

# Another Reason to Add Quercetin to Your Daily Supplements

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✓ Fact Checked

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## STORY AT-A-GLANCE

- › Researchers recommend administering quercetin with vitamin C, because vitamin C helps recycle oxidized quercetin, thereby producing a synergistic effect and enhancing quercetin's antiviral capability
- › Quercetin promotes SIRT2, thereby inhibiting the NLRP3 inflammasome assembly involved with COVID-19 infection. It also transports zinc across cellular membranes
- › Quercetin binds to the spike protein of SARS-CoV (the virus responsible for SARS), thereby inhibiting its ability to infect host cells. It has also been identified as one of several molecules most likely to inhibit the SARS-CoV-2 spike protein from interacting with human cells
- › Quercetin also inhibits platelet aggregation, and many COVID-19 patients suffer abnormal blood clotting
- › Turkish researchers are currently conducting a nonrandomized trial on quercetin. COVID-19 patients are receiving 1,000 mg of quercetin per day as an active treatment, while front-line health care workers are receiving 500-mg doses as a prophylaxis

I've previously reviewed the similarities between the flavonoid quercetin and the drug hydroxychloroquine, discussing the possibility of using quercetin in lieu of the drug against COVID-19. We're now also starting to see quercetin mentioned more often in the scientific literature on COVID-19.

## Quercetin Highlighted in COVID-19 Medical Literature

For example, a review article<sup>1</sup> published in the June 19, 2020, issue of *Frontiers in Immunology* highlights quercetin's usefulness as a COVID-19 treatment, especially in conjunction with vitamin C. Quercetin is also featured in a review<sup>2</sup> of emerging COVID-19 research published in the *Integrative Medicine* journal. As reported by *MedPage Today*:<sup>3</sup>

*"Quercetin ... promotes SIRT2, which then inhibits the NLRP3 inflammasome assembly involved with COVID-19 infection, said Samuel F. Yanuck, DC, of the Program on Integrative Medicine at the University of North Carolina Chapel Hill School of Medicine, who co-authored a review<sup>4</sup> of emerging research on the subject. It also plays a role in facilitating zinc transportation across lipid membranes, Yanuck said.*

*'It's not a bizarre or experimental substance and given it has these potential important biological roles, I think it's worth being considered as part of an overall strategy,' Yanuck told MedPage Today, adding that quercetin would need to be one part of a multifactorial treatment regimen ...*

*COVID-19 has been associated with high levels of interleukin-6, depleted levels of interferons, and a cytokine storm that damages the body and is related to respiratory failure, said Ruben Colunga Biancatelli, MD, of Old Dominion University in Norfolk, Virginia, and first author of a paper on quercetin and vitamin C as a potential therapy for treating SARS-CoV-2 in *Frontiers in Immunology*.<sup>5</sup>*

*Using this rationale, researchers are postulating that vitamin C should be administered with quercetin because it can recycle oxidized quercetin, producing a synergistic effect and enhancing quercetin's antiviral capability, Biancatelli added."*

## Why Quercetin May Offer Hope Against COVID-19

There are solid reasons to suspect quercetin can be effective against SARS-CoV-2, the virus that causes COVID-19 disease. For example, quercetin has been shown to:

Bind to the spike protein of SARS-CoV (the virus responsible for severe acute respiratory syndrome or SARS), thereby inhibiting its ability to infect host cells.<sup>6</sup> Using the supercomputer SUMMIT, researchers at Oak Ridge National Lab also identified quercetin as one of the molecules that might inhibit the SARS-CoV-2 spike protein from interacting with human cells.<sup>7,8</sup>

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Inhibit lipopolysaccharide (LPS)-induced tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) production in macrophages.<sup>9</sup> (TNF- $\alpha$  is a cytokine involved in systemic inflammation, secreted by activated macrophages, a type of immune cell that digests foreign substances, microbes and other harmful or damaged components.)

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Inhibit the release of proinflammatory cytokines and histamine by modulating calcium influx into the cell.<sup>10</sup>

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Stabilize mast cells and regulate the basic functional properties of immune cells, thereby allowing it to inhibit “a huge panoply of molecular targets in the micromolar concentration range, either by down-regulating or suppressing many inflammatory pathways and functions.”<sup>11</sup>

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Act as a zinc ionophore, i.e., a compound that shuttles zinc into your cells.<sup>12</sup> This is one of the mechanisms that can account for the effectiveness seen with hydroxychloroquine, which is also a zinc ionophore.

