Investigation of potential effects of quercetin on COVID-19 treatment: a systematic review of randomized controlled trials

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ABSTRACT

Objectives: The COVID-19 pandemic has rapidly become a global health crisis. Currently, there are no proven, reliable, specific treatments for COVID-19. Alongside drug interventions, supportive treatments are implemented during the disease. Quercetin, recognized for its antiviral, anti-inflammatory, anti-aging, and antioxidant properties, is under evaluation in this study for its potential impact on preventing, influencing the course, and mitigating the severity of COVID-19.

Methods: A thorough search was conducted across scientific databases, including PubMed, Embase, Web of Science, SAGEpub, Copernicus, Cochrane Library, ScienceDirect, Elsevier, Scopus, Google Scholar, EBSCOhost, Crossref, Ovid-LWW, and DergiPark databases, between 1 November 2021 and 1 April 2022 to ensure a comprehensive inclusion of relevant studies.

Results: Thirteen randomized controlled clinical trials (five published, eight unpublished) were identified. Existing literature supports quercetin's role as a potent free radical scavenger with robust antioxidant properties. It exhibits anti-inflammatory characteristics by inhibiting lipid peroxidation and restraining pro-inflammatory enzymes such as lipoxygenase and phospholipase A2. Scholarly discourse suggests that quercetin supplementation within the 500-1500 mg range leads to favorable outcomes, including quicker patient discharge, reduced inflammation, increased respiratory rate, accelerated viral clearance, and an improved disease prognosis. However, it is noted that intervention durations vary across studies.

Conclusions: The analysis of the studies suggested that quercetin is a promising therapeutic agent that can cause a decrease in disease symptoms, frequency of hospitalization, hospital stay, need for non-invasive oxygen treatment, need for intensive care, and mortality. Nonetheless, more clinical studies are needed to better understand quercetin's curative effects on COVID-19 infection.

Keywords: Quercetin, COVID-19, randomized controlled trials

INTRODUCTION

Coronaviruses, which are a large family of viruses, involve many subspecies, ranging from those that cause mild infection, such as a common cold, to those that cause severe respiratory syndrome and severe infections. The outbreak of COVID-19 (SARS-CoV-2), a novel type of coronavirus that emerged in Wuhan, China in December 2019, has spread rapidly around the world and has become a pandemic.[1] According to the data from the World Health Organization, 774,954,393 cases have been detected worldwide since the first reported case, and as of 17 March 2024 and 7,040,264 of these cases have resulted in death.[2] COVID-19 can be asymptomatic and have a wide clinical spectrum, ranging from mild symptoms similar to upper respiratory tract infection to life-threatening signs of sepsis in a person.[3]

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Currently, there are no specific treatments for COVID-19 that have been proven to be reliable and effective. However, since the data obtained from SARS and influenza suggest that it is more useful to start antiviral treatment early, it is recommended that antiviral drugs should be started as early as possible.[4] In addition to drug treatment during the course of the disease, some supportive treatment practices may also be included. As part of the studies evaluating the use of vitamins and minerals in the COVID-19 process, it has been suggested that the use of vitamin C and zinc in pharmacological doses may also benefit. In addition, it is thought that some bioactive compounds such as phytochemicals with antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties may have a positive effect on the disease.[5,6]

When studies related to phytochemicals are considered as subheadings, the existence of studies conducted with quercetin was found to be attractive.[7-9] Quercetin is a flavonoid found in various foods such as apples, onions, grapes, berries, blueberries, strawberries, cilantro, dill, coffee, tea, oranges, lettuce, potatoes, and tomatoes.[10-13] Quercetin has been reported to exhibit antiviral, anti-inflammatory, anti-aging, and antioxidant bioactivity.[11-13] It exerts its antioxidant effect by removing free radicals and maintaining oxidative balance, and its anti-inflammatory and anti-allergic effects by inhibiting the lipoxygenase and cyclooxygenase pathway.[12,14]

In clinical studies, quercetin has been shown to have antiviral[15,16] and anti-inflammatory effects[16], relieve respiratory symptoms[16], prevent poor prognosis[17] and reduce hospitalization[18] in COVID-19 patients.

