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Quercetin in the treatment and prevention of COVID-19

COVID-19 tedavi ve profilaksisinde Quercetin

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SUMMARY

Coronavirus Disease-19 (COVID-19) is a disease that started at the end of 2019 and continues to affect all the world as a pandemic. There is no definitive cure for COVID-19 yet. The disease is characterized by excessive immune activity, inflammation and coagulopathy. Many agents have been tried for treatment and prevention. Flavonoids are valuable natural food components with antioxidant, anti-inflammatory and anticoagulant properties. Quercetin, the best known flavonoid, is one of the most studied and beneficial one. Quercetin, which has been shown to be effective in many viral diseases, is mainly used in diseases such as cardiovascular disease and diabetes, which are associated with chronic inflammation. it is an important candidate for the treatment and prophylaxis of COVID-19, thanks to its powerful anti-inflammatory, antioxidant and immune-modulating effects.
Keywords: Quercetin, COVID-19, Treatment

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ÖZET

Coronavirüs Hastalığı-19 (COVID-19), 2019 yılının sonlarında başlayan ve pandemi olarak tüm dünyayı etkisi altına almaya devam eden bir hastalıktır. Henüz COVID-19 için kesin bir tedavi yoktur. Hastalık aşırı immünite aktivitesi, inflamasyon ve koagülopati ile karakterizedir. Tedavi ve profilaksi için birçok ajan denenmiştir. Flavonoidler, antioksidan, antienflamatuar ve antikoagülan özelliklere sahip değerli doğal gıda bileşenleridir. En iyi bilinen flavonoid olan Quercetin, en çok çalışılan ve faydası görülenlerden biridir. Birçok viral hastalıkta etkili olduğu gösterilen Quersetin, ağırlıklı olarak kardiyovasküler hastalık ve diyabet gibi kronik inflamasyonla ilişkili hastalıklarda kullanılmaktadır. Güçlü antienflamatuar, antioksidan ve immünmodülatör etkileri sayesinde COVID-19 tedavisi ve profilaksisi için önemli bir adaydır.
Anahtar sözcükler: Quercetin, COVID-19, tedavi

INTRODUCTION

After their discovery in the 1960s, Coronaviruses were associated with the outbreaks; Severe Acute Respiratory Syndrome (SARS) in 2003 and Middle East Respiratory Syndrome (MERS) in 2012 (1, 2). They came to the fore again with the cases of viral pneumonia with unexplained and severe illness in December 2019, in Wuhan, China. This new type of coronavirus was named as novel coronavirus-19 (nCoV19) by the World Health Organization (WHO) on January 12, 2020. On February 11, 2020, the disease was named as COVID-19 (3). WHO declared a pandemic on March 11, 2020, as a result of the disease that spread in China and then all over the world within a month (4). This date is also the date when the first case was seen in Turkey.

Currently, there is no definitive treatment for this disease, whose vaccination applications continue. However, many agents are being tested and evaluated in the treatment and prophylaxis of COVID-19. Quercetin, a well known flavonoid, which has been proven in powerful anti-inflammatory, antioxidant and antiviral activities, seems promising as an anti-COVID-19 treatment option in the light of the data obtained.

SARS-CoV2

Coronaviruses are enveloped, positively polarized, single-stranded RNA viruses (5). When the virus enters the host cell, viral RNA reaches the nucleus for replication. Viral mRNA is used for the biosynthesis of viral proteins. Later, new viral structures are created. Coronaviruses consist of spike protein, membrane, envelope and nucleocapsid (6). Spike protein is responsible for binding to host cell receptors and the cell membrane. SARS-CoV2 is structurally very similar to SARS-CoV. Angiotensin converting enzyme 2 (ACE2) has been defined as the receptor for SARS-CoV2 (7). Tissues with ACE2 expression are at high risk for COVID-19 (8). This diversity of distribution also explains the multiple organ failure that may develop during the course of the disease (9). Since ACE2 expression is higher in the lung epithelial cells in the alveolar space, the entry and damage of the virus is significant in lungs (10,11).

Flavonoids

Flavonoids are natural herbal metabolites containing benzopyrone ring in polyphenolic structure, which are generally found in fruits, vegetables and various beverages (12,13). In nature flavonoids function as UV filters, signal molecules, phytoalexins, and detoxifying/antimicrobial agents for the plants and protect them from all biotic/abiotic stresses (14).

