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Review

The pharmacological mechanism of quercetin as adjuvant therapy of COVID-19

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Abstract

The emergence of novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused the global outbreak and major public health concern. After the outbreak human-to-human transmission was confirmed with or without symptoms of upper and lower respiratory tract involvement. Up to date, there has been evidence that COVID-19 is beyond that of a typical pulmonary disease and revealing pathomechanics of COVID-19-associated acute respiratory distress syndrome (CARDS), which include severe inflammation and pulmonary edema leading to impaired alveolar homeostasis, and resulting in an alteration of lung physiology, lung fibrosis, inflammation of endothelium, vascular thrombosis, as well as exaggerated immune response. Concerning this pathophysiology, the use of quercetin as phytotherapeutic may merit in the management of COVID-19 patients. In this review, the authors wish to elaborate on the molecular effect of quercetin on SARS-CoV-2 by giving a detailed mechanism of quercetin against the binding of the S-protein of the virus to angiotensin-converting enzyme 2 (ACE2) receptors, the main protease (M^{pro}) or 3C-like protease ($3CL^{pro}$), papain-like protease (PL^{pro}), and RNA-dependent RNA polymerase (RdRP). Recent clinical evidence supporting the use of quercetin in COVID-19 management is also discussed in this paper.

Keywords: Quercetin; phytotherapeutic; COVID-19; antiviral; anti-inflammatory; anti-fibrosis

Introduction

Since the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in Wuhan, Hubei Province, China, in December 2019, it has caused a global outbreak and major public health concern. The human-to-human transmission was confirmed to elicit both asymptomatic and symptomatic respiratory disease, known as Coronavirus Disease (COVID-19). Numerous efforts in the medical field have been undertaken to cease the spread of this virus and to determine accurate strategies in treating individuals with confirmed positive SARS-CoV-2 infection [1]. Globally, the COVID-19 pandemic has affected more than 298 million patients and 5.4 million deaths have been reported to the World Health Organization (WHO) during the writing of this review [2]. Ergo, scientists and researchers are racing the clock and breaking records to develop COVID-19 vaccines and repurpose several therapeutic options to treat mild to severe COVID-19.

Recently, albeit several trials that are underway to produce safe and effective vaccines, in conjunction with its distribution, over 4.9 million vaccine doses have been administered worldwide and obtained emergency use authorization by The United States food and drug administration (FDA) [2]. However, an approach called drug repurposed under ACTIV-6 protocol has been created by the national institute of health (NIH) to explore a pool of up to seven drugs approved by the FDA for other diseases, particularly antiviral drug remdesivir, the anti-inflammatory baricitinib, and corticosteroid (e.g. dexamethasone) for treating mild to moderate COVID-19 [3, 4]. Furthermore, there have been numerous ongoing trials evaluating oral supplements such as zinc, vitamin C, vitamin D, folic acid [5], and flavonoids such as quercetin, as adjuvant pharmacotherapy in the management of COVID-19 [6].

Quercetin (3, 3', 4', 5, 7-pentahydroxyflavone) (C15H10O7) is a major polyphenol that belongs to the flavonoid family. It is categorized as flavonol, one of the six subclasses of flavonoid compounds. Being the most abundant form of flavonoid molecules, quercetins are ubiquitously distributed in a variety of dietary plants, including apple, berries, onion, kale, tea, tomato, grape, as well as nuts. Furthermore, it is also affordably marketed in the form of tablet dietary supplements. Various in vitro and animal model studies have shown that quercetin has numerous physiological effects, including antioxidant, anti-inflammatory, immunomodulatory, and antiviral properties. There is well-documented evidence pointing toward its effects in attenuating lipid peroxidation, platelet aggregation, and capillary permeability, which cumulatively result in cardioprotective effects, as well as anti-carcinogenic properties [7]. Too few human studies address the effectiveness of quercetin, specifically in the management of viral respiratory infection. Notwithstanding, some human studies have provided significant results in specific populations with non-infectious causes of respiratory disease [8-11].

Current evidence shows the specific pathomechanics of COVID-19-associated acute respiratory distress syndrome (CARDS), which include severe inflammation and pulmonary edema leading to impaired alveolar homeostasis, and alteration of lung physiology, and resulting in lung fibrosis, inflammation of endothelium, vascular thrombosis, as well as an exaggerated immune response [12].

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Concerning this pathophysiology, the use of quercetin may merit in the management of COVID-19 through its antiviral, anti-inflammatory, anti-fibrotic, and immunomodulatory effects. In this narrative review, we aim to discuss the evidence related to its antiviral and anti-inflammatory effects in molecular and preclinical studies, and the currently available studies evaluating the use of quercetin as an adjuvant pharmacotherapy of COVID-19.