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Boost interferon response to viruses, including SARS-CoV-2, by inhibiting the expression of casein kinase II (CK2)<sup>13</sup> – CK2 is an enzyme that is fundamental to controlling homeostasis at the cellular level. There is evidence that it down-regulates the ability a cell has to generate Type 1 interferon when attacked by a virus.

It does this by inhibiting retinoic acid-inducible gene I (RIG-I),<sup>14</sup> which has protein sensors that signal genetic expression of type 1 interferon by identifying the

replication of RNA viruses, such as SARS-CoV-2. Quercetin inhibits the expression of CK2, which slows the replication of RNA viruses.<sup>15</sup>

Interferons are a subset of cytokines discovered in 1957.<sup>16</sup> These cells are often the initial defense against viruses. There are two types and three forms of interferon. Within Type 1 interferon, there are alpha and beta. Type 2 interferon has the gamma form.<sup>17</sup>

The different types are based on the function of the cytokine. Type 1 interferons help cells resist viruses. Type 2 aids in responding to infections and cancer growth. The name "interferon" came from the ability of Type 1 to interfere with the virus's ability to duplicate. A cell secretes interferons when a foreign substance, like a virus, is detected.

However, the interferon does not function by attacking the virus. Instead, it tells the infected cell and the cells that surround the infected cell to make proteins that stop viral replication. In a nutshell, quercetin stops CK2 from interfering with the action of Type 1 interferon so cells receive the signal to stop viral replication.

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Modulate the NLRP3 inflammasome, an immune system component involved in the uncontrolled release of proinflammatory cytokines that occurs during a cytokine storm.<sup>18</sup>

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Prevent a wide variety of dangerous viruses from entering cells, including Ebola.<sup>19</sup>

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Exert a direct antiviral activity against SARS-CoV<sup>20,21,22</sup> — Quercetin's general antiviral capacity has been attributed to three primary mechanisms of action:

1. Inhibiting the virus' ability to infect cells
  2. Inhibiting replication of already infected cells
  3. Reducing infected cells' resistance to treatment with antiviral medication
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## Quercetin Studied as COVID-19 Treatment and Prophylaxis

As reported by MedPage Today,<sup>24</sup> Dr. Hasan Önal is currently conducting an open-label nonrandomized trial<sup>25</sup> on quercetin in Turkey. COVID-19 patients are given 1,000 milligram (mg) of quercetin per day as an active treatment, while front-line health care workers are receiving 500-mg doses as a prophylaxis. As noted by the researchers:<sup>26</sup>

*“Quercetin is reported to be effective on treatment and prophylaxis of other SARS like coronavirus infections, as a strong antioxidant and scavenger flavonoid without any adverse events. Upon this data, the investigators hypothesize that quercetin can be effective on both prophylaxis and treatment of COVID-19 cases. Therefore, the aim of this study to evaluate the possible role of quercetin on prophylaxis and treatment of COVID-19.”*

## Vitamin C Enhances Quercetin's Efficacy

Vitamin C has been shown to enhance plasma quercetin levels,<sup>27,28</sup> and the duo is the subject of the Frontiers in Immunology review article,<sup>29</sup> “Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19),” mentioned earlier.

**“ There is evidence that vitamin C and quercetin co-administration exerts a synergistic antiviral action due to overlapping antiviral and immunomodulatory properties and the capacity of ascorbate to recycle quercetin, increasing its efficacy.”**

That review, by the way, was co-written by Dr. Paul Marik, who in 2017 discovered a highly effective [vitamin C-based sepsis treatment](#). In “Quercetin and Vitamin C,” Marik and co-authors point out that:<sup>30</sup>

*“Ascorbic acid is a crucial vitamin necessary for the correct functioning of the immune system. It plays a role in stress response and has shown promising results when administered to the critically ill.*

*Quercetin is a well-known flavonoid whose antiviral properties have been investigated in numerous studies. There is evidence that vitamin C and quercetin co-administration exerts a synergistic antiviral action due to overlapping antiviral and immunomodulatory properties and the capacity of ascorbate to recycle quercetin, increasing its efficacy.*