Quercetin inhibits the entry of the virus into the cell by blocking the angiotensin-converting enzyme-2 (ACE2) receptor in patients with SARS and MERS, as well as resists the coronavirus by regulating the cell unfolded protein response (UPR), inhibiting the cell cycle, and lowering the level of interleukin-(IL) 6.[8,9,12,19]

The aim of this study is to understand the relationship between quercetin and COVID-19 more decisively and to comprehend the effect of quercetin supplementation on the course of COVID-19 disease through a systematic review in which promising potential therapeutic properties of quercetin are handled based on the clinical studies where quercetin and COVID-19 infection were examined together.

METHOD

This systematic review was written as a result of scrutinizing the up-to-date randomized controlled clinical trials conducted to investigate the effect of quercetin on the treatment of COVID-19 infection. During this review, the effect of antiviral, anti-inflammatory, antioxidant, and immunomodulatory activities of quercetin on disease prophylaxis, course and severity was evaluated. This study was conducted in accordance with the PRISMA-P protocol (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols)[20] and the Covidence systematic review design, which is a key component of the Cochrane review production tools.[21]

Inclusion and Exclusion Criteria
The studies included in this systematic review are randomized controlled clinical trials conducted on individuals aged 18 years and over in 2020 and later published in English or Turkish. Case-control, case series, cross-sectional studies, in vivo, in vitro, animal studies, in silico studies, review studies, and clinical trials in which quercetin and different phytochemicals were evaluated together, as well as studies on a nutrient extract and its quercetin content, were not included in this systematic review.

Participants
Of the five studies handled in the current systematic review, participants in 2 studies investigating the prophylactic effect of quercetin were volunteers aged 18 years and over without allergic response to quercetin. The 11 studies evaluating the effect of quercetin on disease course and severity were conducted with COVID-19 positive patients aged 18 years and older without allergic response to quercetin. No restrictions were made on gender, ethnicity, and the region in which the study was conducted.

Ways of Intervention
In the studies, participants were given between 500-1000 mg of quercetin orally or 500-1500 mg of quercetin phytosome (500 mg of quercetin phytosome contains 200 mg of quercetin) in addition to standard treatment in the intervention groups.

Preliminary Results
The preliminary results from randomized controlled trials examining the efficacy of quercetin in the prophylaxis,

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Main Points

- Quercetin demonstrates potent antioxidant and anti-inflammatory properties in COVID-19 treatment.
- Favorable outcomes with quercetin supplementation, including quicker patient discharge and improved disease prognosis.
- Quercetin though further clinical studies are warranted for a comprehensive understanding of its efficacy against COVID-19.

course and severity of COVID-19 disease indicate a reduction in the development of disease symptoms, frequency of hospitalization, length of hospital stay, need for non-invasive oxygen treatment, need for intensive care and mortality.

Literature Search

In this systematic review, a comprehensive search was conducted on PubMed, Embase, Web of Science, SAGEpub, Copernicus, Cochrane Library, ScienceDirect, Elsevier, Scopus, Google Scholar, EBSCOhost, Crossref, Ovid-LWW, and DergiPark databases between 1 November 2021 and 1 April 2022. Unpublished studies have also been identified from clinical trial registration platforms (http://clinicaltrials.gov/). In addition, a manual search was conducted for reference lists of extended studies. Literature searching was conducted with the keywords [(quercetin OR kuarsetin) AND (COVID-19 OR COVID19 OR SARS-CoV-2 OR SARS-COV-2 OR Koronavirüs OR Coronovirus)]''. The PRISMA flow charts of the published

and unpublished literature search processess were shown in Figure 1.

