Received: 18 June 2021 | Revised: 19 March 2022 | Accepted: 26 March 2022

DOI: 10.1002/ptr.7461

REVIEW

WILEY

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

Anil Pawar[1] | Maria Russo[2] | Isha Rani[3] | Kalyan Goswami[4] | Gian Luigi Russo[2] | Amit Pal[4]

[1]Department of Zoology, DAV University, Jalandhar, India

[2]National Research Council, Institute of Food Sciences, Avellino, Italy

[3]Department of Biochemistry, Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Maharishi Markandeshwar University (MMU), Ambala, India

[4]Department of Biochemistry, AIIMS, Kalyani, India

**Correspondence**
Amit Pal, Department of Biochemistry, AIIMS, Kalyani-741235, West Bengal, India.
Email: maximus1134@gmail.com

Gian Luigi Russo, National Research Council, Institute of Food Sciences, Via Roma, 64 – 83100 – Avellino, Italy.
Email: glrusso@isa.cnr.it

**Funding information**
The present work has been partially supported by the in-house CNR grant: FUNZIONAMENTO ISA (DBA.AD005.178 – CUP B32F11000540005).

## 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

**Abbreviations:** $3CL^{pro}$, Chymotrypsin-like protease; AC, Adenylyl cyclase; ACE2, Angiotensin-converting enzyme 2; ACH, Acetylcholine chloride; AMPK, AMP-activated protein kinase; Ang, Angiotensin; AP1, Activator protein 1; ARDS, Acute respiratory distress syndrome; ARE, Antioxidant response element; ASM, Airway smooth muscle; Bcl-2, B-cell lymphoma 2; BMI, Body mass index; cAMP, cyclic adenosine monophosphate; COPD, Chronic obstructive pulmonary disease; COVID-19, Coronavirus disease of 2019; CREB, CCAAT/enhancer binding protein; DABK, Des-Arg9- bradykinin; DG, Diglycerides; EPAC, Exchange proteins activated by cAMP; ERK, Extracellular-signal-regulated kinase; FDA, US Food and Drug Administration; FFAs, Free fatty acids; GK, Glucose kinase; GLUT4, Glucose transporter type 4; GSEA, Gene Set Enrichment Analysis; HFD, High fat diet; HIV, Human immunodeficiency virus; HSL, hormone sensitive lipase; IL, Interleukin; IR, Insulin receptor; JNK1, c-Jun N-terminal kinase; LEP-R, Leptin receptor; LPS, Lipopolysaccharide; LVDCCs, L-type voltage-dependent $Ca^{2+}$ channels; MAPK, Mitogen-activated protein kinase; MERS-CoV, Middle Eastern Respiratory Syndrome coronavirus; MG, Monoglycerides; $M^{pro}$, Main protease; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NO, Nitric oxide; Nrf2, Nuclear transcription factor; NSPs, Non-structural proteins; p38 MAPK, p38 mitogen-activated protein kinases; PAI, Plasminogen activator inhibitor-1; PAMPs, Pathogen-associated molecular patterns; PDE, Phosphodiesterase; PGC1α, Peroxisome proliferator-activated receptor-gamma coactivator-1alpha; PKA, Protein Kinase A; $PL^{pro}$, Papain-like protease; ppa1/ab2, Polyproteins a1/ab2; PPARγ, Peroxisome proliferator-activated receptor γ; Rb, Retinoblastoma protein; RBD, Receptor-binding domain; RdRp, RNA dependent RNA polymerase; ROS, Reactive oxygen species; RV, Rhinovirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SGLT 1, Sodium-dependent glucose transporter; STZ, Streptozotocin; TF, Tissue factor; TGs, Triglycerides; TMPRSS2, Transmembrane serine protease 2; TNF-α, Tumor necrosis factor-alpha; UCP1, Uncoupling protein 1; UPR, Unfolded protein response; Va, Active factor Va; VIIa, Active factor VIIa; Xa, Active factor Xa; Zn, Zinc.

  

the clinical manifestations of the disease in patients with comorbid conditions. 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

## 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 lipoxygenase 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 Batiha 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 Petrillo, 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 (Mehrbod 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).

The broad array of quercetin medicinal properties suggests possible clinical efficacy in Coronavirus disease-19 (COVID-19) (Bernini & Velotti, 2021; Derosa et al., 2021; Di Pierro, Derosa, et al., 2021; Di Pierro, Iqtadar, et al., 2021; Shohan et al., 2022) with comorbidities like hypertension, diabetes mellitus, obesity, Chronic obstructive pulmonary disease (COPD), coagulopathy and cytokine storm, all conditions emerging as a potential cause of severity and fatality among COVID-19 patients (Xu et al., 2020; Zhang et al., 2020). In preparing the present narrative review, data from PubMed, Scopus, EMBASE, Web of Science, Cochrane library, and Google Scholar databases have been retrieved to identify relevant studies concerning quercetin, flavonoids, COVID-19, and the above-mentioned pathologies.

This review article discusses the possible use of quercetin in the adjuvant therapy against COVID-19 and associated pathological factors responsible for the increasing mortality among COVID-19 patients.

## 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, S 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., 2020a). 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 ($PL^{pro}$) (Figure 1). The net result of quercetin action is a significant reduction of the SARS-CoV- 2 potential infectivity (Huang et al., 2020a). $PL^{pro}$ 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 ($3CL^{pro}$), also known as the main protease ($M^{pro}$) 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 $3CL^{pro}$ in vitro with an $IC_{50}$ (50% inhibitory concentration) of 73 μM. A similar study by Park et al. (2017) revealed that quercetin inhibited SARS-CoV proteases ($3CL^{pro}$ [IC50 of 52.7 μM]) and ($PL^{pro}$ [IC50 of 8.6 μM]) as well as the Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) protease ($3CL^{pro}$ [IC50 of 34.8 μM]) in vitro. More recently, the screening

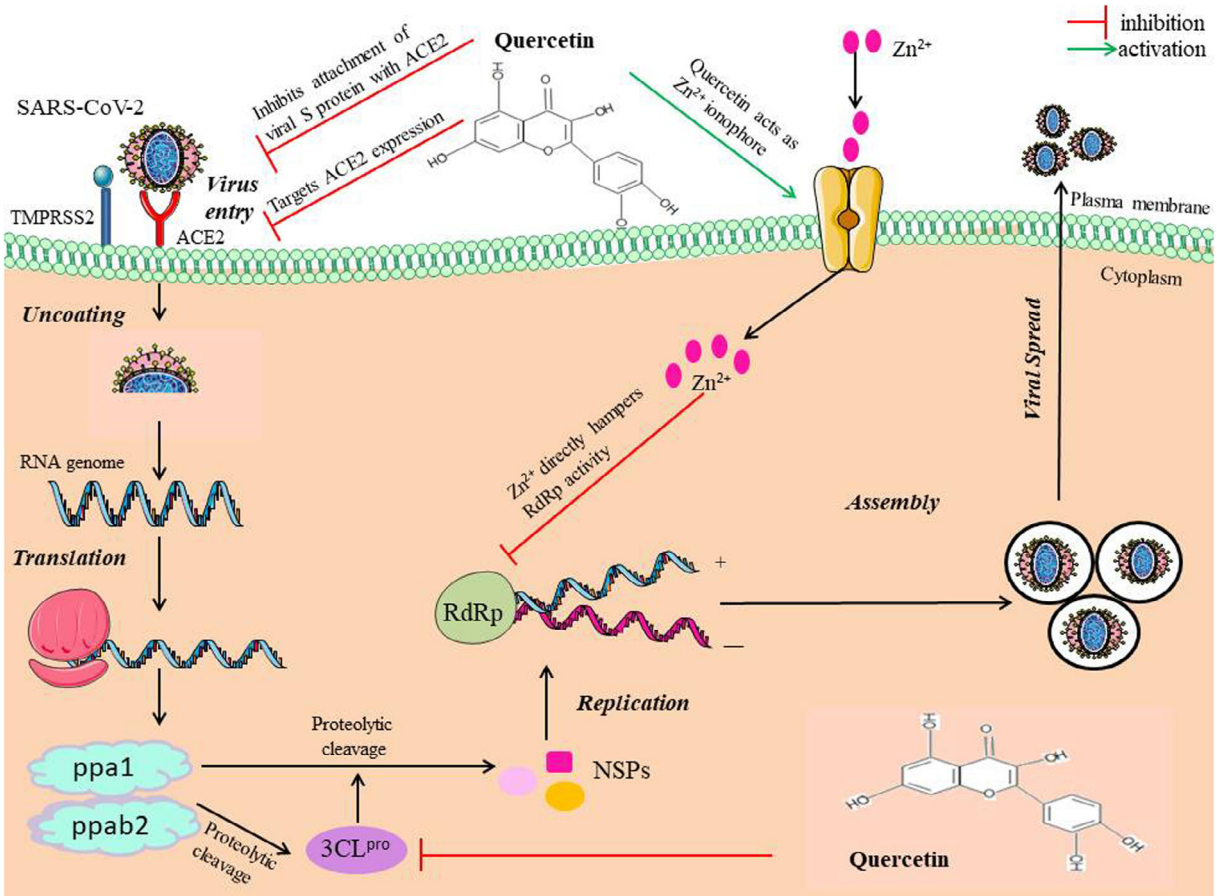


**FIGURE 1** The neutralizing effect of quercetin on SARS-CoV-2 virus. Quercetin acts as an ACE2 receptor blocker by binding to the RBD domain of viral S-protein. It also targets ACE2 expression, and thus affects viral entry. Simultaneously, quercetin affects $3CL^{pro}$ (viral main proteinase), an essential component of the viral replication cycle and thus hampers the activation of individual proteins. Quercetin also acts as Zn ionophore to increase intracellular Zn concentration which inhibits viral RdRp activity in a dose-dependent manner. $3CL^{pro}$, coronavirus main proteinase; ACE2, angiotensin-converting enzyme 2; NSPs, non-structural proteins, ppa1/ab2, polyproteins a1/ab2; RBD, receptor-binding domain; RdRp, RNA-dependent RNA polymerase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2; Zn, zinc

of a chemical library consisting of about 150 compounds, identified quercetin as a potent inhibitor of SARS-CoV-2 $3CL^{pro}$ ([$K_i$~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 $3CL^{pro}$ 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 (Bernini & 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 $p16^{INK4}$ and retinoblastoma protein (Rb), p53, and $p21^{CIP1}$ 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 flatted 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 $p16^{INK4}$ 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" (Krishnamurthy et al., 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 senolytics, 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 Desatinib 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.[1] 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, Giacconi, 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 bronchorelaxation 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