Molecular Effect of Quercetin to Coronaviruses

The SARS-CoV-2 pandemic has highlighted the vast multitude replication [14]. SARS-CoV-2 spike protein (S-protein), which constitutes receptor-binding domain (RBD), S1 and S2 subunits, human ACE2 receptors, type II transmembrane serine protease, and cathepsin B/L are the pivotal targets for inhibition of the viral entry [13]. Nevertheless, several compounds and drugs are designed and even repurposed to directly act on SARS-CoV-2 conserved enzymes $3CL^{pro}$ or main protease (M^{pro}), PL^{pro}, NSP12, and RNA-dependent RNA polymerase (RdRP) [14]. In this following section, we discuss the antiviral mechanisms of quercetin and its derivatives on coronaviruses of the Coronaviridae family, including SARS-Associated Coronavirus (SARS-CoV), Middle-East respiratory syndrome coronavirus (MERS-CoV), and novel SARS-CoV-2, done by but not limited to computational or in silico approaches.

Inhibition of S-protein interaction to ACE2 receptors

As aforementioned, S-protein can interact with ACE2 receptors in the human body and mediates the viral entry. This S-protein is activated by an enzyme called furin, through its specific recognition site toward the enzyme. Milanovic et al. conducted a computational study using an acid-base equilibrium approach and molecular docking simulations to evaluate the inhibitory effect of quercetin and its metabolites, compared to chloroquine, hydroxychloroquine, and cinanserin hydrochloride that suppress furin and interfere with the S-protein of SARS-CoV-2. It showed that acid-base forms of quercetin and its oxidative metabolite benzofuranone 2-(3,4-dihydroxy benzoyl)-2,4,6-trihydroxy-3(2H) benzofuranone bind to human furin with a better competitive inhibitory activity than those of chloroquine and hydroxychloroquine at physiological pH. Quercetin and benzofuranone induce alterations in the native conformation of furin and distort its active site. Likewise, their binding affinity toward furin is comparable to those of approved drugs but less comparable in binding to the S-protein. Hence, the approved drugs are still essential for specific binding to S-protein [15].

Among natural flavonoids and synthetic indole chalcones tested computationally by Vijaya Kumar et al., quercetin showed highly potent inhibition against S-protein, dimerization, and catalytic activity of the SARS-CoV-2 M^{pro} [16]. The inhibition of S-protein was shown by tight binding affinity of quercetin to amino residues of SARS-CoV-2, including Spike Receptor Binding Domain (SRBD), consisting of Gly496, Asn501, Tyr505, and Tyr453 with a binding energy of -7.8 kcal/mol. On the other hand, quercetin interacted with amino residues of Glu288, Asp289, Glu290 on M^{pro} dimerization sites and interacted with Leu286 residues on the M^{pro} enzymatic regulatory sites. Moreover, quercetin interacted with β-hairpin residues of NSP12, thus interfering with the stabilization of RdRp of SARS-CoV-2 [16].

Quercetin along with vitamin D and estradiol, namely tripartite combination, were tested by genomic-guided tracing of SARS-CoV-2 targets in human cells [17]. ACE2 and furin play a significant role in SARS-CoV-2 entry to human cells and are expressed in multiple cells and tissues. The tripartite combination from the study was able to regulate the expression of ACE2 and furin by several mechanisms. From the gene expression omnibus (GEO) database, quercetin appears to inhibit the expression of several potential SARS-CoV-2 infection-promoting genes like c-FOS in rat and human cells, including Runx1 in rat cells and HNF4a in human cells. C-FOS, Runx1, and HNF4a are reported as activators of the ACE2. Further, the Gene Set Enrichment Analyses (GSEA) demonstrated that quercetin administration renders significant decreases in ACE2 expression during the differentiation of intestinal cells in the human model. Intriguingly, quercetin alters approximately 30% of the expression of the genes (98 out of 332), which encode protein targets of SARS-CoV-2 in human cells; hence it is the potential to interfere with 85% (23 out of 27) SARS-CoV-2 proteins. In combination with vitamin D, it may alter the activity of SARS-CoV-2 proteins in human cells, almost 93% (25 out of 27). In the mouse model, quercetin exerts an inhibitory effect toward ACE2 by enhancing the activity of GATA5 (repressor) inhibitory activity on surfactant protein-C (SFTPC) gene expression. On the other hand, quercetin upregulates INSIG1 (activator) in the human intestinal cells, allowing inhibition of another activator gene, HIF1a, and ACE2 subsequently [17].

A computational study using traditional Chinese medicine systems pharmacology (TCMSP) Database and Analysis Platform was done to explore quercetin, puerarin, and kaempferol activities in blocking SARS-CoV-2 replication [18]. Among these three compounds, quercetin demonstrated the highest binding affinity to ACE2 with dissociation constant, $K_D = 4.83x10^{-6}$ M, and was considered to have remarkable value for an unmodified compound. Additionally, it also demonstrated higher binding affinity to SARS-CoV-2, SRBD with $K_D = 2.41x10^{-8}$ M; and more notably, it almost suppressed the viral binding to ACE2 receptor identified by Surface Plasmon Resonance (SPR) assay. These dual actions both on SARS-CoV-2 spike protein and ACE2 receptor may generate a better antiviral synergistic effect on SARS-CoV-2. Further exploration of quercetin was also performed by Gene Ontology (GO) functional enrichment analysis. It revealed that quercetin was closely linked to inflammatory response, signal transduction, response to drugs, gene transcription and expression, apoptosis, and oxidation-reduction process. These inhibitory mechanisms are summarized in Figure 1.