Most flavonoids are known as flower pigments. However, their presence in nature is not limited to flowers, they are obtained from many parts of plants (15). Basically, fruits, leaf stems, roots, grains, nuts, vegetables, flowers and seeds are rich sources of flavonoids. More than 10,000 flavonoid compounds have been isolated and identified (16,17).

Flavonoids are associated with positive health effects and are essential ingredients in a variety of dietary, pharmaceutical, medical, and cosmetic applications (18). These flavonoids, which are very valuable dietary components known to have many beneficial biochemical and antioxidant effects, are used in the treatment of many diseases such as cancer, Alzheimer's disease, and atherosclerosis (19,20). They are therapeutic agents with anticancer, antioxidant, antibacterial, antiviral, antiangogenic, antimalarial, neuroprotective and antiproliferative activities. (21-25). They have become particularly popular by preventing cardiometabolic diseases and slowing down the decline in cognitive performance due to aging process (26,27).

Quercetin

Flavonoids are subdivided into flavones, flavonols, isoflavones, and anthocyanidins. These subgroups are quite common in nature (28). For example, narigenin and hesperetin are found in citrus fruits and grapes, while anthocyanidins and quercetin are found in mulberry (29,30).

The most studied flavonols are kaempferol, quercetin, myricetin and fisetin. Onions, cabbage, lettuce, tomatoes, apples, grapes, and some other fruits are rich sources of flavonols. Besides fruits and vegetables, tea and red wine are also sources of flavonols. Flavonols are the most common dietary group of flavonoids, and quercetin can be shown as the best example of this group (31). Quercetin is most commonly found in berry fruits, but also in buckwheat, onion, kale, broccoli, apple, orange, black tea, and green tea (32).

Flavonoids are mostly obtained from the consumption of fruits, vegetables and tea. Daily intake is known to range from 5 to 100 mg / day. Quercetin and glycosides are about 75% of dietary flavonoids (33).

In nature, quercetin is found predominantly in O-glycosidic form. Apart from this form, a monosaccharide such as glucose / galactose / rhamnose or a disaccharide, which is usually rutinose, can also be found attached to the 3,7 and 4 'positions. Although the sugar part is usually O-glycosidically bound, it can sometimes be found as C-glycosidic. Quercetin glycosides are most frequently seen as 4'-O-glycosides in onions (34).

Epidemiological studies show that a diet rich in flavonoids is closely related to a reduction in the incidence of various diseases associated with aging (35). As a dietary ingredient, quercetin has unique biological properties that improve mental and physical performance and reduce the risk of infection (36).

Quercetin, like other flavonoids, is known to inhibit lipid peroxidation, platelet aggregation, capillary permeability and stimulate mitochondrial biogenesis in addition to showing anticancer, anti-inflammatory, antiallergic, antioxidant,

antidiabetic, vasoprotective, antihypertensive, hypolipidemic, antithrombotic activities (37-42).

Effects of Quercetin on SARS-CoV2

1. Viral Features

There is a large literature supporting the antiviral properties of quercetin, both *in-vitro* and *in-vivo*. Initial *in-vivo* studies, a positive effect was observed with treatment with quercetin in immunocompetent mice infected with Mengo virus (43).

In-silico and *in-vitro* studies have shown that quercetin can interfere with various stages of coronavirus entry and replication cycle, such as papain-like protease (PLpro), 3C-like protease (3CLpro) and nucleoside-triphosphatase (NTPase) / helicase. Combination of quercetin with vitamin D and vitamin C is known to exert synergistic antiviral and immunomodulatory effects (44).

Effects on many respiratory system viruses were observed in other cell culture studies. It suppresses cytopathic effects caused by rhinovirus, ecovirus (types 7, 11, 12 and 19), coxacivirus (A21 and B1), and polioviruses (type 1 Sabin) (45,46).

In rhinovirus infected mice, quercetin treatment reduces viral replication and alleviates virus-induced airway cholinergic hypersensitivity (47).

In a randomized, double-blind, placebo-controlled study evaluating individuals over the age of 40 who received 1000 mg of quercetin, it was found that the quercetin group had a 36% lower severity of upper respiratory tract infection (URTI) compared to the control group, and the duration of URTI was 31% shorter. (48).