Selection and Evaluation of Studies

To determine the studies to be included in the review, three authors (D.Z.B., Z.A., and M.C.K.) independently reviewed the titles, abstracts and full texts of the obtained articles to assess their suitability (Figure 1). All studies are clinical trials examining the effect of quercetin supplementation on the COVID-19 infection. Individuals included in the studies were people who were actively receiving treatment for COVID-19 infection or receiving prophylactic support against COVID-19 infection. Since the group with the highest level of evidence among the clinical trials was randomized controlled trials, these studies were included in the current systematic review. The randomized controlled trials selected by the three authors were compared and the overlapping studies were eliminated.
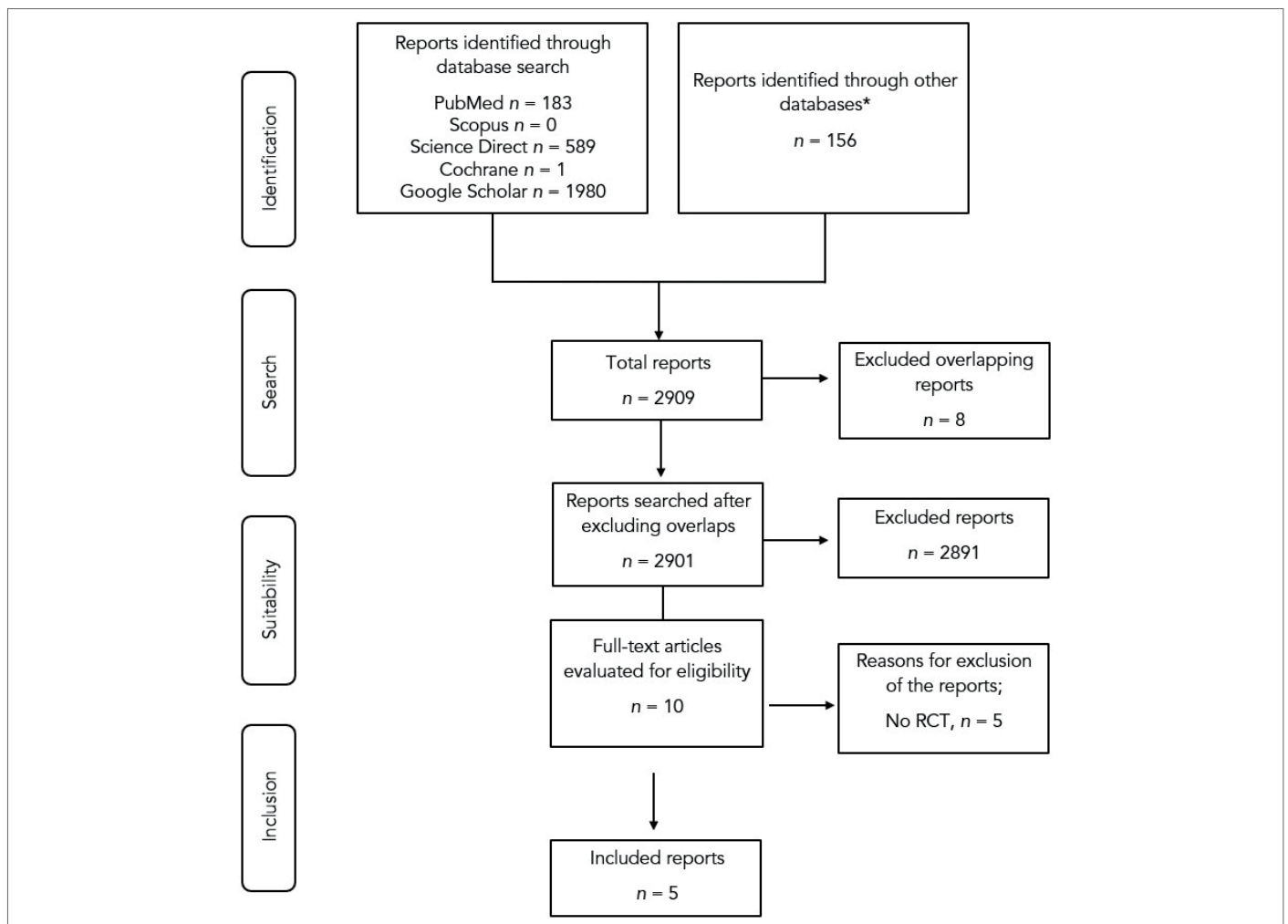

Figure 1. PRISMA flow chart of the literature search process for published clinical studies
*Crossref, Web of Science, SAGEpub, Copernicus, Ovid-LWW, Elsevier, EBSCOhost, DergiPark

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Conducting a meta-analysis instead of a systematic review with selected randomized controlled trials would be the most appropriate way to quantitatively analyze the clinical trials included in the current study. However, because the number of studies obtained as a result of a literature search is less and the results of some of these studies have not yet been published, it is decided that the best way to analyze the data is to conduct a qualitative analysis after consulting several expert statisticians.

