Antiviral Effects of Quercetin and Related Compounds

by Mehdi Chaabi, PhD

The World Health Organization declared COVID-19 a global pandemic on March 11. As of March 31, 2020, the coronavirus had rapidly spread to more than 850,000 people in 202 countries and caused ca. 42,000 deaths. Coronavirus new cases and death toll are increasing exponentially.

To deal with this pandemic situation, many scientists and biopharmaceutical companies all over the world are racing against the clock to find an effective remedy. Among them, Dr. Michel Chrétien, senior researcher at the Montreal Clinical Research Institute (IRCM), proposed the use of a plant-based compound called quercetin to treat COVID-19. Moreover, Dr. Chrétien's team will supervise clinical trials for testing quercetin on patients in China in close collaboration with Chinese health officials, as he recently stated.[1]

In this review, we will find out the latest news in the search for the antiviral effect of quercetin. In fact, quercetin has been the subject of much interest recently due to its emerging antiviral effects. The scientific literature shows that quercetin has been investigated as a potential antiviral agent for over 15 years. This article reviews the known pharmacology and mechanisms of action of quercetin, as well as the evidence pertaining to its antiviral effects. It is noteworthy that high-purity quercetin was given "Generally Recognized As Safe" (GRAS) status in 2010.[2]

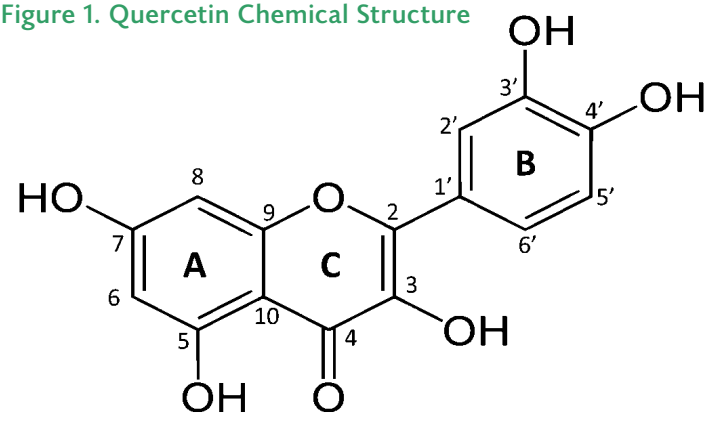
Pharmacology and Pharmacokinetics

Quercetin (3,5,7,3′,4′-pentahydroxyflavone) is a polyphenolic flavonoid found in several plants, notably onions, blueberries, kale, cranberries, broccoli, and green tea. Also, flavonoids serve many roles in plant biology, including scavenging free radicals [3] and regulating enzyme activities. They also have antibacterial and antiviral effects [4] on, among others, pathogenic bacteria; viruses; and *Plasmodium*, *Babesia*, and *Theileria* parasites.[5]

Pharmacologically, quercetin has been examined for its antihypertensive effects,[6] antiproliferative/anti-inflammatory activity,[7] and other properties.

Quercetin has poor water solubility and is often stabilized as quercetin glycosides with glycosyl groups which are released during digestion. On the other hand, consumption of quercetin with a fatty meal enhances absorption,[8] and vitamin C has been shown to improve quercetin absorption and enhance plasma quercetin blood levels.[9] Notably, data suggests that quercetin preferentially accumulates in the lungs, liver, kidneys, and small intestines, with lower levels seen in the brain, heart, and spleen.[10]

Figure 1. Quercetin Chemical Structure



Preclinical Antiviral Data

In vitro data suggests that quercetin may inhibit viral replication of the influenza virus, parainfluenza virus, respiratory syncytial virus, adenovirus, and rhinovirus.[11] Kinker summarizes quercetin activity as interfering with three stages of viral replication:[12]

1. Quercetin blocks endocytosis (uptake of the virus into the host cell) via inhibition of phosphatidylinositol 3-kinase (PI3 kinase).

2. Quercetin blocks transcription of viral genome by inhibiting RNA polymerase and viral protein translation by promoting cleavage of eukaryotic translation initiation factor 4 G (eIF4G).