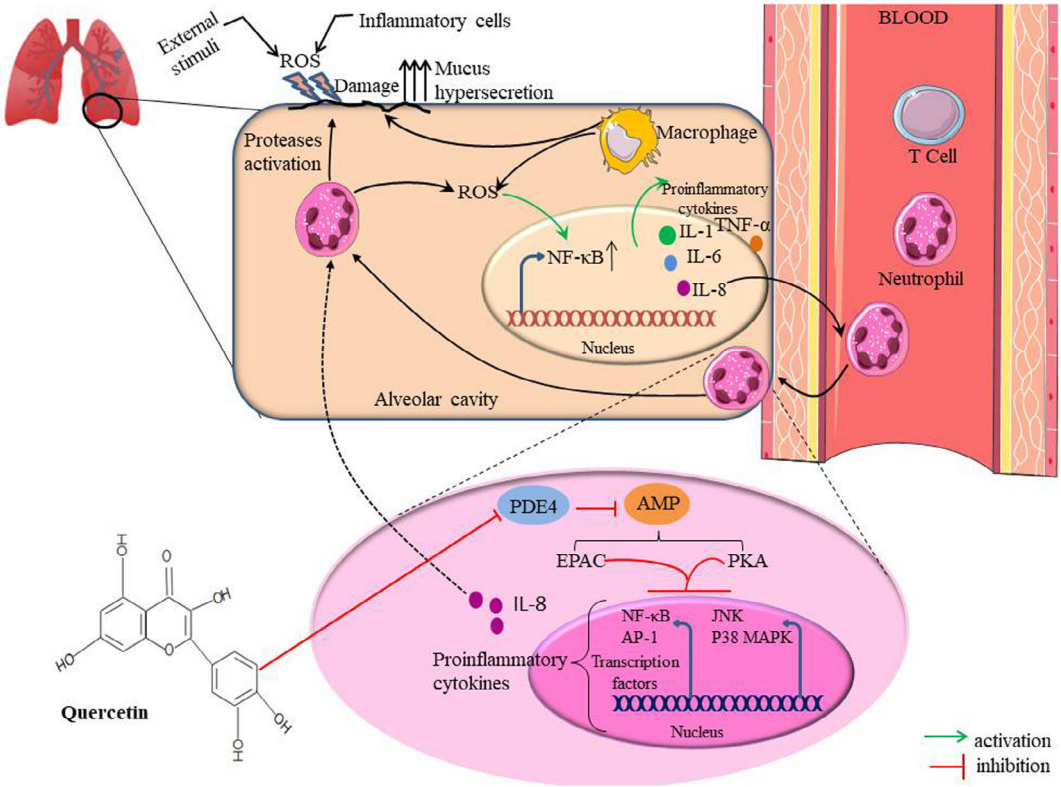


**FIGURE 2** Protective effects of quercetin in COPD. External stimuli or inflammatory cells directly generate ROS which may participate in the direct damage to lung cells, mucus hypersecretion, and accumulation of inflammatory cells (including neutrophils, and macrophages) which further results in exacerbation of ROS, responsible for the induction of redox-sensitive transcription factors, particularly, NF-κB and p38MAPK. Subsequently, it leads to the production of pro-inflammatory cytokines (IL-6, IL-8, IL-1, and TNF-α) and thereby causes the migration primarily of neutrophils from circulation to the inflammatory site, which causes proteases induction, known for airways remodeling and inflammation and thereby contributes to the pathogenesis of COPD. PDE4 reduces cAMP levels in neutrophils and indirectly favors the secretion of inflammatory components through several signaling mechanisms. Quercetin can directly target PDE4 expression and increase cAMP levels which further alleviate inflammatory response. AP1, activator protein 1; cAMP, cyclic adenosine monophosphate; COPD, chronic obstructive pulmonary disease; EPAC, exchange proteins activated by cAMP; JNK1, c-Jun N-terminal kinase; IL, interleukins; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; p38 MAPK, p38 mitogen-activated protein kinases; PDE4, phosphodiesterase 4; PKA, protein kinase A; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha

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

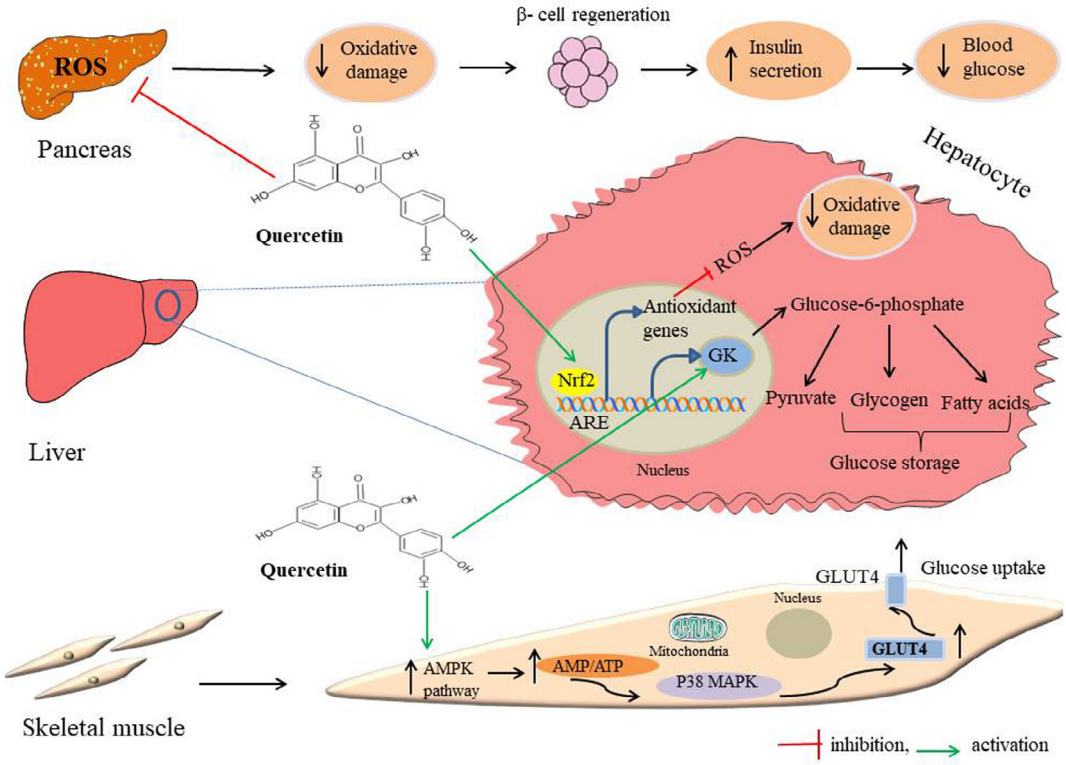


**FIGURE 3** The anti-diabetic or anti-glucose potential of quercetin. Quercetin controls blood glucose homeostasis by interacting with several molecular targets in the pancreas, liver, and skeletal muscle. Quercetin reverses the oxidative damage caused by ROS in the pancreas and promotes β cell regeneration which eventually causes over secretion of insulin to regulate blood glucose. In the liver, quercetin upregulates the expression of antioxidant/defensive genes by increasing the binding of Nrf2 to ARE which further abrogates the oxidative damage induced by ROS. It also increases the activity of the GK enzyme and thereby influences several downstream metabolic pathways, such as enhanced glycogen and fatty acids biosynthesis, responsible for increased glucose storage. In skeletal muscle, quercetin increases glucose uptake by enhancing GLUT4 expression in a p38 MAPK and AMPK dependent manner. AMPK, 5′ AMP-activated protein kinase; ARE, antioxidant response element; GK, glucose kinase; GLUT4, glucose transporter type 4; Nrf2, nuclear transcription factor; p38 MAPK, p38 mitogen-activated protein kinases

(Figure 3). 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, McInnes, & 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 5′ regulatory region of c/EBPα and PPARγ 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 (Ji, 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, Blet, 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, Cucciloni, Eleuteri, Fioretti, & Angeletti, 2006). Quercetin and isoquercetin (quercetin-3-O-β-D-glucoside) exhibit antithrombotic and anticoagulant 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

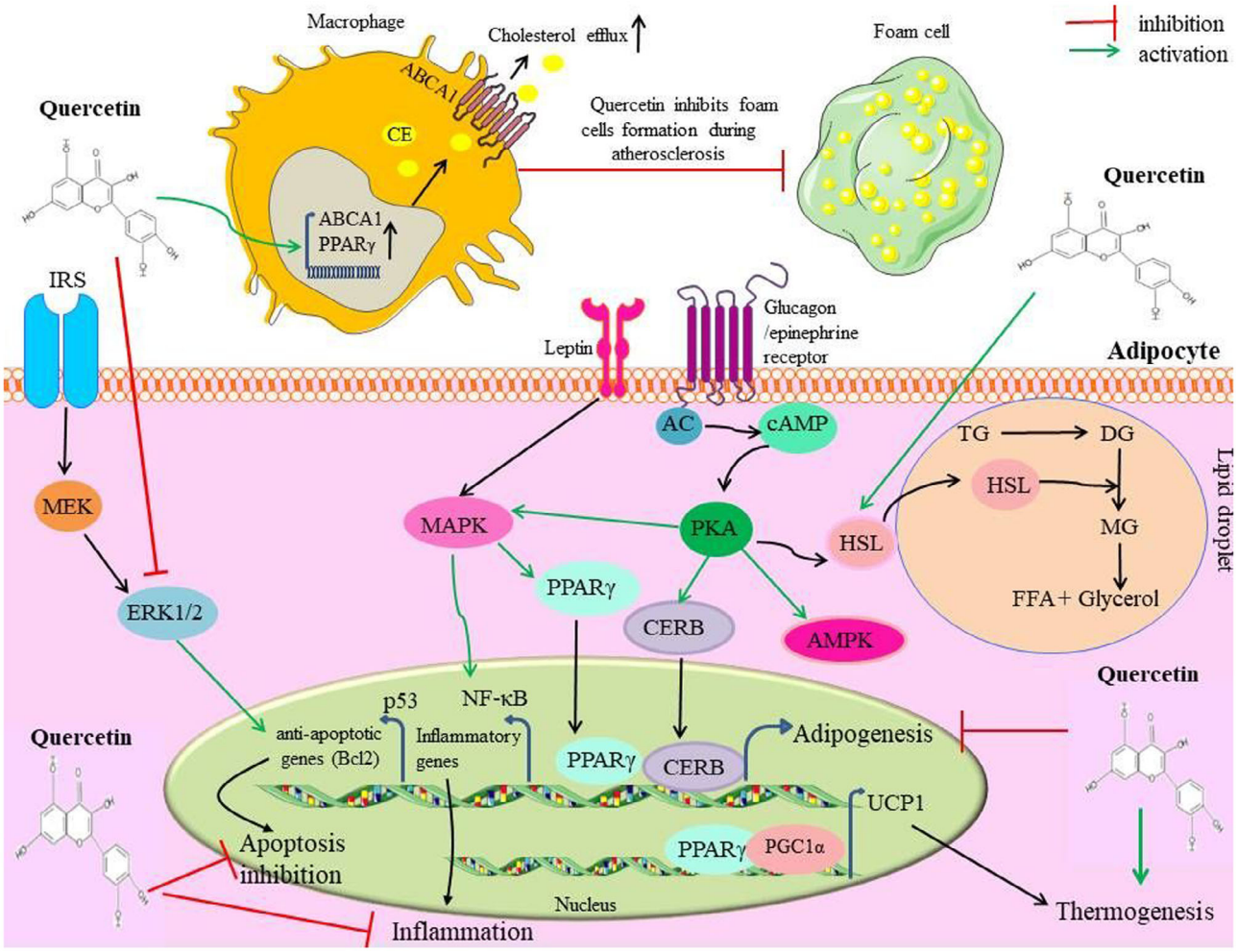


**FIGURE 4** Anti-adipogenesis activity of quercetin. Quercetin exerts a suppressive effect on fat accumulation by activating HSL which converts TGs to FFAs. Moreover, it also stimulates the expression of UCP1 to increase energy expenditure, an important player in the anti-obesity phenomenon. Furthermore, 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; PGC1 α, peroxisome proliferator-activated receptor gamma coactivator 1-α; PKA, protein kinase A; PPARγ, peroxisome proliferator-activated receptor γ; TGs, triglycerides; UCP1, uncoupling protein 1