Quercetin stops viral binding and penetration into the host cell and prevents infection with herpes simplex virus 1,2 (HSV-1, HSV-2) and acyclovir-resistant HSV-1 by suppressing NF-jB activation required for HSV gene expression (49,50).

It has been shown that athletes taking quercetin supplements are protected against stress-induced URTI (51).

In-vitro data revealed that quercetin halts endocytosis by inhibiting phosphatidyl inositol 3-kinase (PI3K), suppresses transcription and translation, and enhances viral clearance by stimulating the mitochondrial antiviral response. Thus, it has been shown that quercetin can inhibit viral replication of influenza virus by interfering with the 3 stages of viral replication (52).

Quercetin; Since it inhibits polymerase, protease, reverse transcriptase, DNA gyrase and binds viral capsid proteins, it has been tested on various types and models in many studies (53,54).

The use of vitamin C and quercetin has been found effective in COVID-19 for both prophylaxis and treatment in high risk individuals. (55).

One of the first studies investigating the effect of quercetin on coronaviruses was conducted in 1990, and it was shown that the infectivity of human and bovine coronaviruses decreased by 50% with a dose of 60 μg / mL quercetin (56).

Luteolin and quercetin have been shown to prevent the entry of SARS-CoV into host Vero cells (57).

SARS-CoV, defined in 2003, is a single-stranded RNA virus that uses ribosome regions to encode 2 replicase glycoproteins, polyprotein 1a (PP1a) and polyprotein 1b (PP1b), which mediate viral replication (58). Once these precursor glycoproteins are produced, the process of protease-mediated lysis begins (59).

The inhibitory effects of quercetin isolated from a yeast species named Pichia pastoris on 3CLpro have been demonstrated. Quercetin-3-O-β-galactoside binds to 3CLpro of SARS-CoV and inhibits its proteolytic activity (60). The binding sites of SARS-CoV2 and SARS-CoV 3CL proteases with quercetin are the same (61). In addition, it has been shown that quercetin binds more strongly to spike protein, ACE2, RNA-dependent RNA polimerase (RdRp) and PLpro than 3CLpro (62). In these contexts, it is predicted that quercetin has a protective and therapeutic role against COVID-19 as well as its known antioxidant and anti-inflammatory properties.

Quercetin also modulates the cellular unfolded protein response (UPR). Since coronaviruses can use UPR to complete all replication cycles, Quercetin can exhibit antiviral activity by modulating this pathway (63).

Coronaviruses are sensitive to the inhibitory effects of zinc, which can prevent viral entry into cells and reduce coronavirus virulence. Quercetin also functions as a zinc ionophore and has been shown to facilitate transport of zinc across lipid membranes. This could theoretically increase the antiviral effects of zinc (64-67).

3CLpro is also essential for MERS-CoV replication and as in SARS-CoV and SARS-CoV2 Quercetin inhibits MERS-CoV's 3CLpro (68).

In a study in which *in-silico* modelling of the interaction between SARS-CoV2 spike protein and ACE2 protein was performed, quercetin was identified as one of the 5 most effective compounds

among drugs, metabolites and natural products that suppress the initial stage of infection (69). In a study conducted in the light of this hypothesis, quercetin demonstrated an anti-infection effect in a cell-virus model. Besides, it inhibited 3CLpro of SARS-CoV *in-vitro* (70).

As a genomic structure, it can be said that SARS-CoV2 is 79% identical to SARS-CoV (71). Therefore, it is not surprising that quercetin shows similar activity in SARS-CoV2.

In evaluations using gene set enrichment assays (GSEA), vitamin D and quercetin have been identified as mitigating agents for COVID-19. Quercetin affects the functions of 85% of the target proteins by making 30% change in the human protein gene coding targeted by SARS-CoV2. Similarly, vitamin D provides a 70% modification in these proteins with the 25% change made in the genes of the SARS-CoV2 target proteins. The target protein change in vitamin D use with quercetin was observed at a rate of 93% (72).

In a clinical study conducted with COVID-19 patients, in combined use of quercetin, zinc, bromelain and vitamin C, positive effects were observed (73).

Quercetin has low bioavailability and therefore requires special formulations to achieve effective blood levels. A clinical trial is being conducted using the phytosomal form of quercetin (74).