3. Quercetin increases viral clearance by enhancing the mitochondrial antiviral response.

In an animal study of influenza infection (H3N2), onset of infection was associated with a significant decrease in the pulmonary concentrations of catalase, reduced glutathione, and superoxide dismutase (antioxidants); supplementation with quercetin given at the same time as inoculation with the virus produced significant increases in the pulmonary concentrations of these antioxidants.[13] A similar study showed that quercetin exerted a mild to moderate protective effect on lung morphology, and a significant decrease in the number of infiltrating cells.[14]

In vitro and animal data suggests promising broad antiviral effects associated with quercetin. Quercetin appears to exert antiviral effects in vitro and/or in vivo against many strains of influenza viruses, Middle East respiratory syndrome-coronavirus (MERS-CoV), severe acute respiratory syndrome associated coronavirus (SARS-CoV), murine coronavirus, dengue virus, hepatitis B virus (HBV), Epstein–Barr virus (EBV), Zika virus, and Ebola virus. Quercetin appears to inhibit early viral entry to cells, inhibit viral RNA/genome replication, and reduce inflammation associated with infection.

Drug Interactions

Quercetin inhibits the P450 CYP3A4 enzyme system[15] and may impact the pharmacokinetics of other substances including medications metabolized through this system. Individuals on medications, especially those on medications with a narrow therapeutic window, should consult their health-care provider prior to use. Quercetin has been shown to enhance the antimicrobial effects of several antibiotics and antifungal medications, including against *Staphylococcus aureus*, multidrug-resistant *E. coli*, and fluconazole-resistant strains of *Candida tropicalis*.[16] Quercetin has also been reported to competitively bind to bacterial DNA gyrase and is, therefore, contraindicated for administration with fluoroquinolone antibiotics (e.g. ciprofloxacin and others ending with -floxacin).[17]

Clinical Trials

A randomized, double-blinded, placebo-controlled trial investigated the effect of two doses of quercetin on viral upper respiratory tract infection in a large community-based sample aged 18–85 years.[18] A total of 1,002 participants were randomized to 500 or 1,000 mg/d or placebo for 12 weeks. Results showed that while there were no overall effects, a subgroup analysis of subjects 40 years of age and older with self-rated good fitness ($n = 325$) showed significantly lower URTI severity (36% reduction, $p = 0.020$) and URTI total sick days (31% reduction, $p = 0.048$) in the quercetin 1,000 mg group compared to placebo.

A randomized, double-blind, placebo-controlled trial investigated the pharmacokinetics and changes in immunological biomarkers associated with supplementation of a herbal formula featuring quercetin.[19] In this study, a total of 48 overweight or obese middle-aged women were treated with an herbal formula rich in bioflavonoids or placebo for 10 weeks. The herbal formula contained 1,000 mg quercetin, 400 mg isoquercetin, 120 mg epigallocatechin (EGCG) from green-tea extract, 400 mg n3-PUFAs (omega-3 polyunsaturated fatty acid with 220 mg eicosapentaenoic acid [EPA] and 180 mg docosahexaenoic acid [DHA]) from fish oil, 1,000 mg vitamin C, 40 mg niacinamide, and