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, & Sobey, 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

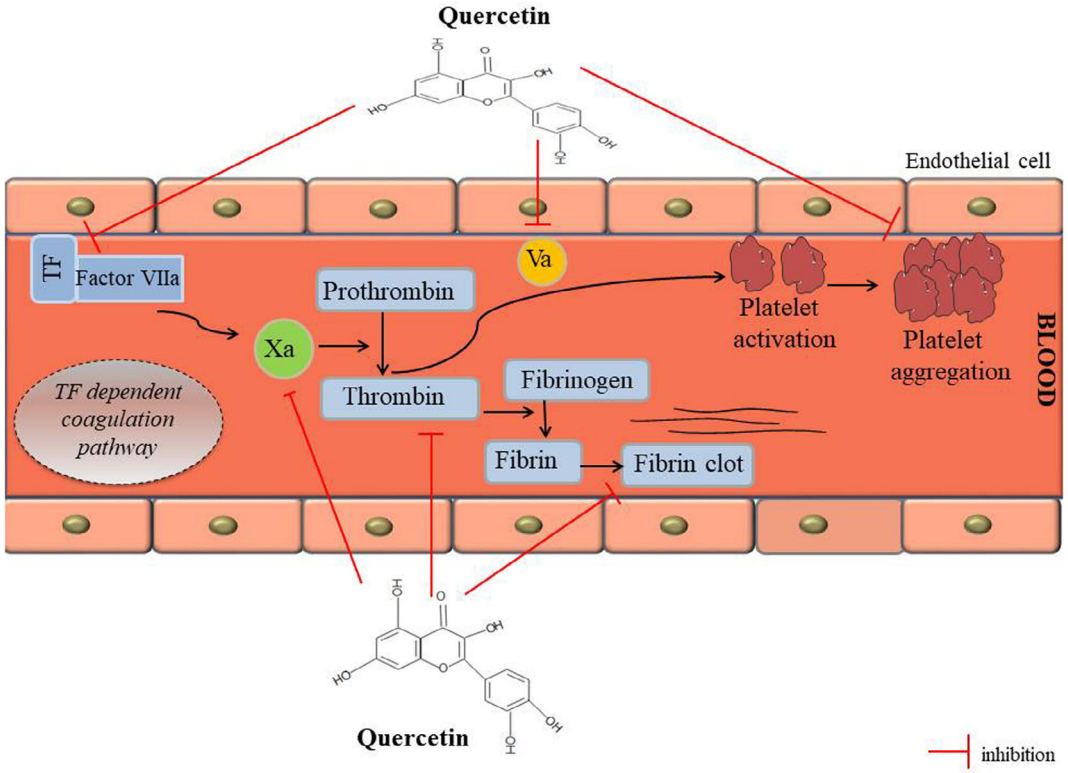


**FIGURE 5** Anti-coagulatory effect of quercetin. The TF-dependent (extrinsic) pathway is the main contributor to the induction of thrombotic events in physiological and pathological conditions through the involvement of several coagulatory factors. Quercetin has been observed to down-regulate the expression of TF which eventually inhibits the activation of factor X (inactive) to factor Xa (active), responsible for thrombin and fibrin clot formation. Quercetin can also directly hinder platelet aggregation, another component for thrombosis by inhibiting factor Va (active). Xa, active factor Xa; TF, tissue factor; VIIa, active factor VIIa; Va, active factor Va

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, Wessmann, & 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, Mengelers, 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 *Psidii guava* 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, isoquercetin (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 (NCT05008003; 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

**TABLE 1** Interventional clinical trials with quercetin monotreatment or in association with other drugs/dietary supplements against COVID-19

| # | 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 1 |
| 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 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 |

**TABLE 1** (Continued)

| # | 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<br>• 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.

deaths, as of January 9, 2022 (source: https://covid19.who.int/). Emerging data clearly suggests that subjects with comorbid conditions, such as asthma, COPD, diabetes, obesity, CVD, cerebrovascular accident, CKD, and cancer, are at higher risk of COVID-19 severity and/or death and need hospitalization (A. K. Singh & Misra, 2020). To combat this dreadful infection, a search for novel therapeutic/add-on options is warranted along with currently ongoing therapies.

The present review is tempting to suggest that, based on circumstantial scientific evidence and preliminary clinical data, the flavonoid quercetin can ameliorate comorbid conditions (COPD, diabetes, obesity, coagulopathy, hypertension, and aging), which increase disease severity and mortality in COVID-19 patients (Figure 6). The rationale behind many of the cited studies in the present work involving quercetin regards the multifaceted beneficial aspects of quercetin supplementation that, along with conventional therapies, might play some role in ameliorating COVID-19 infection and symptoms acting in concert on two parallel and independent paths: inhibiting key factors responsible for SARS-CoV-2 infections and mitigate the clinical manifestations of the disease in patients with comorbidities or in those subjects who are more prone to severe COVID-19 progression. However, 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, $M^{pro}$, TMPRSS2, $PL^{pro}$ 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 $IC_{50}$ 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 remedies 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

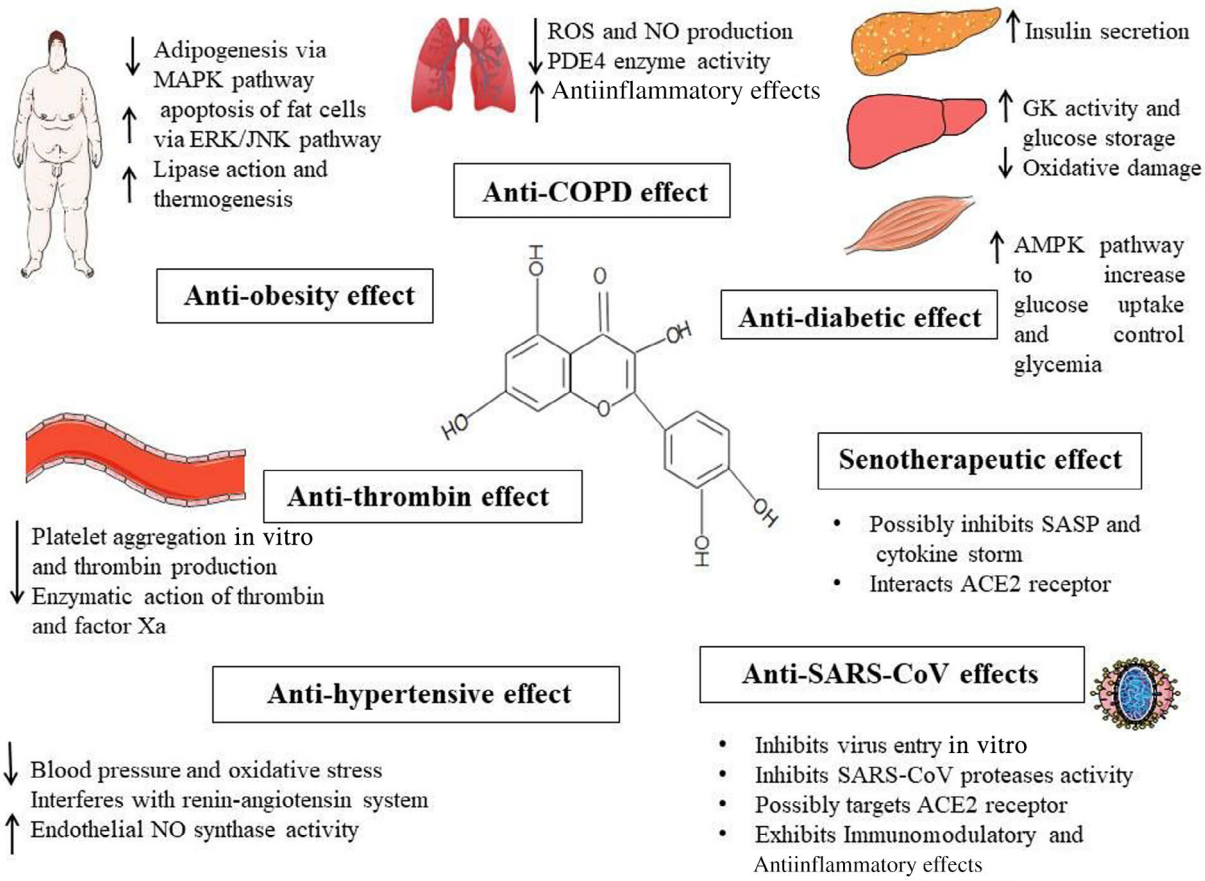


**FIGURE 6** Representation of the pleiotropic beneficial effects of quercetin refers to different comorbid and physiological conditions, which are thought to contribute to the severity of SARS-CoV-2 infection. ACE2, angiotensin-converting enzyme 2; AMPK, 5′ AMP-activated protein kinase; COPD, chronic obstructive pulmonary disease; ERK, extracellular-signal-regulated kinase; GK, glucose kinase; JNK1, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinases; NO, nitric oxide; PDE4, phosphodiesterase 4; ROS, reactive oxygen species; SARS-Co-V, severe acute respiratory syndrome coronavirus; SASP, senescence-associated secretory phenotype

"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 tempted 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.

## ACKNOWLEDGMENTS

Authors duly acknowledge the WHO, NCBI, and NIH for providing free online scientific research articles/information/clinical trials pertaining to COVID-19. Authors also acknowledges the Edraw software and smart servier software for making quercetin chemical structures and other illustrations, respectively.