Risk of Bias

To eliminate the risk of bias in the selection of published and unpublished studies to be included in the review, the studies selected by three authors (D.Z.B., Z.A., and M.C.K.) were subjected to the evaluation of the fourth author (G.K.).

RESULTS

In the results section, we focused on the characteristics of patients, clinical, laboratory, treatment data and outcomes of the studies. The results of 5 studies included in this systematic review were summarized in Table 1. The coding table of the studies comprises the authors of the study, the year of the study, the region/country where the study was conducted, the sampling groups [test (T) and control (C) groups], mean age/range of age, intervention dose, intervention duration, investigated parameters and the main results of the studies.

Characteristics of Studies

A total of 803 patients (ranging from 60 to 429) participated in the 5 studies included in this systematic review.[7,18,22-24] All studies involved participants older than 18 years. Of the five studies, two were from Pakistan[7,22], one was from Italy[23], one was from Turkey[24] and one was from Iran.[18] The treatments were administered orally. Doses of quercetin range from 200 mg/day[23] to 1000 mg/day.[18] In one study, apart from quercetin, vitamin C and bromelain were given as additional supplements.[24] The duration of treatment was different in all studies (from 7 days to 3 months or during the follow-up period) (Table 1).

The findings of five suitable studies included in the systematic review were shown in Table 1. Shohan et al.[18] conducted a randomized controlled trial on 60 patients with severe COVID-19. Those given quercetin alongside antiviral drugs showed significantly lower fatigue and weakness symptoms, reduced levels of inflammatory markers, and a shorter hospital stay compared to the control group (p<0.05). Di Pierro et al.[22] conducted two trials, one on outpatients and another on hospitalized patients. In both trials, quercetin supplementation alongside standard treatment led to better clinical outcomes, reduced virus persistence, and lower hospitalization rates compared

to the control groups (p<0.05). Rondanelli et al.[23] studied healthcare workers without COVID-19 infection. Those supplemented with quercetin had a lower risk of contracting COVID-19 compared to the control group, with one participant showing higher clinical remission (p<0.05). Önal et al.[24] studied hospitalized adults with COVID-19. Quercetin supplementation alongside standard treatment led to significantly reduced inflammation markers and improved blood parameters, although it did not reduce the frequency of severe events like respiratory failure (p<0.05).

Clinical Symptoms

Two studies that examined the effect of quercetin on COVID-19 infection, involving 162 participants, reported that quercetin significantly decreases the duration of conversion from positive to negative and reduces the severity of symptoms.[22,23] In a study conducted with 429 participants, there was no difference between the groups in terms of the frequency of events, while pulmonary findings were better in the quercetin group.[24] Three studies conducted on 254 participants reported a decrease in fatigue[7,18,22] and 2 studies involving 194 participants reported a decrease in fatigue and an improvement in appetite.[7,22]

Laboratory Data

Some studies reported that quercetin supplementation reduced serum CRP levels significantly in individuals with COVID-19[18,24], decreased serum ferritin levels significantly[22,24] and reduced LDH levels (p<0.05).[18,22] Although the values were within the normal range, a study reported that serum hemoglobin levels were partially increased in the quercetin group compared to the control group (p<0.05).[18] In another study, no significant difference was found in terms of serum hemoglobin values between quercetin and control groups.[22] In one of the two studies examining serum platelet and lymphocyte levels after quercetin intervention, a slight but non-significant decrease in lymphocytes was observed, while there was no difference in platelet levels (p>0.05).[22] In another study, it was reported that the increase in the number of platelets and lymphocytes was significantly higher in the quercetin-receiving group (p<0.05).[24]

Duration of Hospitalization

Two studies involving 212 participants showed that quercetin intake was associated with shorter hospitalization.[7,18]

Intensive Care Requirement and Mortality

The effect of quercetin on intensive care needs and mortality was investigated in 3 studies. In two studies, there were no significant differences in terms of mortality, duration of admission to the ICU and the number of

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Table 1. Results of randomized controlled trials included in the present systematic review

