 years and older/all sex          | 2     |
| 10 | NCT04851821            | - Drug: Quercetin (no information available on quercetin dose)                     | Treatment/randomized/parallel assignment with double masking to study the effects of phytotherapy in COVID-19 patients | 80/18 years and older/all sex           |       |
| 11 | NCT04844658            | - Drug: NASAFYTOL® (no information available on quercetin dose)<br>- Drug: FULTIUM® -D3 800 | Treatment/randomized/parallel assignment/open label to study the efficacy of Nasafytol® in COVID-19 hospitalized patients | 50/18 years and older/all sex           | NA    |
| 12 | NCT05008003            | - Drug: Standard of care<br>- Dietary supplement: Combination of curcumin, quercetin (260 mg/day for 14 days) and vitamin D | Interventional/randomized/parallel assignment/open label to assess the efficacy of vitamin D, quercetin and curcumin in combination in the early symptoms of COVID-19 | 100/18 years and older/all sex          | NA    |
methodological approaches and technologies are already available producing the cal investigations, both on cellular or animal models mimicking or rep-
These studies need to be confirmed and reinforced by robust preclini-
computational analysis supported in several (but not all cases) by extended to SARS-CoV-2 and the abundance of studies based on ceration that, along with conventional therapies, might play some role in ameliorating COVID-19 infection and symptoms acting in con-
cet on two parallel and independent paths: inhibiting key factors responsible for SARS-CoV-2 infections and mitigate the clinical mani-
festations of the disease in patients with comorbidities or in those subjects who are more prone to severe COVID-19 progression. How-
ver, in both cases, we are in a very early, although promising, phase of knowledge and in this review, we tried to analyze the strengths and weaknesses of this hypothesis.

In the last 2 years, we assisted in a proliferation of studies dealing with the anti-COVID-19 properties of natural compounds or extracts and quercetin falls perfectly in this category, as we discussed above. The common and main weakness of these studies is represented by the scarce data obtained on the SARS-CoV virus that have been extended to SARS-CoV-2 and the abundance of studies based on computational analysis supported in several (but not all cases) by in vitro tests that employed recombinant targets (e.g., Spike protein, Mpro, TMPRSS2, PLpro proteases, etc.). Of course, this is not enough. These studies need to be confirmed and reinforced by robust preclinical investigations, both on cellular or animal models mimicking or reproducing the “real” infection by SARS-CoV-2. Fortunately, these methodological approaches and technologies are already available and, in our opinion, it is just a matter of time before getting definitive conclusions on this issue, considering the driving force that scientists are globally pushing in searching for effective natural remedies to fight, ameliorate or prevent COVID-19 infection. These studies are also mandatory to shed light on an additional criticism often moved to the field, for example, the lack or limited specificity of the different natural compounds under investigation. In fact, many studies compare a list of phenolic compounds, or other phytochemicals, retrieving minimal differences in terms of binding energy to the identified targets (e.g., Spike or SARS-CoV/SARS-CoV-2 proteases) or IC50 values in the enzymatic inhibitory assays against SARS-CoV/SARS-CoV-2 proteins. This broad spectrum of activity and the absence of a clear specificity of action, if confirmed, will open to exploring the attractive hypothesis that mixtures of different natural compounds can exert synergistic effects on multiple viral targets. If this strategy will take hold, it will be accompanied by a higher possibility of success being supported by the convincing computational and pre-clinical studies mentioned above.

A second and proper criticism that is generally moved to the use of natural compounds or extracts as potential anti-COVID-19 reme-
dies is the absence of clinical studies to support, confirm or contradict the data deriving from experimental studies. This does not seem to be the case with quercetin. In fact, as reported in Table 1, a significant number of clinical studies are ongoing in this direction. Unfortunately, as mentioned above, only in a few cases the trial outputs have been published. Important indications arise from two studies performed by the same research group demonstrating that a phytosome complex (Quercetin Phytosome®) containing an equivalent of quercetin corresponding to up to 600 mg/day in combination with standard care was safe and significantly reduced the time lasting from a positive test to negativization in COVID-19 patients (Di Pierro, Derosa, et al., 2021; Di Pierro, Iqtadar, et al., 2021). In a very recent study, the potential protective effects of quercetin against COVID-19 were assessed in a prospective, randomized, controlled cohort trial where supplementation with the same Quercetin Phytosome® complex for 3 months (corresponding to an equivalent of 250 mg quercetin twice a day) was administered to healthy subjects versus placebo. In the

| #    | Clinical trial ID code | Intervention/drug(s) | Types of intervention/allocation | No. of subjects/age/sex | Phase |
|------|------------------------|----------------------|---------------------------------|-------------------------|-------|
| 13   | NCT05037240            | • 1,000 mg/day quercetin for 3 months versus placebo | Interventional/randomized/parallel assignment/double label to study the effects of quercetin in the prevention of COVID-19 infection | 80/18 years and older/ all sex | NA    |
| 14   | NCT05045937            | • Drug: Ivermectin  
• Others: Vitamin C, vitamin D, quercetin (no information available on quercetin dose), zinc, budesonide, aspirin, tylenol, ibuprofen, IV infusion, monoclonal antibodies, COVID vaccine, melatonin, niacin, albuterol, remdesivir | Observational/prospective study to assess the efficacy of ivermectin as an outpatient treatment option for COVID-19 | 1,000/12 years to older/ all sex | NA    |