In vitro assays to demonstrate quercetin and its metabolites in inhibiting recombinant human ACE2 (rhACE2) activity was done by Liu et al. [19]. Among the polyphenols tested, quercetin was the most potent inhibitor against rhACE2 activity with a half-maximal inhibitory concentration (IC_{50}) of 4.48 μM. The results also showed that by the presence of 5-100 μM quercetin, the reaction rate of 50 ng/mL rhACE2 was concentration- and time-dependent at 37°C. After 2.5 minutes, the rhACE2 IC_{50} of quercetin raised from approximately 4.48 μM to 29.5 μM at 10.5 minutes. Since rhACE2 activity is raised with temperature, the inhibition of this enzyme depends on different stages of temperature. Quercetin was also shown to decrease the affinity of rhACE2 to the Mca-APK (Dnp) substrate and lower the rhACE2 catalytic efficiency (K_{cat}/K_m). Consistently, it exerted a dual inhibition action by increasing Km (affinity) and decreasing Vmax of rhACE2. On the other hand, the inhibition of rhACE2 was also demonstrated by quercetin glycosides and quercetin metabolites like isorhamnetin, tamarixetin, 3,4-dihydroxyphenylacetic acid, and quercetin-3-glucuronide, as they decreased the K_m and K_{cat}/K_m values [19].

Inhibition of SARS-CoV-2 $3CL^{pro}$

In this study, a natural compound called quercetin-3-beta-galactoside was identified as an inhibitor of the protease by molecular docking, SPR/FRET-based bioassays, and mutagenesis studies [20]. The results revealed that Gln189 was pointed to be an important amino residue that plays a role in binding interactions between quercetin-3-β-galactoside with SARS-CoV $3CL^{pro}$ in wild and mutant type (Q189A). Albeit, SARS-CoV $3CL^{pro}$ Q189A preserved the same bi-

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ological activity level as its wild type; in fact, the binding affinity of quercetin-3-β-galactoside to SARS-CoV 3CL^{pro} Q189A was reduced. Further, the enzymatic activity of these two protease types expressed in *E. coli*-M15 was similar. Quercetin-3-β-galactoside rendered a significant and dose-dependent increment in SPR response units and demonstrated slow-dissociation curves and characteristics of fast-binding. Also, it acted competitively. The IC_{50} value of the quercetin inhibiting the SARS-CoV-3CL^{pro} catalytic activity was calculated to be 42.79 ± 4.97 μM. Whereas, the IC_{50} value of the quercetin against the mutant type Q189A, was calculated to be 2-fold greater than the wild-type, 27.89 ± 10.06 μM. Moreover, among eight derivatives of quercetin-3-β-galactoside synthesized in this study, four exhibited a remarkable inhibition percentage at 50μM, more than 50%, designating that these derivatives were potent candidate inhibitors of SARS-CoV-3CL^{pro} [20].

There has been evidence pointing out that the structural basis of the main protease of SARS-CoV-2, SARS-CoV, and MERS-CoV with a conserved active site are similar based on homology modeling studies [21, 22]. Further, it is also highlighted that the binding of lead compounds is similar between the main proteases of SARS-CoV-2 and SARS-CoV, based on the protonation state of the Cys-His catalytic dyad [14]. It is also known that the high sequence identity for main protease 3CL^{pro} between SARS-CoV and MERS-CoV is 95% [23]. In accordance with the previous study, quercetin displayed a good inhibition against recombinant SARS-CoV 3CL^{pro} expressed in Pichia pastoris with an IC_{50} value of 73 μM. Along with other flavonoids tested, quercetin also demonstrated greater than 80% inhibition toward the catalytic activity of recombinant 3CL^{pro} and rendered docking energy of -10.2 kcal/mol. Thus, these findings suggest that quercetin has the potential to be an inhibitor candidate for SARS-CoV3CL^{pro} [24]. Among forty flavonoids tested for inhibition against MERS-CoV 3CL^{pro} catalytic activity, quercetin-3-β-D-glucoside showed prominent inhibition in a dose-dependent manner with an IC_{50} value of 37.03 μM. Likewise, the molecular docking results indicated that the hydroxymethyl group of quercetin glucoside was able to form hydrogen bonds with Glu169, hence contributing to a higher affinity to the S1 side of the MERS-CoV 3CL^{pro} [25].

Explorations of phytochemical potential to tackle SARS-CoV-2 have been done extensively. Jia et al. elucidated the underlying mechanism of Reduning Injection (RDNI), which is a patented traditional Chinese medicine for COVID-19 treatment [26]. They used a combination of modeled Vero E6 cells and computational studies. The results showed that quercetin, among the compounds analyzed from the RDNI, displayed potential in the regulatory mechanism of SARS-CoV-2 3CL^{pro}, ACE2, and PL^{pro} with a binding energy of less than -5 kJ/mol on molecular docking analysis. In the protein microarray analysis, quercetin as a component of RDNI was shown to inhibit cytokine expression, including IL-1α, IL-1β, IL-4, IL-6, IL-8, and TNF-α. These inhibitory mechanisms are summarized in Figure 1. From pathway enrichment analysis, the researchers suggested that RDNI is capable of regulating inflammation through PI3K/AKT, FOXO, MAPK, and T cell receptor signaling pathways. Likewise, RDNI effectively suppresses the overexpression of MAPKs, PKC, and p65 based on Western blot analysis [26].