## 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.

## ORCID

*Anil Pawar* https://orcid.org/0000-0001-9545-3325
*Maria Russo* https://orcid.org/0000-0001-8385-9184
*Isha Rani* https://orcid.org/0000-0002-0291-9008
*Kalyan Goswami* https://orcid.org/0000-0002-5052-0675
*Gian Luigi Russo* https://orcid.org/0000-0001-9321-1613
*Amit Pal* https://orcid.org/0000-0001-9916-3309

## REFERENCES

Abian, O., Ortega-Alarcon, D., Jimenez-Alesanco, A., Ceballos-Laita, L., Vega, S., Reyburn, H. T., … Velazquez-Campoy, A. (2020). Structural stability of SARS-CoV-2 3CLpro and identification of quercetin as an inhibitor by experimental screening. *International Journal of Biological Macromolecules*, *164*, 1693–1703. https://doi.org/10.1016/j.ijbiomac.2020.07.235

Ackermann, M., Verleden, S. E., Kuehnel, M., Haverich, A., Welte, T., Laenger, F., … Jonigk, D. (2020). Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *The New England Journal of Medicine*, *383*(2), 120–128. https://doi.org/10.1056/NEJMoa2015432

Ader, P., Wessmann, A., & Wolffram, S. (2000). Bioavailability and metabolism of the flavonol quercetin in the pig. *Free Radical Biology & Medicine*, *28*(7), 1056–1067. https://doi.org/10.1016/s0891-5849(00)00195-7

Ahn, J., Lee, H., Kim, S., Park, J., & Ha, T. (2008). The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways. *Biochemical and Biophysical Research Communications*, *373*(4), 545–549. https://doi.org/10.1016/j.bbrc.2008.06.077

Alessi, J., de Oliveira, G. B., Schaan, B. D., & Telo, G. H. (2020). Dexamethasone in the era of COVID-19: Friend or foe? An essay on the effects of dexamethasone and the potential risks of its inadvertent use in patients with diabetes. *Diabetology & Metabolic Syndrome*, *12*, 80. https://doi.org/10.1186/s13098-020-00583-7

Al-Samkari, H., Karp Leaf, R. S., Dzik, W. H., Carlson, J., Fogerty, A. E., Waheed, A., … Rosovsky, R. P. (2020). COVID-19 and coagulation: Bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*, *136*(4), 489–500. https://doi.org/10.1182/blood.2020006520

American Diabetes Association. (2010). Diagnosis and classification of diabetes mellitus. *Diabetes Care*, *33*(Suppl 1), S62–S69. https://doi.org/10.2337/dc10-S062

Antonioli, L., Colucci, R., Pellegrini, C., Giustarini, G., Sacco, D., Tirotta, E., … Fornai, M. (2016). The AMPK enzyme-complex: From the regulation of cellular energy homeostasis to a possible new molecular target in the management of chronic inflammatory disorders. *Expert Opinion on Therapeutic Targets*, *20*(2), 179–191. https://doi.org/10.1517/14728222.2016.1086752

Arias, N., Macarulla, M. T., Aguirre, L., Martínez-Castaño, M. G., & Portillo, M. P. (2014). Quercetin can reduce insulin resistance without decreasing adipose tissue and skeletal muscle fat accumulation. *Genes & Nutrition*, *9*(1), 361. https://doi.org/10.1007/s12263-013-0361-7

Bai, W., Wang, C., & Ren, C. (2014). Intakes of total and individual flavonoids by US adults. *International Journal of Food Sciences and Nutrition*, *65*(1), 9–20. https://doi.org/10.3109/09637486.2013.832170

Batiha, G. E., Beshbishy, A. M., Ikram, M., Mulla, Z. S., El-Hack, M., Taha, A. E., … Elewa, Y. (2020). The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: Quercetin. *Foods (Basel, Switzerland)*, *9*(3), 374. https://doi.org/10.3390/foods9030374

Bernini, R., & Velotti, F. (2021). Natural polyphenols as Immunomodulators to rescue immune response homeostasis: Quercetin as a research model against severe COVID-19. *Molecules (Basel, Switzerland)*, *26*(19), 5803. https://doi.org/10.3390/molecules26195803

Bhaskar, S., Kumar, K. S., Krishnan, K., & Antony, H. (2013). Quercetin alleviates hypercholesterolemic diet induced inflammation during progression and regression of atherosclerosis in rabbits. *Nutrition (Burbank, Los Angeles County, Calif.)*, *29*(1), 219–229. https://doi.org/10.1016/j.nut.2012.01.019

Bhutto, Z. A., He, F., Zloh, M., Yang, J., Huang, J., Guo, T., & Wang, L. (2018). Use of quercetin in animal feed: Effects on the P-gp expression and pharmacokinetics of orally administrated enrofloxacin in chicken. *Scientific Reports*, *8*(1), 4400. https://doi.org/10.1038/s41598-018-22354-1

Bijak, M., Ziewiecki, R., Saluk, J., Ponczek, M., Pawlaczyk, I., Krotkiewski, H., … Nowak, P. (2014). Thrombin inhibitory activity of some polyphenolic compounds. *Medicinal Chemistry Research: An International Journal for Rapid Communications on Design and Mechanisms of Action of Biologically Active Agents*, *23*(5), 2324–2337. https://doi.org/10.1007/s00044-013-0829-4

Blagosklonny, M. V. (2020). From causes of aging to death from COVID-19. *Aging*, *12*(11), 10004–10021. https://doi.org/10.18632/aging.103493

Bravo, L. (1998). Polyphenols: Chemistry, dietary sources, metabolism, and nutritional significance. *Nutrition Reviews*, *56*(11), 317–333. https://doi.org/10.1111/j.1753-4887.1998.tb01670.x

Brito, J., Lima, W. G., Cordeiro, L., & da Cruz Nizer, W. S. (2021). Effectiveness of supplementation with quercetin-type flavonols for treatment of viral lower respiratory tract infections: Systematic review and meta-analysis of preclinical studies. *Phytotherapy Research: PTR*, *35*(9), 4930–4942. https://doi.org/10.1002/ptr.7122

Bule, M., Abdurahman, A., Nikfar, S., Abdollahi, M., & Amini, M. (2019). Antidiabetic effect of quercetin: A systematic review and meta-analysis of animal studies. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association*, *125*, 494–502. https://doi.org/10.1016/j.fct.2019.01.037

Camell, C. D., Yousefzadeh, M. J., Zhu, Y., Prata, L., Huggins, M. A., Pierson, M., … Robbins, P. D. (2021). Senolytics reduce coronavirus-related mortality in old mice. *Science (New York, N.Y.)*, *373*(6552), eabe4832. https://doi.org/10.1126/science.abe4832

Cao, H., Jia, Q., Yan, L., Chen, C., Xing, S., & Shen, D. (2019). Quercetin suppresses the progression of atherosclerosis by regulating MST1-mediated autophagy in ox-LDL-induced RAW264.7 macrophage foam cells. *International Journal of Molecular Sciences*, *20*(23), 6093. https://doi.org/10.3390/ijms20236093

Chan, A. L., Huang, H. L., Chien, H. C., Chen, C. M., Lin, C. N., & Ko, W. C. (2008). Inhibitory effects of quercetin derivatives on phosphodiesterase isozymes and high-affinity [$^3$H]-rolipram binding in guinea pig tissues. *Investigational New Drugs*, *26*(5), 417–424. https://doi.org/10.1007/s10637-008-9114-7

Chee, Y. J., Ng, S., & Yeoh, E. (2020). Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. *Diabetes Research and Clinical Practice*, *164*, 108166. https://doi.org/10.1016/j.diabres.2020.108166

Chen, G., Wu, D., Guo, W., Cao, Y., Huang, D., Wang, H., … Ning, Q. (2020). Clinical and immunological features of severe and moderate coronavirus disease 2019. *The Journal of Clinical Investigation*, *130*(5), 2620–2629. https://doi.org/10.1172/JCI137244

Chen, L., Li, J., Luo, C., Liu, H., Xu, W., Chen, G., … Jiang, H. (2006). Binding interaction of quercetin-3-β-galactoside and its synthetic derivatives with SARS-CoV 3CL$^{pro}$: Structure-activity relationship studies reveal salient pharmacophore features. *Bioorganic & Medicinal Chemistry*, *14*(24), 8295–8306. https://doi.org/10.1016/j.bmc.2006.09.014

Chen, S., Jiang, H., Wu, X., & Fang, J. (2016). Therapeutic effects of quercetin on inflammation, obesity, and type 2 diabetes. *Mediators of Inflammation*, *2016*, 9340637. https://doi.org/10.1155/2016/9340637

Chen, X., Yin, O. Q., Zuo, Z., & Chow, M. S. (2005). Pharmacokinetics and modeling of quercetin and metabolites. *Pharmaceutical Research*, *22*(6), 892–901. https://doi.org/10.1007/s11095-005-4584-1

Chiang, L. C., Chiang, W., Liu, M. C., & Lin, C. C. (2003). In vitro antiviral activities of *Caesalpinia pulcherrima* and its related flavonoids. *The Journal of Antimicrobial Chemotherapy*, *52*(2), 194–198. https://doi.org/10.1093/jac/dkg291

Choi, H., Kim, C. S., & Yu, R. (2018). Quercetin upregulates uncoupling protein 1 in white/brown adipose tissues through sympathetic stimulation. *Journal of Obesity & Metabolic Syndrome*, *27*(2), 102–109. https://doi.org/10.7570/jomes.2018.27.2.102

Choi, J. H., Kim, K. J., & Kim, S. (2016). Comparative effect of quercetin and quercetin-3-O-β-d-glucoside on fibrin polymers, blood clots, and in rodent models. *Journal of Biochemical and Molecular Toxicology*, *30*(11), 548–558. https://doi.org/10.1002/jbt.21822

Craig, M. E., Hattersley, A., & Donaghue, K. C. (2009). Definition, epidemiology and classification of diabetes in children and adolescents. *Pediatric Diabetes*, *10*(Suppl 12), 3–12. https://doi.org/10.1111/j.1399-5448.2009.00568.x

Crespy, V., Morand, C., Manach, C., Besson, C., Demigne, C., & Remesy, C. (1999). Part of quercetin absorbed in the small intestine is conjugated and further secreted in the intestinal lumen. *The American Journal of Physiology*, *277*(1), G120–G126. https://doi.org/10.1152/ajpgi.1999.277.1.G120

Culpitt, S. V., Rogers, D. F., Fenwick, P. S., Shah, P., De Matos, C., Russell, R. E., … Donnelly, L. E. (2003). Inhibition by red wine extract, resveratrol, of cytokine release by alveolar macrophages in COPD. *Thorax*, *58*(11), 942–946. https://doi.org/10.1136/thorax.58.11.942

Cushnie, T. P., & Lamb, A. J. (2005). Antimicrobial activity of flavonoids. *International Journal of Antimicrobial Agents*, *26*(5), 343–356. https://doi.org/10.1016/j.ijantimicag.2005.09.002

da Silva Araújo, N. P., de Matos, N. A., Antunes Mota, S. L., de Souza, A. B. F., Cangussú, S. D., de Menezes, R. C. A., & Bezerra, F. S. (2020). Quercetin attenuates acute lung injury caused by cigarette smoke both in vitro and in vivo. *COPD*, *17*(2), 205–214. https://doi.org/10.1080/15412555.2020.1749253

Dabbagh-Bazarbachi, H., Clergeaud, G., Quesada, I. M., Ortiz, M., O'Sullivan, C. K., & Fernández-Larrea, J. B. (2014). Zinc ionophore activity of quercetin and epigallocatechin-gallate: From Hepa 1-6 cells to a liposome model. *Journal of Agricultural and Food Chemistry*, *62*(32), 8085–8093. https://doi.org/10.1021/jf5014633

Dabeek, W. M., & Marra, M. V. (2019). Dietary quercetin and kaempferol: Bioavailability and potential cardiovascular-related bioactivity in humans. *Nutrients*, *11*(10), 2288. https://doi.org/10.3390/nu11102288

Dai, X., Ding, Y., Zhang, Z., Cai, X., Bao, L., & Li, Y. (2013). Quercetin but not quercitrin ameliorates tumor necrosis factor-alpha-induced insulin resistance in C2C12 skeletal muscle cells. *Biological & Pharmaceutical Bulletin*, *36*(5), 788–795. https://doi.org/10.1248/bpb.b12-00947

Debiaggi, M., Tateo, F., Pagani, L., Luini, M., & Romero, E. (1990). Effects of propolis flavonoids on virus infectivity and replication. *Microbiologica*, *13*(3), 207–213.