*Safe, cheap interventions which have a sound biological rationale should be prioritized for experimental use in the current context of a global health pandemic.*

*We present the current evidence for the use of vitamin C and quercetin both for prophylaxis in high-risk populations and for the treatment of COVID-19 patients as an adjunct to promising pharmacological agents such as Remdesivir or convalescent plasma.”*

## **Vitamin C and Quercetin Both Provide Antiviral Protection**

In summary, aside from having direct viricidal effects, vitamin C:<sup>31</sup>

Supports lymphocyte activity	Increases interferon-alpha production
Modulates cytokines	Reduces inflammation
Improves endothelial dysfunction	Restores mitochondrial function

All of these effects contribute to vitamin C's antiviral effects. Like vitamin C, quercetin also has antioxidant, anti-inflammatory, antiviral, immunoprotective and immunomodulatory properties. According to Marik's review paper, many of quercetin's antiviral effects are attributable to its inhibition of:<sup>32</sup>

- Polymerases
- Proteases
- Reverse transcriptase
- DNA gyrase
- Viral capsid proteins

Quercetin also inhibits platelet aggregation,<sup>33</sup> which is pertinent with regard to COVID-19, seeing how many patients suffer abnormal blood clotting. It also has powerful anti-inflammatory effects, inhibiting lipid peroxidation and proinflammatory mediators.<sup>34</sup>

## **Quercetin and Vitamin C Work Synergistically**

Marik's paper goes on to explain the synergistic antiviral action of the two compounds together:<sup>35</sup>

*“Quercetin spontaneously oxidizes to form O-semiquinone and O-quinone/quinone methide (QQ), which can bind protein thiols forming toxic compounds. This process of both anti- and pro-oxidant effects has been named the “quercetin paradox.”*

*However, QQ can be recycled into quercetin by electron donors like NADPH or ascorbate, or form together, with glutathione either 6-glutathionyl-quercetin or 8-glutathionyl-quercetin (GSQs).*

*Importantly, if ascorbate or glutathione levels are insufficient, quercetin may be shunted to QQ and exert prooxidant effects. Therefore, we stress the importance for its co-administration with vitamin C ...*

*Even though QQ exhibits a higher affinity for glutathione than for vitamin C, the methylated metabolites of quercetin show a higher preference for ascorbate than for thiols, suggesting a cycling of activity which will exert anti-oxidant effects ...*

*The supraphysiological concentrations of ascorbate achieved with intravenous administration (i.v. 3 gr q6) are capable of free radical scavenging and electron donation, preventing either quercetin or glutathione oxidation.*

*In this scenario, ascorbate may exert antioxidant and immunoprotective effects, quercetin and its metabolites exert a concurrent antiviral response and, if quercetin-oxidized compounds are formed, they can be partially recycled by ascorbate and transported by glutathione, thus preventing their possible toxicity.*

*A multi-drug approach with quercetin and vitamin C may disrupt virus entry, replication, enzyme activity and assembly, and concurrently fortify the immune response promoting early IFNs production, modulating interleukins, promoting T cell maturation, and phagocytic activity.*

*Quercetin and ascorbic acid co-administration represents an experimental strategy for prophylaxis and treatment of several respiratory viruses, such as SARS-CoV-2.”*

## **Optimal Dosing**

According to “Quercetin and Vitamin C,”<sup>36</sup> both vitamin C and quercetin have excellent safety profiles, and oral supplementation with quercetin at doses up to 1 gram (1,000 mg) per day for three months has not resulted in any significant side effects.

“Only higher intravenously administered doses up to 51.3 mg/Kg (around 3,591 mg per individual) were associated with renal toxicity,” the paper notes. The following table shows the proposed dosages for concurrent use of vitamin C and quercetin, either as a prophylactic for high-risk groups, and/or treatment for mild to severe COVID-19 disease.



	Quercetin	Vitamin C
Prophylaxis	250–500 mg BID	500 mg BID
Mild cases	250–500 mg BID	500 mg BID
Severe Cases*	500 mg BID	3 gr q6 for 7 days

\*ARDS-like presentation, require assisted ventilation/intubation, ICU hospitalization.

