Long-Term Care Updates

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Quercetin: A Natural Remedy for COVID-19?

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Introduction

As the COVID-19 pandemic drags on and the associated death toll rises, people across the globe are longing for the discovery of a safe and effective treatment. Although treatments such as remdesivir and certain monoclonal antibodies have shown efficacy against the SARS-CoV-2 virus, they come with their own, sometimes serious, adverse effects and may not be available for the non-hospitalized or in areas with limited resources.

Some researchers have started exploring natural medicines, such as quercetin, as a potential agent for treatment against COVID-19. Quercetin is said to have antioxidant, anti-inflammatory, anti-viral, and immunomodulating properties, and researchers have been investigating these beneficial effects for decades. Recently, a supercomputer modeling study identified quercetin as one of the top 5 scoring ligands for binding to the viral spike protein of SARS-CoV-2.[1] This sparked new interest in quercetin as having a potential protective effect against COVID-19. There have been many journal articles published recently supporting its theoretical and in vitro efficacy and a few small, non-placebo-controlled studies in COVID-19 patients testing this theory. Let's take a closer look at quercetin. What is it? Is it safe? And what does the available clinical evidence have to say about it's potential for the prevention or treatment of COVID-19?

What is Quercetin?

Quercetin is a naturally occurring plant flavonoid found in many fruits and vegetables such as onions, kale, broccoli, berries, and apples with particularly high concentrations in fruit skins.[2] On average, dietary intake of quercetin is between 5 mg and 40 mg per day.[3] Quercetin is soluble in lipids but poorly soluble in water, causing its poor absorption and low bioavailability (about 3-17%) when taken orally as a supplement. However, lipophilic formulations and combination with vitamin C and bromelain can increase its bioavailability. [4,5]

In vitro and animal studies suggest that quercetin has antioxidant, anti-inflammatory, and immunomodulatory effects. Additionally, quercetin appears to have antiviral effects, *in vitro*. Its proposed antiviral mechanisms include inhibition of virus entry, inhibition of viral DNA and RNA polymerase, inhibition of proteases, and/or blocking protein binding necessary for viral replication. Quercetin is hypothesized to inhibit the COVID-19 infective process by binding to SARS-CoV-2 3CL protease, thereby inhibiting the virus's proteolytic ability and/or blocking the binding of the viral spike protein to the angiotensin converting enzyme-2 (ACE2) protein of the host epithelial cell resulting in inhibition of viral entry.[6,7,8]

Is Quercetin Available?

One appealing quality of quercetin is its widespread, over-the-counter availability. It most commonly comes in 500 mg capsules and is available in a variety of formulations. These include products aimed at increasing quercetin's bioavailability (e.g., quercetin in combination with vitamin C or bromelain; Quercetin Phytosome) which are available for purchase in the U.S. from online stores. A bottle of 60 capsules of quercetin 500 mg costs about $10-$15 and Quercetin Phytosome costs about $10-$36.[9]

Is Quercetin Safe?

Several studies suggest that quercetin is safe, with no evidence of toxicity or clinically important adverse effects, in doses up to 1000 mg/day for up to 12 weeks.[2,3] A review of data related to the safety of quercetin by Harwood et al concluded supplemental quercetin to be safe and reports no findings of significant adverse effects.[10] Similarly, there were no reports of adverse effects thought to be related to quercetin use in any of the studies described below which evaluated quercetin's role against COVID-19.[1,5,11,12] The U.S. Food and Drug Administration (FDA) classifies quercetin as a GRAS (Generally Recognized as Safe) substance.[5] However, there are some potential drug interactions to be aware of. Quercetin has the potential to increase serum concentrations of caffeine, cyclosporine, diclofenac, fexofenadine, midazolam, pravastatin, warfarin, phenytoin, and tolbutamide.[2] Quercetin is not known to be a safety concern in the elderly. Of the studies below, one trial by Di Pierro et al included 16 patients greater than 60 years old, and the study by Onal et al enrolled 175 patients 60 years of age or older. Neither of the studies reported different effects in the elderly population.[1,12]