Authors and Year	Region/Country where the study was conducted	Sampling (T/C)	Age (I/C)	Intervention	Duration	Researched Parameters	Results
Shohan et al.[18], 2022	Ahvaz Razi Training Hospital, Iran	60 (30/30)	I:52.7±13.1 C:50.9±10.3	C: Standard treatment I: 1000 mg Quercetin orally + standard treatment	7 days	Clinical symptoms IL-1β, TNF-α, and IL-6 BUN, Cr, SGOT, SGPT, Total/Direct Bilirubin, ALP, LDH, quantitative CRP, ESR, D-dimer, CK-mb, and quantitative Troponin saturation, pulse, respiratory rate, body temperature, blood pressure, and the hospital stay duration	Quercetin was significantly associated with relatively early discharge and low serum levels of ALP, q-CRP, and LDH (p<0.05), There was a significant increase in hemoglobin level and respiratory rate (values within the normal range) (p<0.05), no significant differences in mortality, ICU hospitalization frequency, and ICU hospitalization duration in patients receiving Quercetin (p>0.05).
Di Pierro et al.[22], 2021a	King Edward University, Department of Medicine, Pakistan	42 (21/21)	42.5 ± 3.3 56.2 ± 3.3	C: Standart treatment I: 1500 mg Quercetin phytosome orally + standard treatment for 7 days, then 1000 mg Quercetin phytosome orally + standard treatment for the next 7 days	14 days	RT-PCR, CRP, LDH, ferritin, D-dimers, hemoglobin, WBC, platelets, neutrophils, lymphocytes, the course of symptoms related to COVID-19, need for hospitalization, compliance with treatment, tolerability and side effects	After 1 week of treatment, the SARS-CoV-2 test was negative in 16 patients in the Quercetin group, all the symptoms of 12 patients were mitigated, and the SARS-CoV-2 test result of 2 patients in the control group was negative, and the symptoms of 4 patients were partially recovered. At week 2, the remaining 5 patients of the Quercetin group returned negative in SARS-CoV-2 test results, while 17 of the remaining 19 patients in the control group turned negative at week 2, one at week 3, and one patient continued to be positive (p<0.05). Quercetin significantly (p<0.05) reduced LDH (%-35.5) and ferritin (35.5% and 40%, p<0.05%), Quercetin reduced CRP and D-dimer but was not statistically significant (p>0.05).

T: Test group; C: Control group; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; BUN, blood urea nitrogen; Cr, creatinine; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; ALP, alkaline phosphatase; LDH, Lactate dehydrogenase; ESR, erythrocyte sedimentation rate; CK-mb, creatine kinase-mb; ICU, intensive care unit; RT-PCR, real time-PCR; WBC, white blood cells.

Table 1. Results of randomized controlled trials included in the present systematic review

Authors and Year	Region/Country where the study was conducted	Sampling (T/C)	Age (I/C)	Intervention	Duration	Researched Parameters	Results
Di Pierro et al.[7], 2021b	Liaquat University of Medicine and Health Sciences, Pakistan	152 (76/76)	18-80	C: Standard treatment I: 1000 mg Quercetin phytosome orally + standard treatment	30 days	Length of hospital stay, need for non-invasive oxygen treatment, need for ICU hospitalization, mortality, compliance, tolerability, and side effects	There was a decrease in the frequency and duration of hospitalization (p=0.001), the need for non-invasive oxygen treatment (p<0.05), progression to ICU, and mortality in the Quercetin-receiving group (p<0.05).
Rondanelli et al.[23], 2022	Pavia, Italy	120 (60/60)	T:50.8±12.1 C:47.7±13.6	C: Placebo (food ingredient) I: 500 mg Quercetin phytosome orally	3 months	RT-PCR COVID symptoms Mortality	In COVID-19 infection, Quercetin was 14% more protective than placebo (p<0.05).
Önal et al., 2021	Kanuni Sultan Süleyman Training and Research Hospital, Turkey	429 (49/380)	T: 30-90 C: 18-100	C: Standard treatment I: 1000 mg Quercetin, 1000 mg vitamin C, 100 mg bromelain orally + standard treatment	During the follow-up period	COVID symptoms, Lymphopenia, thrombocytopenia, CRP, LDH, D-Dimer, ferritin, Procalcitonin, Hgb Pulmonary findings, Hospital follow-up duration, discharge rate, and case rate	While the decrease in CRP and ferritin levels was significantly higher in the Quercetin group (p<0.05), the increase in the platelet and lymphocyte counts was significantly higher (p<0.05), and the case frequency was not found different between the groups (p<0.05), Quercetin had a positive effect on pulmonary findings and laboratory parameters (p<0.05).