Considering the bioavailability problem, it is thought that the use of diluted quercetin in low doses as nasal spray in its early stages may prevent viral entry into the cell and provide less disease progression and hence hospitalization rate (75).

Quercetin, with its well-known pharmacokinetics, absorption, distribution and metabolism properties, is a potential agent for antiviral therapies based on viral protease inhibition, as it effectively suppresses enzymes essential for replication in coronaviruses.

2. Immunity and Inflammation

The main elements of innate immunity in the respiratory tract are epithelial cells, alveolar macrophages and dendritic cells. (76). T cell mediated immune response occurs as a result of antigen presentation of dendritic cells and macrophages. The cells involved in the response are CD8 + and CD4 + T cells. CD4 + T lymphocytes activate B lymphocytes and provide virus-specific antibody production, while CD8 + T lymphocytes kill virus-infected cells (77). Cytokine release from these cells also has an important role in the immune response and thus the severity of the disease. Studies Studies have revealed an increase in plasma levels of interleukin-1β (IL-1β), interleukin-1 receptor antagonist (IL-1RA), interleukin-2 (IL-2), interleukin-7 (IL-7), interleukin-8 (IL-8), interleukin-10 (IL-10), interferon-ɣ (IFN-ɣ), monocyte chemoattractant peptide-1 (MCP-1), macrophage inflammatory protein-1A (MIP-1A), macrophage inflammatory protein-1B (MIP-1B), granulocyte colony stimulating factor (G-CSF) and tumor necrosis factor-α (TNF-α) in COVID-19 patients. These levels were found to be significantly higher in patients followed up in the intensive care unit compared to other inpatients. (78). In particular, interleukin-6 (IL-6) has been shown to be the dominant cytokine in macrophage activation syndrome (MAS) and cytokine storm (79). Again, involvement of more than 50% of the lung parenchyma in patients with acute respiratory distress syndrome (ARDS), was found to be associated with high IL-6 (80).

Quercetin has been reported as a substance known to have potent and long-lasting anti-inflammatory capacity (81). Quercetin has anti-inflammatory potential that can be observed in different cell types in both animal and human models (82-89).

In-vitro studies using various cell lines have show that quercetin suppresses lipopolysaccharide (LPS) -induced TNF-α production in macrophages and LPS-induced IL-8 production in lung A549 cells (83). Moreover, it has been shown that quercetin may decrease the mRNA levels of LPS-induced TNF-α and interleukin-1α (IL-1α) in glial cells (84).

Quercetin suppresses the production of inflammation-producing enzymes cyclooxygenase (COX) and lipoxygenase (LOX) (85,86). Proinflammatory cytonkines have also been shown to reduce the release of tryptase and histamine (87). In a study, anti-inflammatory activity was demonstrated through a decrease in the expression of vascular cell adhesion molecule-1 (VCAM-1) and CD80 (88). The immunomodulatory and immunosuppressive effects of quercetin, on dendritic cell functions have been shown (89).

Quercetin dose-dependently decreases messenger RNA, intracellular adhesion molecule-1 (ICAM-1), IL-6, IL-8 and MCP-1 levels (90).

While increasing the production of IFN-γ, it decreases the production of interleukin-4 (IL-4). With these properties, it can be said that quercetin is a valuable flavonid with beneficial immunomodulatory effects (91).

Quercetin prevents TNF-α from activating signal transmission pathways such as nuclear factor-κB (NF-κB), which are powerful triggers of inflammation and cytokine storm observed in COVID-19. Quercetin also increases the peroxisome proliferator-activated receptor γ (PPARγ) activity, which is antagonist with NF-κB. This is one of its indirect anti-inflammatory effects. Thanks to these two mechanisms, TNF-α-mediated activation of inflammation cascades is prevented (92,93).

It is known that SARS-CoV2 activates NOD-, LRR- and protein containing pyrin domain 3 (NLRP3) inflammasome (94,95). Among many flavonoids, quercetin differs *in-vitro* by reducing the NLRP3 inflammatory signaling pathway and gene expression of NF-kB, TNF-α, IL-6, IL- 1β and interleukin-18 (IL-18) (96).