Clinical Trials

In one small, randomized, controlled, open-label clinical trial published by Di Pierro et al, 42 outpatients confirmed to be COVID-19 positive by PCR test were randomized so that half received the standard of care (SC) while the other half received SC plus supplementation with Quercetin Phytosome (QP). Quercetin Phytosome, which is formulated with sunflower phospholipids, is up to 20 times more bioavailable than the standard form of quercetin. At the time of enrollment, there was no significant difference between the groups in terms of sex, comorbidities, symptoms, or inflammatory markers such as C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and D-dimer. However, there was a significant difference in average age which was 42.5 in the QP group vs 56.2 in the control group ($p=0.0056$). The treatment group was instructed to take one tablet of QP, equivalent to 200 mg of quercetin, three times a day for one week and then one tablet twice daily for the following week. Data were collected at follow-up visits at the end of week 1 and end of week 2. After 1 week, 16 patients tested negative for SARS-CoV-2 by PCR test in the QP group vs 2 patients who tested negative in the control group. Twelve patients in the QP group reported improvement in symptoms vs 4 patients who reported symptom improvement in the control group. At the end of week 2, all 21 patients in the QP group tested negative while 19 out of 21 patients in

the control group tested negative. QP was well tolerated by the treatment group. No patients experienced toxicities and reported side effects were similar between the treatment and control group. One patient in the control group was hospitalized and expired at day 20 post enrollment. Although this trial shows promising results after 1 week, it is important to keep in mind the major limitations of this study. This study evaluated a very small sample size. One patient in the control group had worsening severity of COVID-19 and died which likely would have resulted in a significant increase in inflammatory markers at day 7, causing concern for unfairly skewed inflammatory data in favor of the QP group. Also, this study was not blinded and placebo-controlled; therefore, it cannot account for the placebo effect in the treatment group, particularly for patient-reported subjective data such as symptom improvement. Lastly, it is probable that the large difference in age between the groups, with the QP group averaging 13.7 years younger than the control group, had an effect in the COVID-19 disease course since it is known that increasing age is a risk factor for worse clinical outcomes and those of younger age tend to recover quicker.[11]

In a similar randomized, controlled, open-label trial conducted by Di Pierro et al, researchers evaluated the effect of QP supplementation on treating early symptoms of COVID-19 and preventing progression to severe disease. One hundred fifty-two outpatients with confirmed COVID-19 were randomized (1:1) into 2 groups: those who would receive SC and those who would receive SC plus one tablet of QP, corresponding to 200 mg of quercetin, twice daily for 30 days. There was no statistically significant difference between the two groups in terms of sex, age, or age stratification. However, there was a significant difference in patients with comorbidities between groups (QP 38.2% vs SC 59.2%, p=0.0092). The results showed better outcomes in the QP group compared to the control group for all primary endpoints: need for hospitalization (QP 9.2% vs SC 28.9%, p=0.0016, RR=0.32, NNT=6), length of hospitalization (QP 9.2% vs SC 28.9%, p=0.0016), need for non-invasive oxygen therapy (QP 1.3% vs SC 6.77%, p=0.0001, RR=0.067, NNT=6), progression to intensive care unit (QP 0% vs SC 10.5%, p=0.0211, NNT=10), and death (QP 0% vs SC 3.9%, p=0.04, NNT=26). These impressive results are limited by lack of placebo-control and the large inequality in patients with comorbidities between groups. It is known that patients with comorbidities are at higher risk for worse clinical outcomes from COVID, which likely impacted these results. Because of this, the researchers conducted a subgroup analysis of only the subjects without comorbidities and found statistically significant improvements in the QP group compared to the SC group in terms of days of hospitalization (1.25 vs 5.14, p=0.0097) and patients who needed oxygen (0 vs 4, p=0.0055). However, no differences in the rate of hospitalization, ICU admission, or death were reported between the groups in this subgroup analysis. Another significant limitation is the researchers' omission of baseline symptoms of the two groups. Without this, we cannot rule out that the SC group may have had more severe disease than the QP group even before intervention initiation.[12]