T: Test group; C: Control group; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; BUN, blood urea nitrogen; Cr, creatinine; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; ALP, alkaline phosphatase; LDH, Lactate dehydrogenase; ESR, erythrocyte sedimentation rate; CK-mb, creatine kinase-mb; ICU, intensive care unit; RT-PCR, real time-PCR; WBC, white blood cells.

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cases admitted to the ICU.[18,24] Another study reported that the results of ICU hospitalization and mortality were significantly better in the quercetin group, however, it was not statistically significant when patients with comorbidity were excluded and healthy individuals were evaluated. This may be due to the small number of patients.[7]

Respiratory Rate, Non-Invasive and Invasive Mechanical Ventilation

Although the values measured in a study were between the normal ranges, the respiratory rate was partially increased in the quercetin group compared to the control group (p<0.05).[18] Di Pierro et al.[7] reported that the need for oxygen treatment of a patient in the control group was 13 times higher than that of a patient in the quercetin group.

Tolerance and Side Effects

Two studies involving 194 participants reported that compliance with treatment was high, quercetin supplementation was well tolerated and no specific side effects were reported by patients.[7,22]

DISCUSSION

This systematic review examining the effects of quercetin supplementation on COVID-19 prophylaxis and the treatment process in patients diagnosed with COVID-19 are that quercetin prevents the formation and progression of the disease and reduces the levels of inflammatory markers related to the pathogenesis of the disease.

Quercetin acts as a free radical scavenger, and both in vitro and in vivo studies have shown that quercetin is a powerful antioxidant.[25] Quercetin supplementation in the diet of mice infected with the influenza virus was observed to significantly reduce levels of both superoxide radicals and lipid peroxidation products, suggesting that the use of quercetin as an antiviral treatment to mitigate the cytopathological effects of virus infections may be useful.[26] In addition, quercetin has been reported to have anti-inflammatory properties that include inhibitory effects on lipid peroxidation and proinflammatory enzymes such as lipoxygenase and phospholipase A2. It has been suggested that this anti-inflammatory effect is partially mediated by flavonoid activity on arachidonic acid metabolism and related leukotriene/prostaglandin pathways. In addition, quercetin has been shown to reduce the release of lipopolysaccharide-stimulated TNF-α, IL-6, and IL-1 from macrophages.[27] Inhibition of proinflammatory cytokines may be especially important in the pulmonary phase of COVID-19 (cytokine storm). CRP is an inflammatory biomarker for IL-6 that reflects proinflammatory cytokine levels and is one of the most important prognostic markers in patients with COVID-19 infection.[28,29] Quercetin exhibits important immunomodulatory properties in people with COVID-19 infection.[30] However, quercetin has a similar effect to anti-COVID-19 drugs due to its inhibitory effect on platelet aggregation and mast cell activation.[31]

In a phase-II clinical trial, isoquercetin, a quercetin derivative with 5 times higher intestinal absorption, significantly reduced D-Dimer levels by inhibiting disulfide isomerase which activates clotting factors and by preventing blood clotting in metastatic late-stage cancer patients.[31] The practical use of quercetin, like most polyphenols, is limited by its low solubility and oral absorption. Recently, it has been shown that quercetin (Quercetin Phytosome®) coated with sunflower lecithin reaches plasma levels up to 20 times higher in humans, without any noticeable side effects.[32] Phytosome is a technological form developed in order for phytochemicals to resemble the cell membrane structure by forming complexes with phospholipids and thereby increasing bioavailability by facilitating their absorption.[33] In addition, Quercetin Phytosome® has a strong safety profile.[33] Interaction between Quercetin Phytosome® and the human microbiota has also been elucidated.[34] The Quercetin Phytosome® formulation was found to be more stable than the non-formulated quercetin after interaction with the intestinal microbiota.[35] Phytosome slows down the intestinal microbial degradation of quercetin, allowing it to have more time and better dispersion for absorption of the free molecule.[34] Of the 5 studies included in the current systematic review, three utilized the Quercetin Phytosome®[7,22,23] and two utilized the quercetin.[18,24]