A screening study by computational and biophysical methods was previously done by Abian et al. to identify the inhibitory activity of natural quercetin on SARS-CoV-2 3CLpro. The results revealed that quercetin was able to alter the thermal stability of 3CL^{pro} leading to destabilization in a concentration-dependent manner. Isothermal titration calorimetry (ITC) assay demonstrated an interaction between quercetin and SARS-CoV-2 3CL^{pro} and displayed an inhibition constant of approximately 7 μM, which is considered sufficiently good in the preclinical studies [27]. Another in silico study revealed that quercetin among other natural products like hispidulin, cirsimaritin, sulfasalazine, artemisinin, and curcumin demonstrated better affinity against SARS-CoV-2 3CL^{pro} active site, in comparison with hydroxychloroquine. Likewise, quercetin showed better potential inhibitions against SARS-CoV-2 3CL^{pro} and ACE2 than hydroxychloroquine. Albeit, quercetin showed the lowest binding energy to the SARS-CoV-2 3CL^{pro}, as it fitted quite well to the active pocket of the 3CL^{pro} and its hydroxyl groups were able to form hydrogen bonds with amino acid residues of His163 and Leu141 [28]. Modifying the quercetin scaffold is known to be important for quercetin to bind SARS-CoV-2 3CL^{pro} at a molecular level. Seleno-functionalization of quercetin showed higher selectivity in the binding conformation and favorable affinity toward 3CL^{pro}, as compared to its natural compound by molecular docking. The derivative compounds from the seleno-functionalization approach exhibited no cytotoxic effect on Vero cells and exhibited SARS-CoV-2-related cytopathic effect under the inverted light microscope. Likewise, at a lower concentration, the seleno-functionalization of quercetin was able to hamper SARS-CoV-2 replication performed by RT-qPCR [29].

Another common glycosylated conjugate of quercetin, namely rutin (quercetin-3-O-rutinose) constantly showed inhibitory activity to SARS-CoV-2 3CL^{pro}. Rutin binds to the catalytic site of 3CL^{pro} thus inhibiting viral replication. It significantly alters the tertiary structure of the protein and/or the aromatic protein environment side chains. The declining enzymatic activity of 3CL^{pro} due to the rutin inhibitory effect delineates a concentration-dependent fashion. This effect is qualitatively similar to the previous study, utilizing quercetin [27], and stipulating that conjugated moiety of quercetin does not substantially suppress the inhibitory effect of the quercetin scaffold [23]. The results of this study were concordant with a previous study that showed allosteric inhibition of quercetin against SARS-CoV-2 3CL^{pro}. Using molecular docking analysis, the binding affinity of 3CL^{pro} for its substrate polypeptide was significantly reduced when complexed with quercetin [30]. Cherrak et al. through their in silico study also revealed that glycosylated flavonoids were strongly able to inhibit SARS-CoV-2 3CL^{pro}. Their binding against SARS-CoV-2 3CL^{pro} was stronger. The structural and the sugar moieties built in these flavonoids mainly affect the strength of the binding against the 3CL^{pro} active site. The strongest binding is possessed by flavonoids substituted with mono or disaccharides at position C3 of the flavonoid sugar. Among the flavonoids tested, quercetin-3-O-rhamnoside, myricetin 3-rutinoside, and quercetin-3-O-rutinoside (rutin), the latter exhibited the highest score and was stable in the docked 3CL^{pro} complex simulation. Henceforth, rutin is a better candidate to inhibit SARS-CoV-2 3CL^{pro} [31].

Inhibition of RNA-dependent RNA polymerase (RdRp)

To replicate its genome, SARS-CoV-2 does not rely on host polymerase, rather uses the RdRp. Hence-forth, it can be a potential for drug targeting. The RdRp structure of SARS-CoV-2 incorporates three subdomains and the functionally crucial catalytic sites of the RdRp, which include Asp760, Asp761, Cys622, Cys813, Ser759, and Trp617 [32]. Another in silico study consistently showed that quercetin-3-O-rutinoside (rutin), quercetin-3-O-glucuronide, quercetin-3'-O-sulfate along kaempferol were able to inhibit SARS-CoV-2 3CL^{pro} and RdRp that play a role in viral replication stages. Rutin formed hydrogen bonds with 3CL^{pro} through interaction with some amino residues His41 from the catalytic dyad of 3CL^{pro}, and other residues like Thr25, Cys44, Met165, Gln189, and Thr190. Likewise, the results highlighted key interactions between rutin and binding pockets of RdRp via the formation of hydrogen bonds with Asp623 and Arg624 from motif A, and with the catalytic residue Ser759 and Asp760 from motif C. Other glucuronidated and sulfated quercetin demonstrated hydrogen bonds and π-anion interaction with the catalytic residue from motif C. These findings suggested that glucuronidated and sulfated forms of quercetin and kaempferol are promising

candidates for 3CL^{pro} and RdRp inhibitors in SARS-CoV-2 replication [33].