In a prospective cohort study conducted by Onal et al in Turkey, a group of patients who had at least one chronic condition and were hospitalized with moderate-to-severe COVID-19 were randomized to receive SC (n=382) or SC plus supplementation with 500 mg of quercetin, 500 mg of vitamin C, and 50 mg of bromelain (QCB) twice daily (n=52) until hospital discharge, intubation, or death. The supplement of interest in this study was quercetin, but vitamin C and bromelain were added to help improve quercetin's poor bioavailability. The groups were comparable in terms of age, sex, smoking status, and positive COVID-19 PCR test. However, the treatment group (SC + QCB) had a significantly higher proportion of patients with COPD (13.5% vs 5.1%, p=0.02), more severe pulmonary findings at admission as evidenced by chest computerized tomography (p=0.03), and higher proportion of patients with oxygen saturation <93% at admission (50% vs 33.4%, p=0.016). Results showed no statistically significant difference between the groups in terms of the primary endpoints which were intubation or death. However, patients in the QCB group showed a significant reduction in CRP (-34.6 vs. -2.10, p=0.001) and ferritin (-8.1 vs. +22.4) compared to the SC group and showed a trend

of greater reduction in procalcitonin and LDH compared to the SC group which did not reach statistical significance. The supplementation was well tolerated in the treatment group, and no adverse effects related to QCB supplementation were observed in participants.[1]

A prospective, randomized, controlled, open-label cohort study by Arslan et al aimed to test the effectiveness of quercetin and vitamin C as a prophylactic measure to protect against infection with COVID-19. In this study, a group of healthcare workers working in a pandemic hospital in Istanbul in areas at high risk for COVID-19 transmission were randomized to 2 groups: 71 healthcare workers received daily supplementation with 500 mg of quercetin, 500 mg of vitamin C, and 50 mg of bromelain (QCB) in 2 divided doses and 42 healthcare workers acted as the control group and received no supplementation. The groups did not show statistically significant differences in terms of gender, smoking status, or comorbidities at initiation, but did show a significant difference in age (QCB 39 vs control 32.9, $p=0.001$). Results showed that 1 healthcare worker out of 71 (1.4%) in the QCB group and 9 out of 42 (21.4%) in the control group tested positive for COVID-19 during the follow-up period of a maximum of 120 days, none of which needed to be hospitalized. This result was statistically significant ($p=0.001$) and showed that the control group had a 12-fold greater risk of COVID-19 transmission compared to the QCB supplemented group (HR 12.04, 95% CI 1.26-115.06, $p=0.031$). These data show that the QCB group incurred a 93% relative risk reduction of COVID-19 infection, and for every 5 patients treated with QCB instead of placebo, one additional COVID-19 infection will be prevented. The main limitations of this trial are its small sample size and the results have not been peer reviewed or published in a credible medical journal.[5]

Conclusion

Quercetin is a plant flavonoid with antioxidant, anti-inflammatory, and antiviral properties and may have a role in combatting SARS-CoV-2. The data from the studies summarized above show promise for quercetin's potential as a protective agent against COVID-19. However, all of the studies have crucial limitations, so the results should be interpreted with caution and do not provide conclusive evidence. The two studies by Di Pierro et al showed impressive results of much better clinical outcomes and reduced need for hospitalization in the group that received quercetin, but both studies have large inequalities between the treatment and control groups which would favor better results in the treatment group. The study by Onal et al showed no significant difference in intubation or deaths between the groups but did show improved inflammatory markers in the treatment group. This study is also limited by inequality between the treatment and control group which would favor better outcomes in the control group. One possible reason for the large difference in results between the strikingly positive effect seen in the Di Pierro trials and insignificant effect seen in the Onal trial could be that the Di Pierro trials studied unhospitalized patients with mild COVID-19 who were more likely to be in the beginning stages of the disease while the Onal trial studied hospitalized patients with moderate-to-severe COVID-19 who were more likely to be in later stages of disease progression. If quercetin's antiviral mechanism of action is to inhibit viral entry or viral replication, it would make sense that it had a larger beneficial effect for patients who were in earlier stages of disease progression. These results hint that quercetin's role may be prevention of progression to severe COVID instead of treatment or cure of the disease. Another possible reason could be the difference in quercetin formulation, with the Quercetin Phytosome used in the Di Pierro trials having better bioavailability. The study by Arslan et al suggests that quercetin may have a role as prophylaxis against COVID-19 infection. Quercetin's safety profile, availability, and affordability make it an intriguing option as a potential weapon against COVID-19. Overall, quercetin is not currently recommended for prevention or treatment of COVID-19 outside of clinical trials, and more high-quality evidence is needed before its efficacy for COVID-19 can be evaluated. Fortunately, several randomized, placebo-controlled clinical trials are currently underway.[13] Although there is still uncertainty to quercetin's benefit, it is an exciting, prospective agent under investigation as adjunctive therapy for COVID-19 and one to be on the lookout for in the near future.

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