Source: [Frontiers in Immunology June 19, 2020](#), Table 1

## The Importance of Zinc

While Marik’s paper does not address the use of zinc, it seems reasonable to recommend oral zinc supplementation as well, especially if you’re older. In fact, two oft-noted early symptoms of COVID-19 – the loss of taste and smell – are both symptoms of zinc deficiency.

As noted in the Integrative Medicine journal’s review<sup>37</sup> of emerging COVID-19 research, “Zinc plays a crucial role in the function of essentially all immune cells,” and “Deficiency of this critical element has a profound impact on immune response, increasing susceptibility to a variety of infections.” Like quercetin and vitamin C, zinc also has well-known antiviral properties in its own right. As noted in the Integrative Medicine journal’s review:<sup>38</sup>

*“Increasing intracellular zinc concentrations in cell culture impairs the replication of a variety of RNA viruses including SARS-CoV-1 ... In vivo evidence for zinc’s antiviral role comes from a Cochrane review that found zinc intake was associated with a significant reduction in the duration of the common cold.*

*Many of the studies showing benefit when taken during the course of an infection were in the form of a zinc lozenge. It makes sense to utilize this mode of delivery during the acute infection phase ...*

*Anosmia (loss of smell) and dysgeusia (distorted sense of taste) are commonly being reported in patients at every phase of COVID-19. These are also classic symptoms of zinc deficiency.*

*It is too early in the discovery process to determine if this is cause or effect, nonetheless zinc deficiency greatly impairs immune function, especially resistance to viral infections. Notably, inadequate dietary consumption of zinc is found in almost half the older population.”*

## **My Personal Take on This and Strong Recommendations**

I am a huge fan of zinc, quercetin and vitamin C, but it is important to understand some very basic principles before using them. It is clear in my mind that quercetin is far less expensive, is safer and is likely equally effective to hydroxychloroquine at driving zinc into the cell, where it does its job of inhibiting viral replication, and unlike hydroxychloroquine, it reduces inflammatory cytokines and also increases interferon.

However, it is important to understand that if this excellent strategy is going to be optimally effective it needs to be administered early in the disease phase – the earlier the better. Using quercetin and zinc would be best done if you were recently exposed to the virus. This way you can inhibit viral replication and keep the viral load low while your innate immune system does its work in clearing the virus.

With respect to vitamin C, it is my perception that there is major confusion in this area. It can be used in low doses of several hundred milligrams to meet nutritional requirements and support your immune system in the early phase of the illness.

However, if you're really sick and have shortness of breath, and are considering being hospitalized or are already in the hospital, then you need very high doses of vitamin C in the 10 gram to 100 gram-dose per day, either through liposomal or IV administration.

I don't recommend taking high doses of vitamin C unless you are acutely sick. The bulk of the literature reviewed here is promoting the use of vitamin C to regenerate quercetin, but I believe there are far more powerful approaches. What might that be?

It seems obvious to me that quercetin is best taken at night (with zinc) before you go to bed and you haven't eaten for at least three to four hours. You will sleep for eight hours, and if you are metabolically flexible, this is the time that you will dive into nutritional

ketosis. Ketosis will increase your NADPH levels, which is FAR superior to vitamin C at recycling antioxidants like quercetin.

The other benefit of taking quercetin at night is to take advantage of its senolytic action to remove senescent cells, which are similar to nonreplicating cancer cells that secrete powerful proinflammatory cytokines that destroy your health. You can optimize quercetin's senolytic properties if you take it while you are fasting.

## Sources and References

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- <sup>3, 24</sup> [MedPage Today July 1, 2020](#)
- <sup>6</sup> [Journal of Virology 2004 Oct;78\(20\):11334-9](#)
- <sup>7</sup> [ChemRxiv.org March 11, 2020 \(PDF full study\), Table 3](#)
- <sup>8</sup> [Greenstarsproject.org March 27, 2020](#)
- <sup>9, 11</sup> [Nutrients 2016 Mar; 8\(3\): 167, 5.1.2 Mechanism of Action](#)
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- <sup>33, 34</sup> [Frontiers in Immunology June 19, 2020 DOI: 10.3389/fimmu.2020.01451, Biology of Quercetin](#)
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