The interaction of quercetin-3-O-sophoroside with SARS-CoV-2 main proteins was done by docking and molecular dynamic studies [32]. The targeted main proteins were E protein ion channel, helicase ADP site, helicase NCB site, N protein NCB site, 3CL^{pro}, Nsp14 ExoN, Nsp14 N7-MTase, Nsp15 endoribonuclease, Nsp 16 2'-O-MTase, PL^{pro} RdRp with or without RNA. The results demonstrated that quercetin-3-O-sophoroside potentially had the highest binding affinity to the RdRp with RNA, with a considerable value of -9.70 ± 1.58 kcal/mol. It has been shown that quercetin-3-O-sophoroside binds to RdRp with RNA, by forming electrostatic interactions and hydrogen bonding. Likewise, there were hydrophilic interactions between quercetin-3-O-sophoroside with the amino acid residues of Arg555, Asp452, Asp623, Cys622, Lys62, Ser682, Thr556, and RNA G-8 nucleotide (61). Additionally, quercetin-3-O-sophoroside was able to form π-π interactions in the case of RdRp without RNA, and relative to RdRp with RNA, the binding energy was decreased to -8.40 ± 1.12 kcal/mol. These findings suggested that the hydrophilic side chains of the proteins rendered the greatest tendency to interact with quercetin-3-O-sophoroside [32]. These inhibitory mechanisms are summarized in Figure 1.

Inhibition of respiratory infections and inflammations

Despite the aforementioned well-established in silico studies regarding the antiviral properties of quercetin, human studies are still lacking. Moreover, the currently available data assessing the effectiveness of quercetin in respiratory infections and inflammatory diseases are conflicting [8], and more randomized-controlled trials (RCTs) addressing this topic are essential. Heinz et al. conducted one of the randomized double-blinded controlled trials in 2010 to assess the influence of quercetin on the incidence of Upper Respiratory Tract Infection (URTI) in a large community group [9]. Around 1002 participants were enrolled and a standardized Wisconsin Upper Respiratory Symptom Survey (WURSS) recorded the upper respiratory tract outcomes daily for 12 weeks. After randomly distributed, the participants received either placebo (N = 335), 500 mg quercetin/day (Q-500, N=334), or 1000 mg/day of quercetin (Q-1000, N=333). Additionally, the intervention arms also received vitamin C (125 or 250 mg/day) and niacin (5-10 mg/day). After a 12-week study period, plasma quercetin was compared to the pretreatment level and demonstrated a significant increase in both Q-500 and Q-1000, compared to the placebo (P<0.001) with no significant adverse effects occurring in the intervention arm. Despite no significant difference in URTI symptoms, severity, and symptom scores between intervention and control groups, a separate analysis of subjects > 40 years of age showed significantly better fitness level (N = 325), lower URTI severity (36% reduction, P = 0.020), and URTI total sick days (31% reduction, P = 0.048) in the Q-1000 group, compared to the placebo. However, adjustment based on gender, age, and body mass index (BMI) demonstrated an insignificant quercetin-related effect on URTI.

There are some other studies evaluating the efficacy of quercetin in URTI [10] and other lung parenchymal inflammatory diseases, such as sarcoidosis [11]. Those studies have demonstrated some promising results, including a reduction in inflammatory markers, an increase in antioxidant levels, and the incidence of respiratory infections [9-11]. Some provide insight to more usefulness of quercetin in a specific population such as age more than 40-year-old in reducing the severity of the symptoms [9]. However, due to the lack of available human-interventional studies, more research on this topic is needed to further elucidate the role of quercetin in respiratory infection and inflammatory diseases.

Quercetin supplementation and its ongoing clinical trials

Several clinical trials are conducted to elucidate the efficacy of quercetin supplementation in different stages of SARS-CoV-2 infection either in a single or in combination with other interventions. However, among 12 clinical trials data that we retrieved from the clinicaltrials.gov registry presented in Table 1, 6 studies were completed according to the table, in which 3 papers were published interna-