Table 1: Antiviral Effects of Quercetin Mentioned in the Literature

Effect	Virus Strain	Ref.
Antiviral activity and inhibition of murine coronavirus mouse hepatitis virus (MHV) and dengue virus type 2 (DENV-2) by the quercetin-containing fraction of *Houttuynia cordata* plant in vitro.	Mouse hepatitis virus (MHV) and dengue virus type 2 (DENV-2)	[23]
Antiviral activity against Zika virus (ZIKV) in both tissue culture and knockout mice.	Zika virus (ZIKV)	[24]
Antiviral activity against influenza A (H1N1) strain in vitro, and synergy in vivo when combined with standard antiviral drugs, such that "The combination of antioxidants [quercetin] with antiviral drugs synergistically reduces the lethal effects of influenza virus infections" in animal models.	Influenza A (H1N1)	[25]
Inhibition of hepatitis B virus (HBV) replication in vitro.	Hepatitis B virus (HBV)	[26]
Synergistic inhibition when used with *Ganoderma lucidum* (reishi) against Epstein–Barr virus (EBV)–associated gastric carcinoma.	Epstein–Barr virus (EBV)	[27]
Inhibition of DENV-2 and DENV-3 infection, as well as inhibition of proinflammatory cytokines induced by DENV infection, TNF-α, and IL-6 secretion.	Dengue serotypes 2 and 3 (DENV-2 and DENV-3)	[28]
Inhibition of enzymatic activity of MERS-CoV 3CL protease, associated with Middle East respiratory syndrome-related coronavirus (MERS-CoV) infection.	MERS-CoV	[29]
Antiviral effects against influenza A virus (IAV): Periodic treatment with quercetin was effective in reducing IAV infection and differentially regulated the expression of key proteins, including heat shock proteins, fibronectin 1, and prohibitin involved in IAV replication.	Influenza A (IAV)	[30]
Strong inhibition activity against influenza A and B viruses through inhibition of viral RNA polymerase. Quercetin also reduced virus-induced reactive oxygen species and autophagy formation.	Influenza A and B	[31]
Inhibitory activity in the early stage of influenza infection, blocking viral entry to the host cell, for several influenza strains including two strains of H1N1 and H3N2.	Influenza H1N1 and H3N2	[32]
Antiviral effects against the H1N1 influenza virus: "Viral infection led to cell death and increased the gene expression levels of TLR7 signal pathway. Quercetin and oseltamivir increased cell viability and reduced the expression levels of TLR7 signal pathway."	Influenza H1N1	[33]
Quercetin, epigallocatechin gallate, and gallocatechin gallate (GCG) displayed good inhibition toward $3CL^{pro}$, the enzyme needed for viral replication in severe acute respiratory syndrome associated coronavirus (SARS-CoV).	Coronavirus SARS-CoV	[34]
Inhibition of SARS-CoV 3CL protease activity.	Coronavirus SARS-CoV	[35]
Reduction of influenza infection—including morbidity, mortality, and symptom severity—among mice subjected to stressful exercise stimuli.	Influenza	[36]

800 µg folic acid. Blood samples were collected at baseline and after 10 weeks. Results showed that supplementation raised serum levels of quercetin almost four-fold (388%). Although there was no change in C-reactive protein, a marker of acute inflammation, gene set enrichment analysis revealed that there was an upregulation of genes related to interferon-induced antiviral activity in the herbal supplement group compared to placebo.

A phase I trial investigated the potential antiviral effect of quercetin among patients with hepatitis C, caused by the hepatitis C virus (HCV).[20] The study was of the dose-escalation type and aimed to establish safety in 30 untreated patients with chronic HCV infection, as well as to characterize effects on the viral load. Results showed that quercetin was safe in all patients. There were no changes in liver enzymes (aspartate transaminase and alanine transaminase). However, eight of 30 patients showed a "clinically meaningful" decrease in viral load.[21] There was also a tendency for HCV load to decrease in patients with a lower ratio of plasma quercetin relative to dose. Researchers concluded that the data suggested an antiviral effect in some patients.

An herbal formula containing quercetin was evaluated for its effects in patients with oral herpes, caused by the herpes simplex virus.[22] A retrospective chart review examined data from 68 treated patients. Patients were given between one and four capsules daily for between two to 36 months. The herbal

formula contained five ingredients: 100 mg quercetin, 150 mg extract of green tea, 50 mg cinnamon, 25 mg licorice, and 100 µg selenium. Patients were compared to baseline controls (n = 56) and no-treatment controls (n = 12). The formula was deemed "effective in 89.3% of participants": the treatment reduced the mean number of outbreaks per year from 6.0 and 3.6 in the control groups to 2.0 in the treatment group ($p < 0.0001$ and $p = 0.07$). The treatment reduced the mean duration of outbreaks from 9.8 and 5.8 days in the control groups to 3.2 days in the treatment group ($p < 0.0001$ and $p = 0.02$, respectively). There were no reports of adverse events. The herbal formula was also compared to antiviral medications acyclovir and valacyclovir in six tests; in all tests, the herbal formula showed higher efficacy.

In conclusion, quercetin is a lipophilic polyphenolic flavonoid found in many plants. Quercetin appears to inhibit a broad range of viral infections by inhibiting viral entry, replication, and associated inflammation. Human studies have used doses between 400 and 1,000 mg daily. Quercetin may affect pharmacokinetics of drugs metabolized through CYP 3A4 pathways and is contraindicated for individuals taking fluoroquinolone antibiotics. We recommend consulting a licensed health-care provider prior to use to determine whether quercetin supplementation is appropriate for you. •NC

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