Derosa, G., Maffioli, P., D'Angelo, A., & Di Pierro, F. (2021). A role for quercetin in coronavirus disease 2019 (COVID-19). *Phytotherapy Research: PTR*, *35*(3), 1230–1236. https://doi.org/10.1002/ptr.6887

Dhanya, R., Arya, A. D., Nisha, P., & Jayamurthy, P. (2017). Quercetin, a lead compound against type 2 diabetes ameliorates glucose uptake via AMPK pathway in skeletal muscle cell line. *Frontiers in Pharmacology*, *8*, 336. https://doi.org/10.3389/fphar.2017.00336

Dhaun, N., & Webb, D. J. (2019). Endothelins in cardiovascular biology and therapeutics. *Nature Reviews. Cardiology*, *16*(8), 491–502. https://doi.org/10.1038/s41569-019-0176-3

Di Petrillo, A., Orrù, G., Fais, A., & Fantini, M. C. (2022). Quercetin and its derivates as antiviral potentials: A comprehensive review. *Phytotherapy Research: PTR*. *36*(1), 266–278. https://doi.org/10.1002/ptr.7309

Di Pierro, F., Derosa, G., Maffioli, P., Bertuccioli, A., Togni, S., Riva, A., … Ahmed, S. (2021). Possible therapeutic effects of adjuvant quercetin supplementation against early-stage COVID-19 infection: A prospective, randomized, controlled, and open-label study. *International Journal of General Medicine*, *14*, 2359–2366. https://doi.org/10.2147/IJGM.S318720

Di Pierro, F., Iqtadar, S., Khan, A., Ullah Mumtaz, S., Masud Chaudhry, M., Bertuccioli, A., … Khan, S. (2021). Potential clinical benefits of quercetin in the early stage of COVID-19: Results of a second, pilot, randomized, controlled and open-label clinical trial. *International Journal of General Medicine*, *14*, 2807–2816. https://doi.org/10.2147/IJGM.S318949

Dietz, W., & Santos-Burgoa, C. (2020). Obesity and its implications for COVID-19 mortality. *Obesity (Silver Spring, Md.)*, *28*(6), 1005. https://doi.org/10.1002/oby.22818

Dimova, S., Mugabowindekwe, R., Willems, T., Brewster, M. E., Noppe, M., Ludwig, A., … Augustijns, P. (2003). Safety-assessment of 3-methoxyquercetin as an antirhinoviral compound for nasal application: Effect on ciliary beat frequency. *International Journal of Pharmaceutics*, *263*(1-2), 95–103. https://doi.org/10.1016/s0378-5173(03)00363-6

Dock, J. N., & Effros, R. B. (2011). Role of CD8 T cell replicative senescence in human aging and in HIV-mediated immunosenescence. *Aging and Disease*, *2*(5), 382–397.

Dong, J., Zhang, X., Zhang, L., Bian, H. X., Xu, N., Bao, B., & Liu, J. (2014). Quercetin reduces obesity-associated ATM infiltration and inflammation in mice: A mechanism including AMPKα1/SIRT1. *Journal of Lipid Research*, *55*(3), 363–374. https://doi.org/10.1194/jlr.M038786

Donoghue, M., Hsieh, F., Baronas, E., Godbout, K., Gosselin, M., Stagliano, N., … Acton, S. (2000). A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circulation Research*, *87*(5), E1–E9. https://doi.org/10.1161/01.res.87.5.e1

Drummond, G. R., Vinh, A., Guzik, T. J., & Sobey, C. G. (2019). Immune mechanisms of hypertension. *Nature Reviews. Immunology*, *19*(8), 517–532. https://doi.org/10.1038/s41577-019-0160-5

Duarte, J., Pérez-Palencia, R., Vargas, F., Ocete, M. A., Pérez-Vizcaino, F., Zarzuelo, A., & Tamargo, J. (2001). Antihypertensive effects of the flavonoid quercetin in spontaneously hypertensive rats. *British Journal of Pharmacology*, *133*(1), 117–124. https://doi.org/10.1038/sj.bjp.0704064

Egert, S., Wolffram, S., Bosy-Westphal, A., Boesch-Saadatmandi, C., Wagner, A. E., Frank, J., … Mueller, M. J. (2008). Daily quercetin supplementation dose-dependently increases plasma quercetin concentrations in healthy humans. *The Journal of Nutrition*, *138*(9), 1615–1621. https://doi.org/10.1093/jn/138.9.1615

Ehrlich, A., Uhl, S., Ioannidis, K., Hofree, M., Tenoever, B. R., & Nahmias, Y. (2020). The SARS-CoV-2 transcriptional metabolic signature in lung epithelium. *SSRN Electronic Journal*. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3650499

Emami, A., Javanmardi, F., Akbari, A., Kojuri, J., Bakhtiari, H., Rezaei, T., … Falahati, F. (2021). Survival rate in hypertensive patients with COVID-19. *Clinical and Experimental Hypertension (New York, N.Y.: 1993)*, *43*(1), 77–80. https://doi.org/10.1080/10641963.2020.1812624

Farazuddin, M., Mishra, R., Jing, Y., Srivastava, V., Comstock, A. T., & Sajjan, U. S. (2018). Quercetin prevents rhinovirus-induced progression of lung disease in mice with COPD phenotype. *PLoS One*, *13*(7), e0199612. https://doi.org/10.1371/journal.pone.0199612

Ferrario, C. M., Jessup, J., Chappell, M. C., Averill, D. B., Brosnihan, K. B., Tallant, E. A., … Gallagher, P. E. (2005). Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation*, *111*(20), 2605–2610. https://doi.org/10.1161/CIRCULATIONAHA.104.510461

Gale, A. J. (2011). Continuing education course #2: Current understanding of hemostasis. *Toxicologic Pathology*, *39*(1), 273–280. https://doi.org/10.1177/0192623310389474

Galindo, P., Rodriguez-Gómez, I., González-Manzano, S., Dueñas, M., Jiménez, R., Menéndez, C., … Duarte, J. (2012). Glucuronidated quercetin lowers blood pressure in spontaneously hypertensive rats via deconjugation. *PLoS One*, *7*(3), e32673. https://doi.org/10.1371/journal.pone.0032673

Galtier, F. (2010). Definition, epidemiology, risk factors. *Diabetes & Metabolism*, *36*(6 Pt 2), 628–651.

Ganesan, S., Faris, A. N., Comstock, A. T., Chattoraj, S. S., Chattoraj, A., Burgess, J. R., … Sajjan, U. S. (2010). Quercetin prevents progression of disease in elastase/LPS-exposed mice by negatively regulating MMP expression. *Respiratory Research*, *11*(1), 131. https://doi.org/10.1186/1465-9921-11-131

Glinsky, G. V. (2020). Tripartite combination of candidate pandemic mitigation agents: vitamin D, quercetin, and estradiol manifest properties of medicinal agents for targeted mitigation of the COVID-19 pandemic defined by genomics-guided tracing of SARS-CoV-2 targets in human cells. *Biomedicine*, *8*(5), 129. https://doi.org/10.3390/biomedicines8050129

Gonçalves, I., Guimarães, M. J., van Zeller, M., Menezes, F., Moita, J., Simão, P., & GI DPOC-Grupo de Interesse na Doença Pulmonar Obstrutiva Crónica. (2018). Clinical and molecular markers in COPD. *Pulmonology*, *24*(4), 250–259. https://doi.org/10.1016/j.pulmoe.2018.02.005

Green, W. D., & Beck, M. A. (2017). Obesity impairs the adaptive immune response to influenza virus. *Annals of the American Thoracic Society*, *14*(Supplement_5), S406–S409. https://doi.org/10.1513/AnnalsATS.201706-447AW

Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., … China Medical Treatment Expert Group for Covid-19. (2020). Clinical characteristics of coronavirus disease 2019 in China. *The New England Journal of Medicine*, *382*(18), 1708–1720. https://doi.org/10.1056/NEJMoa2002032

Guerrero, L., Castillo, J., Quiñones, M., Garcia-Vallvé, S., Arola, L., Pujadas, G., & Muguerza, B. (2012). Inhibition of angiotensin-converting enzyme activity by flavonoids: Structure-activity relationship studies. *PLoS One*, *7*(11), e49493. https://doi.org/10.1371/journal.pone.0049493

Guo, Y., Mah, E., Davis, C. G., Jalili, T., Ferruzzi, M. G., Chun, O. K., & Bruno, R. S. (2013). Dietary fat increases quercetin bioavailability in overweight adults. *Molecular Nutrition & Food Research*, *57*(5), 896–905. https://doi.org/10.1002/mnfr.201200619

Häckl, L. P., Cuttle, G., Dovichi, S. S., Lima-Landman, M. T., & Nicolau, M. (2002). Inhibition of angiotesin-converting enzyme by quercetin alters the vascular response to brandykinin and angiotensin I. *Pharmacology*, *65*(4), 182–186. https://doi.org/10.1159/000064341

Hamilton, K. E., Rekman, J. F., Gunnink, L. K., Busscher, B. M., Scott, J. L., Tidball, A. M., … Louters, L. L. (2018). Quercetin inhibits glucose transport by binding to an exofacial site on GLUT1. *Biochimie*, *151*, 107–114. https://doi.org/10.1016/j.biochi.2018.05.012

Hamming, I., Timens, W., Bulthuis, M. L., Lely, A. T., Navis, G., & van Goor, H. (2004). Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *The Journal of Pathology*, *203*(2), 631–637. https://doi.org/10.1002/path.1570

Han, M. K., Barreto, T. A., Martinez, F. J., Comstock, A. T., & Sajjan, U. S. (2020). Randomised clinical trial to determine the safety of quercetin supplementation in patients with chronic obstructive pulmonary disease. *BMJ Open Respiratory Research*, *7*(1), e000392. https://doi.org/10.1136/bmjresp-2018-000392

Harwood, M., Danielewska-Nikiel, B., Borzelleca, J. F., Flamm, G. W., Williams, G. M., & Lines, T. C. (2007). A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association*, *45*(11), 2179–2205. https://doi.org/10.1016/j.fct.2007.05.015

Hayflick, L., & Moorhead, P. S. (1961). The serial cultivation of human diploid cell strains. *Experimental Cell Research*, *25*, 585–621. https://doi.org/10.1016/0014-4827(61)90192-6

Henagan, T. M., Lenard, N. R., Gettys, T. W., & Stewart, L. K. (2014). Dietary quercetin supplementation in mice increases skeletal muscle PGC1α expression, improves mitochondrial function and attenuates

insulin resistance in a time-specific manner. *PLoS One*, *9*(2), e89365. https://doi.org/10.1371/journal.pone.0089365