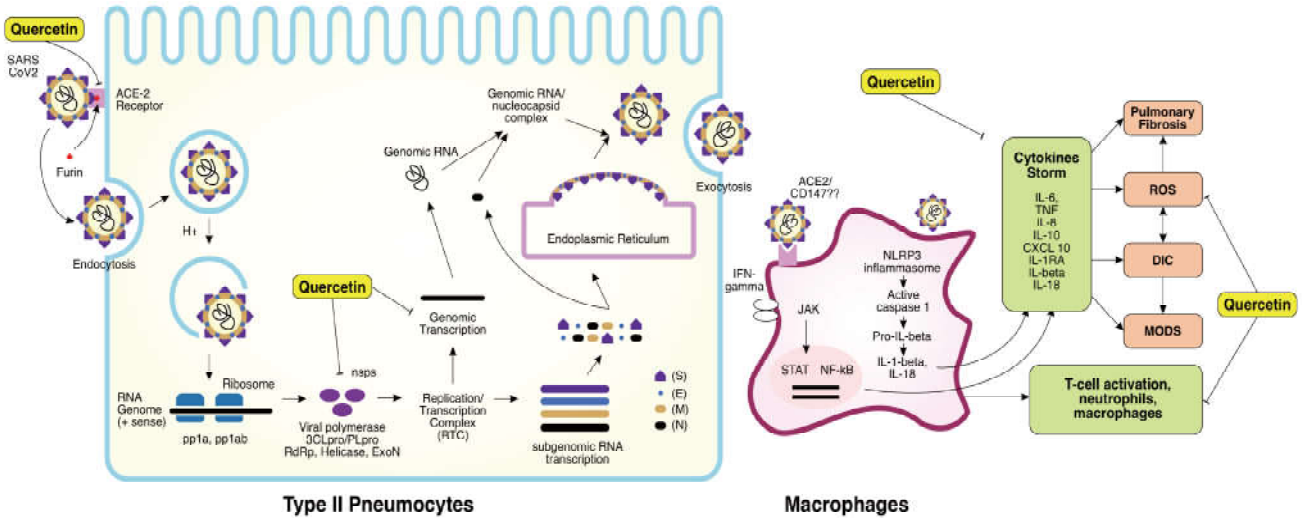

Figure 1.Key components of the pathogenesis of SARS-CoV-2 infection in pneumocytes, stimulating innate immune responses and its sequelae. The proposed mechanism, in which quercetin plays a role in the specific pathway, is presented here. ROS: Reactive Oxygen Species. DIC: Disseminated Intravascular Coagulation. MODS: Multiple Organ Dysfunction Syndrome.

tionally [6, 34, 35]. Table 1 details all the relevant study conducted from this perspective. These studies were in a different phase, as mentioned in the table. However, quercetin phytosome was effective in all these studies, ameliorating the symptoms of COVID-19.

Conclusion and future directions

Multiple in silico approaches have extensively been done to elucidate the ability of quercetin and its metabolites in halting SARS-CoV-2 entry and replication. Quercetin and its metabolites showed abilities to inter-fere with furin, an enzyme that is responsible for S-protein activation on the viral surface, thus inhibiting the interaction between SARS-CoV-2 and ACE2 receptors. Quercetin and its metabolites bind to catalytic sites of SARS-CoV-2 $3CL^{pro}$ and interfere with the $3CL^{pro}$ dimerization by altering the tertiary structure of the protein and/or the aromatic protein environment side chains. Multiple interactions also occur between quercetin and the RdRp structures of SARS-CoV-2, rendering its ability to halt viral replication. Recent clinical trial data support the use of quercetin in terms of prophylaxis and adjuvant therapy of COVID-19. The phytosome formulation is considered a promising ingredient. Hence, we consider quercetin as a good candidate for development and optimization for COVID-19 treatment to a greater extent. Further clinical investigations to assess the safety and efficacy of quercetin, and its interaction with other drugs in the management of COVID-19, are certainly warranted to provide high-quality clinical data and generalizability.

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Competing interests
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Abbreviations
TCMSP, traditional Chinese medicine systems pharmacology; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ACE2, angiotensin-converting enzyme 2; Mpro, main protease; 3CLpro, 3C-like protease; PLpro, Papain-like protease; RdRP, RNA-dependent RNA polymerase; COVID-19, Coronavirus Disease; NIH, national institute of health; CARDS, COVID-19-associated acute respiratory distress syndrome; SARS-CoV, SARS-Associated Coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; WHO, World Health Organization; FDA, food and drug administration; SPR, Surface Plasmon Resonance; GO, Gene Ontology; rhACE2, recombinant human ACE2; IC50, inhibitory concentration; GEO, gene expression omnibus; SPR/FRET, surface plasmon resonance/fluorescence resonance energy transfer; GSEA, Gene Set Enrichment Analyses; ITC, Isothermal titration calorimetry; WURSS, Wisconsin Upper Respiratory Symptom Survey; SFT-PC, surfactant protein-C; RDNI, Reduning Injection

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Table 1. Ongoing Clinical Trials Evaluating the Efficacy of Quercetin Supplement in Management of COVID-19