Abbreviation: NA, not applicable.
“quercetin group,” the protection to contract the COVID-19 infection was 14% compared to the “placebo group” and the complete clinical remission was shorter (7 vs. 15 days) in the former with respect to the latter (Rondanelli et al., 2022). Finally, in a different study, COVID-19 patients receiving for 7 days 1 g of quercetin plus conventional antiviral drugs (remdesivir or favipiravir) showed reduced levels of critical markers involved in COVID-19 severity (e.g., ALP, q-CRP, and LDH) (Shohan et al., 2022).

Although all the above-mentioned clinical studies suffer from the same constraints, for example, small sample size, narrow characteristics of the enrolled subjects, short duration of the trial, a limited number of markers to evaluate the clinical efficacy of quercetin, they reflect a positive trend in considering the capacity of quercetin to attenuate and/or prevent the COVID-19 symptoms that, of course, cannot be generalized but represent a solid base for further studies.

Besides various aforementioned therapeutic properties discussed in previous sections, it is important here to mention that quercetin has molecular and functional resemblance with dexamethasone (Bhutto et al., 2018), a synthetic corticosteroid, which efficaciously had reduced one-third mortality in critically ill COVID-19 patients (RECOVERY Collaborative Group, 2021). As various reports do not recommend the routine use of corticosteroids including dexamethasone in SARS-CoV-2 patients (Alessi, de Oliveira, Schaan, & Telo, 2020), quercetin can be contemplated to have a comparable effect to possibly reduce the cytokine storm like situations in COVID-19 patients (Pawar & Pal, 2020). However, evidential validation of the same through a clinical trial is mandatory.

Similarly, it is tempting to speculate that quercetin might be considered as a potential therapeutic/prophylaxis option for COVID-19 subjects, due to its reported cholesterol-lowering ability (A. C. Li & Glass, 2002; M. Zhang et al., 2016) similarly to fenofibrate, a cholesterol-lowering drug, which demonstrated promising effects against SARS-CoV-2 replication as well as pathogenesis (Ehrlich et al., 2020).

In the Introduction, we mentioned the immunomodulatory and immune-boosting properties of quercetin that have been further discussed in the following paragraphs linking them to the antiinflammatory effects of the molecule. The interesting and new
theory, named “WE Medicine,” indicates the combination of the medical principles regulating Western and Eastern medicine and can help to explain the beneficial effects of natural compounds. In this context, based on the conclusions of a very recent and distinguished article (Shi et al., 2022), it can be hypothesized that the synergistic effects of natural agents can mitigate and/or compensate the drawbacks due to their low absorption, distribution, and metabolism favoring their immune-pharmaceutical effects in modulating the immune effectors’ functions during COVID-19.

In conclusion, the present review is tempting to analyze the strengths and weaknesses of the potential anti-COVID-19 effects of quercetin. Although several limitations have been clearly deciphered and commented on, we do believe that these drawbacks do not outweigh the potential therapeutic/prophylaxis efficacy of quercetin. To draw a final picture, three main conditions need to be satisfied: (a) assessing the molecular mechanisms of the anti-SARS-CoV-2 properties of quercetin that cannot be exclusively based on in silico and in vitro studies; (b) standardizing the therapeutic doses of quercetin, its administration route, quercetin-drug interactions, and toxicity; (c) Completing and confirming the ongoing clinical studies addressing safety and/or efficacy of quercetin in mono-treatments or in association with conventional antiviral drugs in comorbid COVID-19 subjects. The synthesis of all this information will contribute to defining the risks to rewards ratio of the anti-COVID-19 effects of quercetin in favor of the latter.

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CONFLICT OF INTEREST
The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS
Amit Pal: Conceptualization; methodology; writing; supervision; critical reviewing, and editing. Anil Pawar: Writing-original and draft preparation. Isha Rani: Figure making and editing. Maria Russo and Kalyan Goswami: Subsections draft; critical reviewing, and editing. Gian Luigi Russo: Supervision; subsections draft; critical reviewing, and editing.

ENDNOTE
1 https://www.clinicaltrials.gov/ct2/results?cond=COVID-19&term=senolytic+drugs&cntry=&state=&city=&dist=&. https://www.clinicaltrials.gov/ct2/results?recrs=&cond=Covid19&term=quercetin&cntry=&state=&city=&dist=&.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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