It has been shown in obese individuals, that genes related to interferon-mediated antiviral activity are expressed more with the use of an herbal supplement containing 1000 mg of quercetin (97). In another study conducted with obese patients with iron deficiency anemia, quercetin; It has been shown to reduce the level of IL-6, which is an inflammatory marker (98).

25 μM quercetin suppressed the release of IL-1β, IL-6, IFN-γ and TNF-α in human whole blood treated with LPS. Its demonstration of inhibiting proinflammatory cytokines is important for the treatment of many viral diseases. TNF-α serum levels significantly decreased in individuals who received a treatment / support regimen of 150 mg quercetin daily for 6 weeks (37).

Animal coronavirus models have shown that mast cells located in the respiratory submucosa may play a mixed role, including the generation of T helper 2 (Th2) proinflammatory cytokines under the influence of viral stimulation and the release of immunoglobulin E, a type of antibody associated with a Th2-type immune reaction (99).

It has been clinically demonstrated that quercetin regulates human mast cell degranulation and restricts the release of cytokines from these cells, which may be beneficial in cytokine storm (100,101).

Quercetin has antioxidant and anti-inflammatory roles, modulating signal pathways associated with post-transcriptional modulators affecting postviral recovery (102).

3. Oxidative Stress and Mitochondrial Damage

Helicases of SARS-CoV2 contribute to replication with ATP hydrolysis that can occur in the presence of iron. Sufficient amount of iron must be present in host cells for viral replication. The immune system creates a response by reducing the bioavailability of this iron to restrict viral replication. Therefore, reducing the iron of the cell will create an antiviral effect. Hyperferritinemia seen in COVID-19 is a biomarker for cytokine storm. The main role of ferritin during infections is to reduce its cellular level by storing iron. In addition, the increase in ferritin results in macrophage activation and secretion of various inflammatory cytokines. The process of ferroptosis, a kind of programmed non-apoptotic cell death that develops due to this iron accumulation, has been recently described (103).

Ferroptosis causes an irreversible change in mitochondrial morphology. Mitochondria are the basis of cellular oxidative homeostasis. Irregularity in iron metabolism triggers the formation of reactive oxygen radicals and increases oxidative stress. Increased inflammatory / oxidative stress can lead to mitochondrial dysfunction, leading to ferroptosis, platelet damage and eventually multi-organ failure (104).

Extracellular mitochondria, especially platelet mitochondria, are mediators associated with thrombosis formation. Moreover, a mitochondria that has lost its functionality will increase the production of free oxygen radicals by causing iron accumulation. Increased oxygen radicals will cause mitochondrial damage, microbiota dysbiosis and platelet dysfunction (105). Since mitochondria can regulate the immune system in stressful conditions such as viral infections, they can increase inflammation. This imbalanced immune response causes microbiota dysbiosis. Mitochondria are also known to alter the microbiota by modifying intestinal immune cells, epithelial cells and enterochromaffin cells (104). Both thrombosis and dysbiosis are important issues in the pathogenesis of COVID-19 and since these issues need to be addressed in more detail, they will be discussed in separate sections.

SARS-CoV2, like other RNA viruses, can trigger oxidative stress (106). This can be controlled by detecting oxidative stress markers from the blood of patients diagnosed with COVID-19, as was previously seen in HIV samples (107).

It is possible to talk about an oxidative storm in addition to the cytokine storm seen in patients with

COVID-19. The destructive effects of large amounts of free oxygen radicals contribute to lipid peroxidation and protein oxidation, damage to pulmonary alveolar membranes and hyalinization (108).

The elderly, diabetic, or those with cardiovascular disease are already under a certain oxidative stress. Viral infections increase this stress even more. This gives us an idea of why the risk of disease severity increases in elderly and / or those ith comorbidities in COVID-19 (109).

In a study in which the level of free oxygen radicals in sputum samples was determined with a real-time electrochemical diagnosis system with biochemical sensitivity, it was found that this level increased in patients with COVID-19 with extensive lung involvement (110).

In addition to supplements such as N-acetyl cysteine, vitamin C, vitamin E, zinc and selenium; polyphenols are also recommended to reduce oxidative stress caused by COVID-19 and to minimize damage (111).

IL-6 and TNF-α increase superoxide production in neutrophils, and hydrogen peroxide stimulates the release of IL-6 (112-114).