No	Registries	Phase of study	Aim of study	Design	Recruitment status	Location	Estimated samples (actual enrolment)	Primary outcomes & time frame	Interventions	Results
1	NCT 05037240 [35]	N/A	To evaluate the effectiveness of oral quercetin supplementation in the COVID-19 prevention	Prospective, randomized, dou-ble-blinded, controlled trial, parallel assignment	Completed	Italy	120	Absence of COVID-19 infection Time frame: 3 months	1. Placebo 500 mg, 2 times a day 2. Quercetin Phy-tosome (QP) 500 mg, 2 times a day per oral (PO)	1. Within 3 months of supple-mentation: ✓ One out of 60 subjects in the QP group contracted COVID-19 ✓ Four out of 60 subjects in the control group contracted COVID-19 ✓ The QP group showed faster clinical remission compared with the control group 2. At 5 months, the COVID-19 risk of infection was 99.8% in the QP group vs 96.5% in the control group 3. The QP group had a protection factor of 14% more to not contract the COVID-19
2	NCT04578158 [34]	PHASE 3	To investigate quercetin as an adjuvant in community based-subjects, confirmed with positive SARS-CoV-2 infection by RT-PCR	Prospective, randomized, open-la-beled, controlled trial, parallel assignment	Completed	Pakistan	200 (152 outpatients)	Percentage of subjects tested positive for COVID-19 who require hospitalization (from day 1 to day 30) Time frame: 30 days	1. Standard COVID-19 care based on local guidelines 2. Quercetin Phyto-some (QP) 1000 mg/ day PO	1. There was a reduction in: ✓ Length & frequency of hospitalization ✓ Oxygen therapy ✓ No progression to ICU ✓ Decrease in death 2. Quercetin administration with standard care in the early stage of viral infection was able to alleviate the early symptoms and prevent COVID-19 severity
3	NCT04861298 [6]	PHASE 3	To investigate quercetin and as an adjuvant in community based-subjects, confirmed with positive SARS-CoV-2 infection by RT-PCR	Prospective, randomized, open-la-beled, controlled trial, parallel assignment	Completed	Pakistan	200 (42outpatients)	1. Time needed to become negative at the RT-PCR test for SARS-CoV-2 2. Course of WBC, neutrophils, LDH, CRP, D-dimers, ferritin, hemoglo-bin, platelets, and lymphocytes 3. Course of COVID-19- related symptoms 4. Number requir-ing hospitalization Time frame: 2 weeks	1. Standard COVID-19 care based on local guidelines: acetaminophen 500-1000 mg/dose PRN with maximum dose 3000 mg/day and azithromycin 500 mg/day for 3 consec-utive days (n=21) 2. QP600 mg/day PO for the first 7 days, followed by 400 mg/day PO in the remaining 7 days (n=21)	1. Within 1 week of treatment: ✓ 16 patients of the quercetin group were confirmed negative for SARS-CoV-2 by RT-PCR ✓ Twelve patients experienced diminishing all their symptoms ✓ Two patients of standard care group were tested negative ✓ Four patients experienced partial symptoms resolution 2. By the end of the second week: ✓ 5 patients remaining from the quercetin group were tested negative ✓ Nineteen patients remained from the standard care group, 17 were tested negative by week 2, 1 tested negative by week 3, and 1 remained posi-tive by the 20th day 3. Adjuvant therapy with quercetin was able to reduce the level of LDH, ferritin, CRP, and D-dimer by 35.5%, 40%, 54.8%, and 11.9%, respectively