NLRP3 inflammation is defined as an uncontrolled inflammatory weapon that is considered an important therapeutic target associated with COVID-19 infection.[36] Shohan et al.[18], discussed in the present review, considered the inhibitory effect of quercetin on NLRP3 inflammation in a randomized controlled trial and conducted a treatment method based on a combination of quercetin with antiviral drugs in severe COVID-19 patients. According to the results of the study, intake of 1000 mg/day of quercetin for 1 week in addition to antiviral drugs was associated with a reduced length of hospital stay, lower serum levels of q-CRP, LDH, and ALP and a statistically significant increase in respiratory rate and serum hemoglobin level in the intervention group.[18] A study revealed that quercetin, which is from the flavonoid family, is able to regulate the expression of 85% of the structural proteins of the COVID-19 virus.[37] The viral S-protein of SARS-CoV-2 infects the human cell by binding the angiotensin-converting enzyme-2 (ACE-2) receptor. In a study, quercetin and Epicatechin were able to form an interaction with ACE through both the zinc ion of ACE and the amino acids of ACE. The study also showed that the presence of a

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catechol group on the flavonoid increases its power to inhibit ACE. Therefore, quercetin is noted to have the greatest capacity to inhibit ACE among all flavonoids.[38] Other studies have reported that quercetin may lead to the prevention of COVID-19 entry into host epithelial cells as an inhibitor of the acid sphingomyelinase ceramide system which plays an important role in the entry of the virus into respiratory epithelial cells during COVID-19 infection.[39-41] In addition, in a molecular docking study, quercetin was shown to effectively reduce lytic replication of the COVID-19 virus by binding to 3CL and PL proteases and inhibiting the COVID-19 replication cycle.[42] In addition, it has been suggested that quercetin suppresses TNF/TNFR and NLRP3 downstream signals such as Nf-kB and IL-1 and shows inhibitory activity on S protein-ACE2 interaction in rhACE2 cells in vitro.[6,27,43]

The use of immunomodulatory nutraceuticals such as vitamin C and quercetin is also recommended as adjuvant treatment in COVID-19 patients.[44] The prophylactic and therapeutic use of quercetin in combination with bromelain and vitamin C is indicated to be appropriate to increase the bioavailability of antiviral drugs and quercetin.[24] In a case series study, researchers reported that the intake of 800 mg/day of quercetin, 50 mg zinc acetate, 165 mg bromelain, and 1000 mg vitamin C supplements with antiviral medication by patients with COVID-19 infection was safe and improved the course of the disease.[17] It has also been shown to act as a zinc ionophore and increase the entry of zinc into cells to inhibit viral intracellular replication.[45]

According to the results of a randomized controlled trial by Di Pierro et al.[22] discussed in the current review, they observed that the intake of 1500 mg/day of quercetin Phytosome® in the first week and 1000 mg/day of quercetin in the second week (corresponding to 600 mg and 400 mg of quercetin per day, respectively) in addition to standard treatment for 2 weeks disclosed the ability to clear the COVID-19 virus and improve clinical symptoms, and statistically shortened the rate of conversion of RT-PCR test from positive to negative.[22] The shortening of the conversion rate of the RT-PCR test from positive to negative was consistent with the recording of complete clinical remission in the quercetin and placebo groups on the 7th and 17th days, respectively, in the study of Rondanelli et al.[23]. Quercetin supplementation significantly reduced LDH, ferritin, CRP, and D-dimer levels as another result of this study, similar to other studies. Regarding the safety of quercetin use, its hepatic safety was confirmed by stating that it is very well tolerated and not caused different side effects compared to the control group receiving standard treatment.[22,24] The study of Di Pierro et al.[22] has some possible limitations because the sample size of the study is small, it is not performed in double-blind and placebo-

controlled conditions. However, the authors reported that this study is a preliminary study. Although the authors reported that quercetin positively affects LDH, ferritin, and some COVID-19 biomarkers, they did not know the reason why other biomarkers did not change significantly with treatment. In another randomized controlled trial in which 152 patients were given a Quercetin Phytosome® supplement of 1000 mg/day for 30 days and included in this review, Di Pierro et al.[7] associated quercetin supplementation with a significant reduction in length of hospitalization, oxygen need, intensive care unit need and mortality, which are consistent with previous studies.