Free oxygen radicals, which are the products of cytokine storm elements, are among the important responsible for tissue and organ damage (115).

Although the most commonly used antioxidant supplements today are vitamin C and vitamin E, the antioxidant activity of flavonoids is more pronounced than those of these two vitamins (116).

When quercetin is present in the blood, it contributes to vascular health and its conjugated form reduces the risk of cardiovascular diseases. Quercetin and its derivatives provide protection against stroke by preventing thrombosis (117).

Dihydro-quercetin, a dihydroxyflavone, has been observed to reduce free oxygen radical production and lipid peroxidation, and increase the biological functions of antioxidant enzymes in animal models (118).

Quercetin is a potent antioxidant that works as a free radical scavenger by donating 2 electrons through o-quinone / quinone methide in both*in-vitro* and *in-vivo* (119, 120) studies.

In an animal experiment on influenza (H3N2), onset of infection; catalase has been associated with decreased concentrations of glutathione and superoxide dismutase (antioxidants) in the lung. Quercetin supplementation given concurrently with virus inoculation provided significant increases in pulmonary levels of these antioxidants (121).

The onion species named Allium cepa has a rich content of quercetin derivatives and has both antioxidant and antidiabetic effects due to its inhibitory effect on protein tyrosine phosphatase 1B (PTP1B) and its effects that increase glucose uptake (122-124).

4. Thrombosis

COVID-19 is a disease in which procoagulant factors and thus coagulability increase and thromboembolism can be seen. In a study that revealed the relationship of coagulation with ARDS pathogenesis, tissue factor and plasminogen activator inhibitor-1 levels were found to be significantly higher in patients with ARDS than those without ARDS (125).

The significant increase in D-dimers is thought to be due to intense inflammation inducing intrinsic fibrinolysis in the lung. This bi-directional immuno-thrombosis model reveals that heparin shows both anticoagulant and anti-inflammatory activity by inhibiting thrombin (126).

Many cytokines secreted in COVID-19 are prothrombotic. In particular, interleukin-6 (IL-6) has been found to be associated with increased fibrinogen levels (127, 128).

In *in-vitro* human models of SARS-CoV, infected mononuclear cells expressed high levels of procoagulant genes, including fibrinogen, serine protease inhibitors, tissue factor, and factor II and factor X (129, 130). The cells also promote effects such as platelet activation and aggregation, endothelial dysfunction and vasoconstriction by increasing gene expression for Toll-like receptor 9 and thromboxane synthase. Other platelet activation mechanisms such as decreased serum platelet factor 4 and increased beta thromboglobulin have been found to be associated with poor prognosis (131).

Viral infections and sepsis generally trigger innate mechanisms such as activation of tissue factor, complement system C3a and C5a, and von Willebrand factor (132-134).

Activation in the complement cascade activates leukocytes and the increased regional release of proinflammatory cytokines IL-1, IL-6, IL-8, and IFN-ɣ leads to microvascular damage. In animal models of sepsis, inhibition of the complement system has been shown to improve coagulopathy and endothelial dysfunction (135).

The strong antiplatelet and antithrombotic properties of quercetin known since the 1980s are mainly due to its inhibitory effects on cyclooxygenase and lipoxygenase activity in platelets. Lipid peroxides and superoxide anions inhibit prostacyclin and endothelium-derived relaxing factor (EDRF), which have antithrombotic effects. Quercetin shows antithrombotic and vasoprtective effects by increasing the local prostacyclin level and extending the half-life of EDRF (136).

In-vitro studies have shown that quercetin glycosides support thrombin inhibition by activating heparin cofactor II. A quercetin glycoside, quercetin 3,7,3′,4′-tetrasulfate (QTS) has been shown to interact with thromboxane A2 to inhibit platelet aggregation, *in-vivo*. In addition, QTS has been observed to act as a fibrinolytic agent by inhibiting tissue factor expression in human monocyte cell culture. It was observed that QTS at 25 mg/ kg/i.p had the same efficacy as acetyl salisilic asid used at 50 mg/kg/i.p. (137,138).

A study done with biochemical and cytometric processes; demonstrated that quercetin and its metabolites suppressed platelet activation, dense granule secretion, fibrinogen binding to platelets via integrin αIIbβ3, and suppressed all thrombotic effects of platelets and thrombus formation by changing the intracellular ratio of calcium (139).