4	NCT04377789 [36,37]	N/A	To evaluate the possible role of quercetin in prophylaxis and treatment of COVID-19	Prospective, single-center, randomized, open-labeled, controlled trial, parallel assignment	Completed	Turkey	447 inpatients	1. Prevalence of COVID-19 in the quercetin and sham group calculated by questionnaire and medical records 2. Comparison of mortality rate between two groups Time frame: 3 months	1. (Group A): Standard care by local guidelines: Hydroxychloroquine 400 mg/day for another 5 days + Favipiravir 600 mg BID for 4 days, following loading dose on day one (1600 mg BID) 2. (Group B): Standard care + quercetin 1000 mg, bromelain 100 mg, vitamin C 1000 mg: daily in 2 divided doses to 52/447 patients with minimal one chronic disease and moderate to severe symptoms of respiratory infections 3. (Group C): Quercetin treatment group: tested positive for SARS-CoV-2 and treated with Quercetin 1000 mg/day PO	1. No adverse effects recorded related to quercetin, vitamin C, and QCB supplementation 2. Group B showed a significantly higher number of COPD and TB cases, more severe pulmonary findings, a significantly higher proportion of subjects with SpO_2 <93 mmHg at admission &/or follow-up, significantly decreased CRP, procalcitonin, and ferritin. However, there was also a significant increase in lymphocyte count and thrombocyte in this group 3. Group B did not reduce the risk of events during the follow-up period 4. Quercetin, vitamin C, and QCB were effective in the COVID-19 treatment
5	NCT04861298 [38]	N/A	To evaluate the benefit of quercetin for preventing the progression of the disease and improvement of the symptoms in the early stage of COVID-19 infection	Prospective, randomized, open-labeled, controlled trial, parallel assignment	Completed	Pakistan	142 Outpatients	1. Tested negative for SARS-CoV-2 by RT-PCR after a 2-week course of treatment 2. Symptoms improvement from day 1-14 Time frame: 2 weeks	1. Standard care by local guidelines 2. Standard care + quercetin for 2 weeks (QP600 mg/day PO in the first week, followed by 400 mg/day PO in the second week)	Not yet available
6	NCT04468139 [39]	PHASE 4	To evaluate zinc, quercetin, bromelain, and vitamin C on the clinical outcomes of patients infected with COVID-19	A prospective, randomized, open-labeled, controlled trial	Recruiting	Saudi Arabia	60 inpatients	1. Length of stay at the hospital after treatment and days to discharge (time frame: 28 days) 2. Measurement of serum zinc level before and after treatment (5-10 days) Time frame: 28 days	Quercetin 500 mg/day + bromelain 500 mg/day + zinc 50 mg/day + vitamin C 1000 mg/day PO	Not yet available
7	NCT04851821 [40]	PHASE 1	To evaluate the effectiveness of quercetin in the COVID-19 treatment	A prospective, randomized, double-blinded, controlled trial	Completed	Tunisia	80 outpatients	1. Number of patients who visit the emergency department (10 days after intervention) Time frame: 10 days	1. Quercetin group: Quercetin 1 tablet TID for 10 days 2. Placebo group: Placebo 1 tablet TID for 10 days	Not yet available
8	NCT04622865 [41]	PHASE 2	To evaluate the efficacy of masitinib and isoquercetin combination for moderate to severe COVID-19 patients	Prospective, randomized, triple-blinded, controlled trial, parallel assignment	Recruiting	France	200	1. Clinical status of the patient at day 15 based on a 7-point scale Time frame: 15 days	1. Experimental: Masitinib 3 mg/kg/day PO for 4 days then increased to 4.5 mg/kg/day + isoquercetin 1 g/day + best supportive care (Oxygenation, analgesic, anti-thrombotic, antiviral, or biologic agents) 2. Active comparator: Best supportive care (Oxygenation, analgesic, anti-thrombotic, antiviral, or biologic agents)	Not yet available
9	NCT04853199 [42]	PHASE 1	To evaluate the effectiveness of quercetin in the treatment of SARS-COV-2	Prospective, randomized, triple-blinded, controlled trial, parallel assignment	Recruiting	Tunisia	200	The efficacy measurement from day 10 to 30 Time frame: 10-30 days	1. Experimental: Quercetin group one tablet BID 30 minutes before a meal, for 10 days. 2. Placebo group: Placebo 1 tablet BID 30 minutes before a meal, for 10 days	Not yet available

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10	NCT04590274 [43]	PHASE 1	To evaluate the safety and efficacy of various drugs, antibiotics, and vitamins	Prospective, single-group assignment, open-label, clinical trial	Withdrawn	United States	5000	Percentage of subjects who develop COVID-19 symptoms within 6 months from starting of the study Time frame: 6 months	Experimental Drugs: Hydroxychloroquine 400 mg; azithromycin 500 mg; elemental zinc 50 mg; vitamin C 3000 mg; vitamin D3 5000 IU; N-acetylcysteine 1200 mg; elderberry 600 mg; quercetin 0-600 mg	Not yet available
11	NCT04536090 [44]	PHASE 2	To evaluate the efficacy and safety of isoquercetin (IQC-950AN) in all or a subset of subjects with confirmed COVID-19	A prospective, randomized, open-label, controlled trial	Not yet recruiting	Canada	150	Disease progression as explained by WHO clinical progression scale ≥6 at any time from day 1-28 Time frame: 28 days	1. Experimental: Isoquercetin (IQC-950AN) 1000 mg orally twice a day on day one, followed by 500 mg twice a day for the remaining 27 days 2. No intervention: Standard of care based on national guidelines.	Not yet available
12	NCT04844658 [45]	Not Applicable	To evaluate the efficacy and safety of NASAFYTOL® on COVID-19 positive hospitalized patients as a supportive treatment	Prospective, randomized, open-label, controlled trial, parallel assignment	Completed	elgium	50	1) Clinical improvement based on WHO clinical score within 14 days 2) Length of hospitalization 3) In-hospital mortality 4) Time resolution of fever at least 48 hours without antipyretic for 48 hours; ≤36.6°C: axilla or, ≤37.2°C: oral or ≤37.8°C: rectal 5) Proportion of subjects with normalization of temperature or hospital discharge at day 14 6) Proportion of subjects requiring oxygen therapy 7) Number of incidence of adverse events 8) Number of serious adverse events 9) Number of pill count taken by the patient 10) Timing of decreasing half or reaching normal CRP level as compared to the peak level during the trial 11) Timing of normalization of lymphocyte count albumin 12) Serum vitamin D concentration Time frame: 14 days	1. Experimental: NASAFYTOL® 4 capsules BID PO for up to 14 days in support of the standard care of COVID-19 based on local guidelines NASAFYTOL® contains: 1008 mg mixture of turmeric extract and natural quercetin from Sophora japonica L. (Chinese scholar tree) 2. Active comparator: FULTIUM® -D3 800, 1 capsule/day in the morning for up to 14 days in support of the standard care of COVID-19 based on local guidelines Vitamin D, FULTIUM® - D3 800 is a blue soft capsule that contains 800 UI (20 µg) of D3 vitamin (cholecalciferol)	Not yet available