Higham, A., Mathioudakis, A., Vestbo, J., & Singh, D. (2020). COVID-19 and COPD: A narrative review of the basic science and clinical outcomes. *European Respiratory Review: An Official Journal of the European Respiratory Society*, *29*(158), 200199. https://doi.org/10.1183/16000617.0199-2020

Hollman, P. C., de Vries, J. H., van Leeuwen, S. D., Mengelers, M. J., & Katan, M. B. (1995). Absorption of dietary quercetin glycosides and quercetin in healthy ileostomy volunteers. *The American Journal of Clinical Nutrition*, *62*(6), 1276–1282. https://doi.org/10.1093/ajcn/62.6.1276

Hollman, P. C., van Trijp, J. M., Buysman, M. N., van der Gaag, M. S., Mengelers, M. J., de Vries, J. H., & Katan, M. B. (1997). Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man. *FEBS Letters*, *418*(1-2), 152–156. https://doi.org/10.1016/s0014-5793(97)01367-7

Hruby, A., & Hu, F. B. (2015). The epidemiology of obesity: A big picture. *PharmacoEconomics*, *33*(7), 673–689. https://doi.org/10.1007/s40273-014-0243-x

Huang, F., Li, Y., Leung, E. L., Liu, X., Liu, K., Wang, Q., … Luo, L. (2020a). A review of therapeutic agents and Chinese herbal medicines against SARS-COV-2 (COVID-19). *Pharmacological Research*, *158*, 104929. https://doi.org/10.1016/j.phrs.2020.104929

Huang, S., Wang, J., Liu, F., Liu, J., Cao, G., Yang, C., … Xiong, B. (2020b). COVID-19 patients with hypertension have more severe disease: A multicenter retrospective observational study. *Hypertension Research: Official Journal of the Japanese Society of Hypertension*, *43*(8), 824–831. https://doi.org/10.1038/s41440-020-0485-2

Hubbard, G. P., Wolffram, S., Lovegrove, J. A., & Gibbins, J. M. (2004). Ingestion of quercetin inhibits platelet aggregation and essential components of the collagen-stimulated platelet activation pathway in humans. *Journal of Thrombosis and Haemostasis: JTH*, *2*(12), 2138–2145. https://doi.org/10.1111/j.1538-7836.2004.01067.x

Ioannidis, J., Axfors, C., & Contopoulos-Ioannidis, D. G. (2020). Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. *Environmental Research*, *188*, 109890. https://doi.org/10.1016/j.envres.2020.109890

Ji, H. L., Zhao, R., Matalon, S., & Matthay, M. A. (2020). Elevated plasmin(ogen) as a common risk factor for COVID-19 susceptibility. *Physiological Reviews*, *100*(3), 1065–1075. https://doi.org/10.1152/physrev.00013.2020

Jung, C. H., Cho, I., Ahn, J., Jeon, T. I., & Ha, T. Y. (2013). Quercetin reduces high-fat diet-induced fat accumulation in the liver by regulating lipid metabolism genes. *Phytotherapy Research: PTR*, *27*(1), 139–143. https://doi.org/10.1002/ptr.4687

Jung, J. Y., Lim, Y., Moon, M. S., Kim, J. Y., & Kwon, O. (2011). Onion peel extracts ameliorate hyperglycemia and insulin resistance in high fat diet/streptozotocin-induced diabetic rats. *Nutrition & Metabolism*, *8*(1), 18. https://doi.org/10.1186/1743-7075-8-18

Karam, B. S., Chavez-Moreno, A., Koh, W., Akar, J. G., & Akar, F. G. (2017). Oxidative stress and inflammation as central mediators of atrial fibrillation in obesity and diabetes. *Cardiovascular Diabetology*, *16*(1), 120. https://doi.org/10.1186/s12933-017-0604-9

Kaul, T. N., Middleton, E., Jr., & Ogra, P. L. (1985). Antiviral effect of flavonoids on human viruses. *Journal of Medical Virology*, *15*(1), 71–79. https://doi.org/10.1002/jmv.1890150110

Khan, H., Ullah, H., Aschner, M., Cheang, W. S., & Akkol, E. K. (2019). Neuroprotective effects of quercetin in Alzheimer's disease. *Biomolecules*, *10*(1), 59. https://doi.org/10.3390/biom10010059

Kim, D. H., Kim, S. Y., Park, S. Y., & Han, M. J. (1999). Metabolism of quercitrin by human intestinal bacteria and its relation to some biological activities. *Biological & Pharmaceutical Bulletin*, *22*(7), 749–751. https://doi.org/10.1248/bpb.22.749

Kim, H. P., Mani, I., Iversen, L., & Ziboh, V. A. (1998). Effects of naturally-occurring flavonoids and biflavonoids on epidermal cyclooxygenase and lipoxygenase from guinea-pigs. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, *58*(1), 17–24. https://doi.org/10.1016/s0952-3278(98)90125-9

Kim, J. H., Kang, M. J., Choi, H. N., Jeong, S. M., Lee, Y. M., & Kim, J. I. (2011). Quercetin attenuates fasting and postprandial hyperglycemia in animal models of diabetes mellitus. *Nutrition Research and Practice*, *5*(2), 107–111. https://doi.org/10.4162/nrp.2011.5.2.107

Kirkland, J. L., & Tchkonia, T. (2017). Cellular senescence: A translational perspective. *EBioMedicine*, *21*, 21–28. https://doi.org/10.1016/j.ebiom.2017.04.013

Kirkland, J. L., & Tchkonia, T. (2020). Senolytic drugs: From discovery to translation. *Journal of Internal Medicine*, *288*(5), 518–536. https://doi.org/10.1111/joim.13141

Krishnamurthy, J., Torrice, C., Ramsey, M. R., Kovalev, G. I., Al-Regaiey, K., Su, L., & Sharpless, N. E. (2004). Ink4a/Arf expression is a biomarker of aging. *The Journal of Clinical Investigation*, *114*(9), 1299–1307. https://doi.org/10.1172/JCI22475

Lange, P., Ahmed, E., Lahmar, Z. M., Martinez, F. J., & Bourdin, A. (2021). Natural history and mechanisms of COPD. *Respirology (Carlton, Vic.)*, *26*, 298–321. https://doi.org/10.1111/resp.14007

Lee, J. S., Cha, Y. J., Lee, K. H., & Yim, J. E. (2016). Onion peel extract reduces the percentage of body fat in overweight and obese subjects: A 12-week, randomized, double-blind, placebo-controlled study. *Nutrition Research and Practice*, *10*(2), 175–181. https://doi.org/10.4162/nrp.2016.10.2.175

Lee, K. H., Park, E., Lee, H. J., Kim, M. O., Cha, Y. J., Kim, J. M., … Shin, M. J. (2011). Effects of daily quercetin-rich supplementation on cardiometabolic risks in male smokers. *Nutrition Research and Practice*, *5*(1), 28–33. https://doi.org/10.4162/nrp.2011.5.1.28

Lee, S., Yu, Y., Trimpert, J., Benthani, F., Mairhofer, M., Richter-Pechanska, P., … Schmitt, C. A. (2021). Virus-induced senescence is a driver and therapeutic target in COVID-19. *Nature*, *599*(7884), 283–289. https://doi.org/10.1038/s41586-021-03995-1

Leiva Sisnieguez, C. E., Espeche, W. G., & Salazar, M. R. (2020). Arterial hypertension and the risk of severity and mortality of COVID-19. *The European Respiratory Journal*, *55*(6), 2001148. https://doi.org/10.1183/13993003.01148-2020

Lesser, S., Cermak, R., & Wolffram, S. (2004). Bioavailability of quercetin in pigs is influenced by the dietary fat content. *The Journal of Nutrition*, *134*(6), 1508–1511. https://doi.org/10.1093/jn/134.6.1508

Li, A. C., & Glass, C. K. (2002). The macrophage foam cell as a target for therapeutic intervention. *Nature Medicine*, *8*(11), 1235–1242. https://doi.org/10.1038/nm1102-1235

Liang, X., Shi, L., Wang, Y., Xiao, W., Duan, G., Yang, H., & Wang, Y. (2020). The association of hypertension with the severity and mortality of COVID-19 patients: Evidence based on adjusted effect estimates. *The Journal of Infection*, *81*(3), e44–e47. https://doi.org/10.1016/j.jinf.2020.06.060

Liu, P. P., Blet, A., Smyth, D., & Li, H. (2020). The science underlying COVID-19: Implications for the cardiovascular system. *Circulation*, *142*(1), 68–78. https://doi.org/10.1161/CIRCULATIONAHA.120.047549

Liu, Y., Liu, Y., Dai, Y., Xun, L., & Hu, M. (2003). Enteric disposition and recycling of flavonoids and ginkgo flavonoids. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, *9*(5), 631–640. https://doi.org/10.1089/107555303322524481

López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2013). The hallmarks of aging. *Cell*, *153*(6), 1194–1217. https://doi.org/10.1016/j.cell.2013.05.039

Lotito, S. B., Zhang, W. J., Yang, C. S., Crozier, A., & Frei, B. (2011). Metabolic conversion of dietary flavonoids alters their anti-inflammatory and antioxidant properties. *Free Radical Biology & Medicine*, *51*(2), 454–463. https://doi.org/10.1016/j.freeradbiomed.2011.04.032

Luo, X., Xue, L., Xu, H., Zhao, Q. Y., Wang, Q., She, Y. S., … Liu, Q. H. (2018). *Polygonum aviculare* L. extract and quercetin attenuate contraction in airway smooth muscle. *Scientific Reports*, *8*(1), 3114. https://doi.org/10.1038/s41598-018-20409-x

Mackraj, I., Govender, T., & Ramesar, S. (2008). The antihypertensive effects of quercetin in a salt-sensitive model of hypertension. *Journal of Cardiovascular Pharmacology*, *51*(3), 239–245.

Malavolta, M., Giacconi, R., Brunetti, D., Provinciali, M., & Maggi, F. (2020). Exploring the relevance of senotherapeutics for the current SARS-CoV-2 emergency and similar future global health threats. *Cell*, *9*(4), 909.

Mallia, P., Message, S. D., Gielen, V., Contoli, M., Gray, K., Kebadze, T., … Johnston, S. L. (2011). Experimental rhinovirus infection as a human model of chronic obstructive pulmonary disease exacerbation. *American Journal of Respiratory and Critical Care Medicine*, *183*(6), 734–742.

Manach, C., Mazur, A., & Scalbert, A. (2005). Polyphenols and prevention of cardiovascular diseases. *Current Opinion in Lipidology*, *16*(1), 77–84.

Manach, C., Texier, O., Morand, C., Crespy, V., Régérat, F., Demigné, C., & Rémésy, C. (1999). Comparison of the bioavailability of quercetin and catechin in rats. *Free Radical Biology & Medicine*, *27*(11–12), 1259–1266.

Mathers, C. D., & Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine*, *3*(11), e442.

Mehrbod, P., Abdalla, M. A., Fotouhi, F., Heidarzadeh, M., Aro, A. O., Eloff, J. N., … Fasina, F. O. (2018). Immunomodulatory properties of quercetin-3-O-α-L-rhamnopyranoside from *Rapanea melanophloeos* against influenza a virus. *BMC Complementary and Alternative Medicine*, *18*(1), 184.