In the study by Önal et al.[24], included in the current review, quercetin supplementation resulted in a significant reduction in acute phase reactants, despite more advanced lung involvement and COPD. The decrease in serum CRP and ferritin levels was significantly higher in the intervention group than in the control group. It is also suggested that quercetin supplementation has a role in increasing the number of platelets and lymphocytes.[24] The increase in acute phase reactants in COVID-19 is thought to be due to the exaggerated release of proinflammatory cytokines from "hyper-reactive" monocytes.[46] Monocytes play a critical role in the inflammatory response. Active monocytes act on the immune system by providing the secretion of essential cytokines such as IL-6, IL-1, IL-8, and TNF-α, which are pro-inflammatory cytokines.[47,48] Different mechanisms may play a role in the abnormal activation of monocytes in chronic diseases.[47] Flavonoids have the ability to modulate macrophages from pro-inflammatory phenotypes and potentially contribute to the improvement of predetermined inflammatory processes. These findings can be explained by the fact that flavonoids contribute to the transformation of the immunomodulatory effects on macrophages into pro-anti-inflammatory phenotypes.[49]

Among the studies included in this systematic review, the study of Rondanelli et al.[23] is the only study in which the prophylactic effect of quercetin was evaluated. This study indicated that quercetin supplementation was significantly protective against symptomatic coronavirus infection for over a 3-month period. These results are consistent with the results of the study which found that 3 months of quercetin supplementation in healthcare workers was significantly protective.[50] In addition, according to the analyzes conducted in the 5th month of this study, the risk of infection was found to be 99.8% in participants taking quercetin supplements and 96.5% in the control group. It was observed that the quercetin group has 14% more protection factors to prevent contracting COVID-19 infection than the placebo group.[23] In a study of 113 people conducted by Margolin et al.[15], an experimental group of 53 people was given 25 mg of zinc, 10 drops of henna leaf extract, 1000 mg of vitamin C, 1000 IU (25

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µg) of vitamin D3, 400 IU of Vitamin E and 500 mg of l-lysine orally for 20 weeks. As a result of the study, the development of symptoms of the disease was found to be significantly less in the group receiving supplements than in the group not receiving them. However, they participated in a long-term experiment and could regularly use the supplements given separately, thus it can be considered that the people in the experimental group were more cautious about the disease also had an impact on the outcome. It was reported that quercetin is a senolytic agent that can alleviate the course of the disease with the early elimination of aging cells in the management of COVID-19. It is assumed that quercetin is involved in the initial stage of countering cytokine storm and cell aging by activating the immune system. Lee et al.[51] concluded that quercetin can alleviate COVID-19-related pulmonary disorders and systemic inflammation during an active infection, and even alleviate chronic post-infection damage of long-term COVID-19 disease due to its senolytic activity. Limitations of the study discussed in this review were the lack of evaluation of the immune response and cytokine production, the small sample size, the short duration of the intervention, and the inclusion of only health workers.[23]

In conclusion, this systematic review shows that quercetin is promising as a therapeutic agent and may potentially lead to reduced disease symptoms, hospitalization rates, length of hospital stay, need for noninvasive oxygen therapy, need for intensive care, and mortality. Due to the complex pathophysiology of COVID-19 infection, which has not yet been clearly elucidated, further clinical studies are needed to be able to definitively talk about the curative effect of quercetin on COVID-19 infection.

Limitations of the Study
The few number of available studies and the fact that the study designs were not exactly the same constituted the limitations of the study.

Author contributions: Concept – Z.N.B., D.Z.B., M.C.K., G.K.; Design – Z.N.B., D.Z.B., M.C.K., G.K.; Supervision – Z.N.B., D.Z.B., M.C.K., G.K.; Resources – Z.N.B., D.Z.B., M.C.K., G.K.; Materials – Z.N.B., D.Z.B., M.C.K., G.K.; Data Collection and/or Processing – Z.N.B., D.Z.B., M.C.K., G.K.; Analysis and/or Interpretation – Z.N.B., D.Z.B., M.C.K., G.K.; Literature Search – Z.N.B., D.Z.B., M.C.K., G.K.; Writing Manuscript – Z.N.B., D.Z.B., M.C.K., G.K.; Critical Review – Z.N.B., D.Z.B., M.C.K., G.K.

Conflict of interest: The authors declare that there is no conflict of interest.

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