In another study in which the antiplatelet activity of quercetin was evaluated, it was demonstrated that platelet aggregation, granule secretion, ATP release and P-selectin expression were suppressed, platelet cAMP level and vasodilator-stimulated-phosphoprotein phosphorylation were increased. It has been observed to inhibit collagen, ADP and thrombin-induced platelet aggregation. It significantly attenuate thrombin evoked [Ca2+] mobilization (140).

In a study with mice given 200 mg / kg isoquercetin, antithrombotic effects were demonstrated *in-vivo* over a period of 48 hours (141).

It was considered as a potential thrombin inhibitor in an *in-vitro* study in which 30 flavonoids, including quercetin, were evaluated for their antithrombin effects (142).

It is shown that quercetin reduces fibrinogen binding to activated integrin αIIbβ3. Integrin αIIbβ3 is directly related with adhesion and platelet activation. Quercetin is also known as an inhibitor of PI3K. PI3K plays a crucial role in platelet function such as activation, adhesion and aggregation, with Akt, the main target of PI3K signaling (143).

5. Gut Microbiome and Dysbiosis

High levels of proinflammatory cytokines secondary to viral infections can alter the intestinal microbiota and disrupt intestinal integrity. A small dysfunction in the small intestine activates a multifaceted mechanism, including the immune system, which results in microbiota changes and inflammation. Inflammation in the intestines causes an intestinal permeability that allows bacterial antigens and other toxins to pass into the systemic circulation, which may worsen the condition of patients diagnosed with COVID-19 in the septic picture.

Immune responses that develop in response to viral infections such as influenza can lead to consequences such as dysbiosis and increased intestinal permeability (144).

Secondary infections follow the microbial passage that develops due to permeability. Bacterial translocation from the intestine to the lungs has been reported in cases of sepsis and ARDS (145).

It is known that the intestines and lungs are interrelated to regulate the immune response and dysbiosis in the intestinal microbiota contributes to the pathogenesis of lung infections (146). Detection of SARS-CoV2 RNA in fecal sampes may support this transition (147).

In a study in which autopsy series of individuals infected with SARS-CoV were examined, pathological modifications were also observed in the digestive tract, indicating that virus-infected immune cells entered the circulation and damaged enteric cells (148).

These data suggest that coronaviruses can migrate from the lung tissue into the systemic circulation and migrate into intestinal cells through the circulation and lymphatic system.

Flavonoids have regulating and healing effects on microbiota. They suppress inflammation in the intestine. Flavonoids are metabolized by bacteria in the intestinal flora. Its regulatory effects on the intestinal immune system are also known (149).

It has been shown that quercetin supplementation has positive effects on microbiota biodiversity in mice whose microbiota has been modified by antbiotics. Their contributions to intestinal barrier property, villi length and mucosal thickness were also found to be statistically significant. This study demonstrated the healing power and prebiotic effect of quercetin on microbiota (150).

The effect of trans-resveratrol and quercetin on intestinal microbiota was investigated in a study conducted on mice on a high fat / sucrose diet. With the addition of quercetin to the diet, positive changes were observed in the microbiota in addition to changes in the intestinal epithelial level. Quercetin produced an increase in the Firmicutes / Bacteroidetes ratio and some other positive changes in the gut microbiota in mice fed this high fat / sucrose diet. One of these changes is the significant reduction of Erysipelotrichaceae and Bacillus species, which are associated with western-type diets and obesity (151).

CONCLUSION

Quercetin may have beneficial effects by acting directly or indirectly on many parts of COVID-19 pathogenesis. It has been observed in many studies that it has anti-inflammatory, antioxidant, antithrombotic and immunoregulatory and microbiota-regulatory effects in COVID-19 as in some other viral diseases previously reviewed. Quercetin appears to be an important potentially powerful agent for both the treatment and prevention of COVID-19. Its properties to improve the immune system and mitochondrial functions make this valuable flavonoid an important alternative treatment option for COVID-19 alongside all the other candidate drugs. Further studies are needed not only on its efficacy but also on some properties such as dosage, duration of use, and which form to use.

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Conflicts of interest

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Author Contributions

ŞT and HA carried out the literature survey together. ŞT wrote the manuscript. All authors read and approved the final manuscript.

Ethical Statement

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