Meuter, A., Rogmann, L. M., Winterhoff, B. J., Tchkonia, T., Kirkland, J. L., & Morbeck, D. E. (2014). Markers of cellular senescence are elevated in murine blastocysts cultured in vitro: Molecular consequences of culture in atmospheric oxygen. *Journal of Assisted Reproduction and Genetics*, *31*(10), 1259–1267.

Mozzicafreddo, M., Cuccioloni, M., Eleuteri, A. M., Fioretti, E., & Angeletti, M. (2006). Flavonoids inhibit the amidolytic activity of human thrombin. *Biochimie*, *88*(9), 1297–1306.

Nadar, S. K., Tayebjee, M. H., Stowasser, M., & Byrd, J. B. (2020). Managing hypertension during the COVID-19 pandemic. *Journal of Human Hypertension*, *34*(6), 415–417. https://doi.org/10.1038/s41371-020-0356-y

Nemeth, K., & Piskula, M. K. (2007). Food content, processing, absorption and metabolism of onion flavonoids. *Critical Reviews in Food Science and Nutrition*, *47*(4), 397–409. https://doi.org/10.1080/10408390600846291

Nettore, I. C., Rocca, C., Mancino, G., Albano, L., Amelio, D., Grande, F., … Ungaro, P. (2019). Quercetin and its derivative Q2 modulate chromatin dynamics in adipogenesis and Q2 prevents obesity and metabolic disorders in rats. *The Journal of Nutritional Biochemistry*, *69*, 151–162. https://doi.org/10.1016/j.jnutbio.2019.03.019

Nguyen, T. T., Woo, H. J., Kang, H. K., Nguyen, V. D., Kim, Y. M., Kim, D. W., … Kim, D. (2012). Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in *Pichia pastoris*. *Biotechnology Letters*, *34*(5), 831–838. https://doi.org/10.1007/s10529-011-0845-8

Nicholson, S. K., Tucker, G. A., & Brameld, J. M. (2008). Effects of dietary polyphenols on gene expression in human vascular endothelial cells. *The Proceedings of the Nutrition Society*, *67*(1), 42–47. https://doi.org/10.1017/S0029665108006009

Oh, W. J., Endale, M., Park, S. C., Cho, J. Y., & Rhee, M. H. (2012). Dual roles of quercetin in platelets: Phosphoinositide-3-kinase and MAP kinases inhibition, and cAMP-dependent vasodilator-stimulated phosphoprotein stimulation. *Evidence-Based Complementary and Alternative Medicine: eCAM*, *2012*, 485262. https://doi.org/10.1155/2012/485262

Oliveira, E. J., Watson, D. G., & Grant, M. H. (2002). Metabolism of quercetin and kaempferol by rat hepatocytes and the identification of flavonoid glycosides in human plasma. *Xenobiotica; The Fate of Foreign Compounds in Biological Systems*, *32*(4), 279–287. https://doi.org/10.1080/00498250110107886

Oparil, S., Acelajado, M. C., Bakris, G. L., Berlowitz, D. R., Cífková, R., Dominiczak, A. F., … Whelton, P. K. (2018). Hypertension. *Nature Reviews. Disease Primers*, *4*, 18014. https://doi.org/10.1038/nrdp.2018.14

Panuganti, K. K., Nguyen, M., & Kshirsagar, R. K. (2020). *Obesity*. StatPearls Publishing.

Park, J. Y., Yuk, H. J., Ryu, H. W., Lim, S. H., Kim, K. S., Park, K. H., … Lee, W. S. (2017). Evaluation of polyphenols from *Broussonetia papyrifera* as coronavirus protease inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *32*(1), 504–515. https://doi.org/10.1080/14756366.2016.1265519

Patel, H., Chen, J., Das, K. C., & Kavdia, M. (2013). Hyperglycemia induces differential change in oxidative stress at gene expression and functional levels in HUVEC and HMVEC. *Cardiovascular Diabetology*, *12*, 142. https://doi.org/10.1186/1475-2840-12-142

Patel, R. V., Mistry, B. M., Shinde, S. K., Syed, R., Singh, V., & Shin, H. S. (2018). Therapeutic potential of quercetin as a cardiovascular agent. *European Journal of Medicinal Chemistry*, *155*, 889–904. https://doi.org/10.1016/j.ejmech.2018.06.053

Pawar, A., & Pal, A. (2020). Molecular and functional resemblance of dexamethasone and quercetin: A paradigm worth exploring in dexamethasone-nonresponsive COVID-19 patients. *Phytotherapy Research: PTR*, *34*(12), 3085–3088. https://doi.org/10.1002/ptr.6886

Pfeuffer, M., Auinger, A., Bley, U., Kraus-Stojanowic, I., Laue, C., Winkler, P., … Schrezenmeir, J. (2013). Effect of quercetin on traits of the metabolic syndrome, endothelial function and inflammation in men with different APOE isoforms. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD*, *23*(5), 403–409. https://doi.org/10.1016/j.numecd.2011.08.010

Porfidia, A., & Pola, R. (2020). Venous thromboembolism in COVID-19 patients. *Journal of Thrombosis and Haemostasis: JTH*, *18*(6), 1516–1517. https://doi.org/10.1111/jth.14842

Pormohammad, A., Ghorbani, S., Khatami, A., Farzi, R., Baradaran, B., Turner, D. L., … Idrovo, J. P. (2020). Comparison of confirmed COVID-19 with SARS and MERS cases - Clinical characteristics, laboratory findings, radiographic signs and outcomes: A systematic review and meta-analysis. *Reviews in Medical Virology*, *30*(4), e2112. https://doi.org/10.1002/rmv.2112

Pugliese, G., Vitale, M., Resi, V., & Orsi, E. (2020). Is diabetes mellitus a risk factor for COronaVIrus Disease 19 (COVID-19)? *Acta Diabetologica*, *57*(11), 1275–1285. https://doi.org/10.1007/s00592-020-01586-6

Rahman, I. (2006). Antioxidant therapies in COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, *1*(1), 15–29. https://doi.org/10.2147/copd.2006.1.1.15

Rahman, I., & Adcock, I. M. (2006). Oxidative stress and redox regulation of lung inflammation in COPD. *The European Respiratory Journal*, *28*(1), 219–242. https://doi.org/10.1183/09031936.06.00053805

Read, S. A., Obeid, S., Ahlenstiel, C., & Ahlenstiel, G. (2019). The role of zinc in antiviral immunity. *Advances in Nutrition (Bethesda, Md.)*, *10*(4), 696–710. https://doi.org/10.1093/advances/nmz013

RECOVERY Collaborative Group, Horby, P., Lim, W. S., Emberson, J. R., Mafham, M., Bell, J. L., … Landray, M. J. (2021). Dexamethasone in hospitalized patients with Covid-19. *The New England Journal of Medicine*, *384*(8), 693–704. https://doi.org/10.1056/NEJMoa2021436

Reddel, R. R. (2010). Senescence: An antiviral defense that is tumor suppressive? *Carcinogenesis*, *31*(1), 19–26. https://doi.org/10.1093/carcin/bgp274

Rich, G. T., Buchweitz, M., Winterbone, M. S., Kroon, P. A., & Wilde, P. J. (2017). Towards an understanding of the low bioavailability of quercetin: A study of its interaction with intestinal lipids. *Nutrients*, *9*(2), 111. https://doi.org/10.3390/nu9020111

Rondanelli, M., Perna, S., Gasparri, C., Petrangolini, G., Allegrini, P., Cavioni, A., … Riva, A. (2022). Promising effects of 3-month period of quercetin Phytosome® supplementation in the prevention of symptomatic COVID-19 disease in healthcare workers: A pilot study. *Life (Basel, Switzerland)*, *12*(1), 66. https://doi.org/10.3390/life12010066

Roslan, J., Nelli Giribabu, N., Karim, K., & Salleh, N. (2017). Quercetin ameliorates oxidative stress, inflammation and apoptosis in the heart of

streptozotocin-nicotinamide-induced adult male diabetic rats. *Biomedicine and Pharmacotherapy*, *86*, 570–582. https://doi.org/10.1016/j.biopha.2016.12.044

Roy, A. L., Sierra, F., Howcroft, K., Singer, D. S., Sharpless, N., Hodes, R. J., … Anderson, J. M. (2020). A blueprint for characterizing senescence. *Cell*, *183*(5), 1143–1146. https://doi.org/10.1016/j.cell.2020.10.032

Rubino, F., Amiel, S. A., Zimmet, P., Alberti, G., Bornstein, S., Eckel, R. H., … Renard, E. (2020). New-onset diabetes in Covid-19. *The New England Journal of Medicine*, *383*(8), 789–790. https://doi.org/10.1056/NEJMc2018688

Russo, M., Moccia, S., Spagnuolo, C., Tedesco, I., & Russo, G. L. (2020). Roles of flavonoids against coronavirus infection. *Chemico-Biological Interactions*, *328*, 109211. https://doi.org/10.1016/j.cbi.2020.109211

Russo, M., Mupo, A., Spagnuolo, C., & Russo, G. L. (2010). Exploring death receptor pathways as selective targets in cancer therapy. *Biochemical Pharmacology*, *80*(5), 674–682. https://doi.org/10.1016/j.bcp.2010.03.011

Ryu, Y. B., Jeong, H. J., Kim, J. H., Kim, Y. M., Park, J. Y., Kim, D., … Lee, W. S. (2010). Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CL$^{pro}$ inhibition. *Bioorganic & Medicinal Chemistry*, *18*(22), 7940–7947. https://doi.org/10.1016/j.bmc.2010.09.035

Saakre, M., Mathew, D., & Ravisankar, V. (2021). Perspectives on plant flavonoid quercetin-based drugs for novel SARS-CoV-2. *Beni-Suef University Journal of Basic and Applied Sciences*, *10*(1), 21. https://doi.org/10.1186/s43088-021-00107-w

Sanchez, M., Galisteo, M., Vera, R., Villar, I. C., Zarzuelo, A., Tamargo, J., … Duarte, J. (2006). Quercetin downregulates NADPH oxidase, increases eNOS activity and prevents endothelial dysfunction in spontaneously hypertensive rats. *Journal of Hypertension*, *24*(1), 75–84. https://doi.org/10.1097/01.hjh.0000198029.22472.d9

Sargiacomo, C., Sotgia, F., & Lisanti, M. P. (2020). COVID-19 and chronological aging: Senolytics and other anti-aging drugs for the treatment or prevention of corona virus infection? *Aging*, *12*(8), 6511–6517. https://doi.org/10.18632/aging.103001

Sattar, N., McInnes, I. B., & McMurray, J. (2020). Obesity is a risk factor for severe COVID-19 infection: Multiple potential mechanisms. *Circulation*, *142*(1), 4–6. https://doi.org/10.1161/CIRCULATIONAHA.120.047659

Savant, S., Srinivasan, S., & Kruthiventi, A. K. (2021). Potential nutraceuticals for COVID-19. *Nutrition and Dietary Supplements*, *13*, 25–51. https://doi.org/10.2147/NDS.S294231

Scoditti, E., Massaro, M., Garbarino, S., & Toraldo, D. M. (2019). Role of diet in chronic obstructive pulmonary disease prevention and treatment. *Nutrients*, *11*(6), 1357. https://doi.org/10.3390/nu11061357

Serban, M. C., Sahebkar, A., Zanchetti, A., Mikhailidis, D. P., Howard, G., Antal, D., … Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. (2016). Effects of quercetin on blood pressure: A systematic review and meta-analysis of randomized controlled trials. *Journal of the American Heart Association*, *5*(7), e002713. https://doi.org/10.1161/JAHA.115.002713

Shi, S., Wang, F., Yao, H., Kou, S., Li, W., Chen, B., … Wang, Z. (2022). Oral Chinese herbal medicine on immune responses during coronavirus disease 2019: A systematic review and meta-analysis. *Frontiers in Medicine*, *8*, 685734. https://doi.org/10.3389/fmed.2021.685734

Shin, D., Mukherjee, R., Grewe, D., Bojkova, D., Baek, K., Bhattacharya, A., … Dikic, I. (2020). Papain-like protease regulates SARS-CoV-2 viral spread and innate immunity. *Nature*, *587*(7835), 657–662. https://doi.org/10.1038/s41586-020-2601-5

Shohan, M., Nashibi, R., Mahmoudian-Sani, M. R., Abolnezhadian, F., Ghafourian, M., Alavi, S. M., … Khodadadi, A. (2022). The therapeutic efficacy of quercetin in combination with antiviral drugs in hospitalized COVID-19 patients: A randomized controlled trial. *European Journal of Pharmacology*, *914*, 174615. https://doi.org/10.1016/j.ejphar.2021.174615

Sierra, F. (2020). Geroscience and the coronavirus pandemic: The whack-a-mole approach is not enough. *Journal of the American Geriatrics Society*, *68*(5), 951–952. https://doi.org/10.1111/jgs.16489

Singh, A. K., & Misra, A. (2020). Impact of COVID-19 and comorbidities on health and economics: Focus on developing countries and India. *Diabetes & Metabolic Syndrome*, *14*(6), 1625–1630. https://doi.org/10.1016/j.dsx.2020.08.032

Singh, D., Agusti, A., Anzueto, A., Barnes, P. J., Bourbeau, J., Celli, B. R., … Vogelmeier, C. (2019). Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: The GOLD science committee report 2019. *The European Respiratory Journal*, *53*(5), 1900164. https://doi.org/10.1183/13993003.00164-2019

Smith, J. C., Sausville, E. L., Girish, V., Yuan, M. L., Vasudevan, A., John, K. M., & Sheltzer, J. M. (2020). Cigarette smoke exposure and inflammatory signaling increase the expression of the SARS-CoV-2 receptor ACE2 in the respiratory tract. *Developmental Cell*, *53*(5), 514–529.e3. https://doi.org/10.1016/j.devcel.2020.05.012

Sodhi, C. P., Wohlford-Lenane, C., Yamaguchi, Y., Prindle, T., Fulton, W. B., Wang, S., … Jia, H. (2018). Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg$^{9}$ bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. *American Journal of Physiology. Lung Cellular and Molecular Physiology*, *314*(1), L17–L31. https://doi.org/10.1152/ajplung.00498.2016

Song, Y., Manson, J. E., Buring, J. E., Sesso, H. D., & Liu, S. (2005). Associations of dietary flavonoids with risk of type 2 diabetes, and markers of insulin resistance and systemic inflammation in women: A prospective study and cross-sectional analysis. *Journal of the American College of Nutrition*, *24*(5), 376–384. https://doi.org/10.1080/07315724.2005.10719488

Stainer, A. R., Sasikumar, P., Bye, A. P., Unsworth, A. J., Holbrook, L. M., Tindall, M., … Gibbins, J. M. (2019). The metabolites of the dietary flavonoid quercetin possess potent antithrombotic activity, and interact with aspirin to enhance antiplatelet effects. *TH Open: Companion Journal to Thrombosis and Haemostasis*, *3*(3), e244–e258. https://doi.org/10.1055/s-0039-1694028

Stec, D. E., Juncos, L. A., & Granger, J. P. (2016). Renal intramedullary infusion of tempol normalizes the blood pressure response to intrarenal blockade of heme oxygenase-1 in angiotensin II-dependent hypertension. *Journal of the American Society of Hypertension: JASH*, *10*(4), 346–351. https://doi.org/10.1016/j.jash.2016.01.023

Stopa, J. D., Neuberg, D., Puligandla, M., Furie, B., Flaumenhaft, R., & Zwicker, J. I. (2017). Protein disulfide isomerase inhibition blocks thrombin generation in humans by interfering with platelet factor V activation. *JCI Insight*, *2*(1), e89373. https://doi.org/10.1172/jci.insight.89373

Sun, L., Li, E., Wang, F., Wang, T., Qin, Z., Niu, S., & Qiu, C. (2015). Quercetin increases macrophage cholesterol efflux to inhibit foam cell formation through activating PPARγ-ABCA1 pathway. *International Journal of Clinical and Experimental Pathology*, *8*(9), 10854–10860.

Tang, N., Li, D., Wang, X., & Sun, Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis: JTH*, *18*(4), 844–847. https://doi.org/10.1111/jth.14768

Townsend, E. A., & Emala, C. W., Sr. (2013). Quercetin acutely relaxes airway smooth muscle and potentiates β-agonist-induced relaxation via dual phosphodiesterase inhibition of PLCβ and PDE4. *American Journal of Physiology. Lung Cellular and Molecular Physiology*, *305*(5), L396–L403. https://doi.org/10.1152/ajplung.00125.2013

V'kovski, P., Kratzel, A., Steiner, S., Stalder, H., & Thiel, V. (2021). Coronavirus biology and replication: Implications for SARS-CoV-2. *Nature Reviews. Microbiology*, *19*(3), 155–170. https://doi.org/10.1038/s41579-020-00468-6

Vaidyula, V. R., Criner, G. J., Grabianowski, C., & Rao, A. K. (2009). Circulating tissue factor procoagulant activity is elevated in stable moderate to severe chronic obstructive pulmonary disease. *Thrombosis Research*, *124*(3), 259–261. https://doi.org/10.1016/j.thromres.2008.12.030

Vallelonga, F., Carbone, F., Benedetto, F., Airale, L., Totaro, S., Leone, D., … Milan, A. (2020). Accuracy of a symptom-based approach to identify hypertensive emergencies in the emergency department. *Journal of Clinical Medicine*, *9*(7), 2201. https://doi.org/10.3390/jcm9072201

Wang, B., Li, R., Lu, Z., & Huang, Y. (2020). Does comorbidity increase the risk of patients with COVID-19: Evidence from meta-analysis. *Aging*, *12*(7), 6049–6057. https://doi.org/10.18632/aging.103000

Wang, E. (1995). Senescent human fibroblasts resist programmed cell death, and failure to suppress *bcl2* is involved. *Cancer Research*, *55*(11), 2284–2292.

Wang, H., Yuan, Z., Pavel, M. A., Jablonski, S. M., Jablonski, J., Hobson, R., & Hansen, S. B. (2021). The role of high cholesterol in age-related COVID19 lethality. *bioRxiv [Preprint]*. https://doi.org/10.1101/2020.05.09.086249

Williamson, G., Kay, C. D., & Crozier, A. (2018). The bioavailability, transport, and bioactivity of dietary flavonoids: A review from a historical perspective. *Comprehensive Reviews in Food Science and Food Safety*, *17*(5), 1054–1112. https://doi.org/10.1111/1541-4337.12351

Wu, Z., & McGoogan, J. M. (2020). Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*, *323*(13), 1239–1242. https://doi.org/10.1001/jama.2020.2648

Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., … Wang, F. S. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet. Respiratory Medicine*, *8*(4), 420–422. https://doi.org/10.1016/S2213-2600(20)30076-X

Yamamoto, Y., & Oue, E. (2006). Antihypertensive effect of quercetin in rats fed with a high-fat high-sucrose diet. *Bioscience, Biotechnology, and Biochemistry*, *70*(4), 933–939. https://doi.org/10.1271/bbb.70.933

Yan, R., Zhang, Y., Li, Y., Xia, L., Guo, Y., & Zhou, Q. (2020a). Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science (New York, N.Y.)*, *367*(6485), 1444–1448. https://doi.org/10.1126/science.abb2762

Yan, Y., Yang, Y., Wang, F., Ren, H., Zhang, S., Shi, X., … Dong, K. (2020b). Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. *BMJ Open Diabetes Research & Care*, *8*(1), e001343. https://doi.org/10.1136/bmjdrc-2020-001343

Yang, D. K., & Kang, H. S. (2018). Anti-diabetic effect of cotreatment with quercetin and resveratrol in streptozotocin-induced diabetic rats. *Biomolecules & Therapeutics*, *26*, 130–138. https://doi.org/10.4062/biomolther.2017.254

Yi, L., Li, Z., Yuan, K., Qu, X., Chen, J., Wang, G., … Xu, X. (2004). Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. *Journal of Virology*, *78*(20), 11334–11339. https://doi.org/10.1128/JVI.78.20.11334-11339.2004

Zhang, H., Yu, D., Sun, J., Liu, X., Jiang, L., Guo, H., & Ren, F. (2014). Interaction of plant phenols with food macronutrients: Characterisation and nutritional-physiological consequences. *Nutrition Research Reviews*, *27*(1), 1–15. https://doi.org/10.1017/S095442241300019X

Zhang, J. J., Dong, X., Cao, Y. Y., Yuan, Y. D., Yang, Y. B., Yan, Y. Q., … Gao, Y. D. (2020). Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*, *75*(7), 1730–1741. https://doi.org/10.1111/all.14238

Zhang, M., Xie, Z., Gao, W., Pu, L., Wei, J., & Guo, C. (2016). Quercetin regulates hepatic cholesterol metabolism by promoting cholesterol-to-bile acid conversion and cholesterol efflux in rats. *Nutrition Research (New York, N.Y.)*, *36*(3), 271–279. https://doi.org/10.1016/j.nutres.2015.11.019

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., … Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet (London, England)*, *395*(10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

Zhu, J., Ji, P., Pang, J., Zhong, Z., Li, H., He, C., … Zhao, C. (2020a). Clinical characteristics of 3062 COVID-19 patients: A meta-analysis. *Journal of Medical Virology*, *92*(10), 1902–1914. https://doi.org/10.1002/jmv.25884

Zhu, L., She, Z. G., Cheng, X., Qin, J. J., Zhang, X. J., Cai, J., … Li, H. (2020b). Association of Blood Glucose Control and Outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metabolism*, *31*(6), 1068–1077.e3. https://doi.org/10.1016/j.cmet.2020.04.021

Zimmet, P. Z. (2017). Diabetes and its drivers: The largest epidemic in human history? *Clinical Diabetes and Endocrinology*, *3*, 1. https://doi.org/10.1186/s40842-016-0039-3

**How to cite this article:** Pawar, A., Russo, M., Rani, I., Goswami, K., Russo, G. L., & Pal, A. (2022). A critical evaluation of risk to reward ratio of quercetin supplementation for COVID-19 and associated comorbid conditions. *Phytotherapy Research*, *36*(6), 2394–2415. https://doi.org/10.1002/ptr.7461