

# Zinc Is Key for COVID-19 Treatment and Prevention

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✓ Fact Checked

January 11, 2023

## STORY AT-A-GLANCE

- › Zinc prevents viral replication inside your cells, but is poorly absorbed. Zinc ionophores (zinc transport molecules) such as quercetin, epigallocatechin-gallate (EGCG) and the drug hydroxychloroquine facilitate zinc uptake
- › A combination of zinc with a zinc ionophore was in 2010 shown to inhibit SARS coronavirus in vitro. In cell culture, it also blocked viral replication within minutes
- › Zinc deficiency impairs immune function
- › Preliminary research found COVID-19 patients with plasma zinc levels below 50 mcg/dl at admission had a 2.3 times greater risk of in-hospital death than those with a zinc level of 50 mcg/dl or higher
- › Other research found COVID-19 patients were more likely to be deficient in zinc than healthy controls. Zinc deficient patients also had worse outcomes and higher rates of death. While 70.4% of zinc deficient patients developed complications, only 30% of those with sufficient levels developed complications

Your immune system is your first line of defense against all disease, especially infectious disease, and there are many different ways to boost your immune system and improve its function. One nutrient that plays a very important role in your immune system's ability to ward off viral infections is zinc.

**Zinc** gluconate,<sup>1</sup> zinc acetate<sup>2</sup> and zinc sulphate<sup>3</sup> have all been shown to reduce the severity and duration of viral infections such as the common cold. Zinc also appears to

be the key ingredient in treatment protocols using hydroxychloroquine (HCQ).

The reason for this is because HCQ is a zinc ionophore (zinc transport molecule),<sup>4,5</sup> meaning it's a drug that improves your cells' uptake of zinc. Once inside your cells, zinc prevents viral replication.<sup>6</sup> This is also why zinc and zinc ionophores need to be taken very early in the illness, or as a prophylactic.

The problem is that zinc is largely insoluble and cannot easily enter through the fatty wall of your cells. Getting all the way into the cell is crucial, as this is where the viral replication occurs. This is why zinc ionophores are so important.

Aside from hydroxychloroquine, other natural, and safer, zinc ionophores include quercetin and epigallocatechin-gallate (EGCG). If given early, zinc along with a zinc ionophore should, at least theoretically, help lower the viral load and prevent the immune system from becoming overloaded.

## **Zinc Is Crucial for Healthy Immune Function**

Zinc is crucial for healthy immune function<sup>7</sup> – like vitamin D, it actually helps regulate your immune function<sup>8</sup> – and a combination of zinc with a zinc ionophore was in 2010 shown to inhibit SARS coronavirus in vitro. In cell culture, it also blocked viral replication within minutes.<sup>9</sup>

Importantly, zinc deficiency has been shown to impair immune function.<sup>10</sup> As noted in a 2013 paper on zinc deficiency:<sup>11</sup>

*"Zinc is a second messenger of immune cells, and intracellular free zinc in these cells participate in signaling events. Zinc ... is very effective in decreasing the incidence of infection in the elderly. Zinc not only modulates cell-mediated immunity but is also an antioxidant and anti-inflammatory agent."*

Similarly, the September 2020 paper in Medical Hypotheses, "Does Zinc Supplementation Enhance the Clinical Efficacy of Chloroquine / Hydroxychloroquine to Win Today's Battle Against COVID-19?" points out that:<sup>12</sup>

*"Besides direct antiviral effects, CQ/HCQ [chloroquine and hydroxychloroquine] specifically target extracellular zinc to intracellular lysosomes where it interferes with RNA-dependent RNA polymerase activity and coronavirus replication.*

*As zinc deficiency frequently occurs in elderly patients and in those with cardiovascular disease, chronic pulmonary disease, or diabetes, we hypothesize that CQ/HCQ plus zinc supplementation may be more effective in reducing COVID-19 morbidity and mortality than CQ or HCQ in monotherapy. Therefore, CQ/HCQ in combination with zinc should be considered as additional study arm for COVID-19 clinical trials."*

## **Low Zinc Levels Increase COVID-19 Death Risk**

Preliminary data also suggest people with low zinc levels are more likely to die from COVID-19 than those with higher levels. The research<sup>13,14,15,16,17</sup> was presented at the European Society of Clinical Microbiology and Infectious Disease (ESCMID) Conference on Coronavirus Disease,<sup>18</sup> held online September 23 through September 25, 2020, and posted<sup>19</sup> on the preprint server medRxiv October 11, 2020.

**“ Each unit increase of plasma zinc at admission to hospital was associated with a 7% reduced risk of in-hospital mortality. Having a plasma zinc level lower than 50 mcg/dl at admission was associated with a 2.3 times increased risk of in-hospital death compared with those patients with a plasma zinc level of 50 mcg/dl or higher.”**

In the video above, Dr. John Campbell reviews this and other zinc research. As noted by the authors of this study,<sup>20</sup> "Zinc balances immune responses and also has a proven

direct antiviral action against some viruses." As mentioned, zinc's primary antiviral action is to impair viral replication inside the cell.

To evaluate the importance of plasma zinc levels on COVID-19 outcomes, the researchers did a retrospective analysis of 249 COVID-19 patients admitted to a hospital in Barcelona, Spain, between March 15 and April 30, 2020, for whom fasting plasma zinc levels were recorded. The average patient age was 63.

Patients who had low zinc levels upon admission were found to have higher levels of inflammation during the course of their illness, and they were also more likely to die from complications related to COVID-19. As reported by Medical Xpress:<sup>21</sup>

*"Mean baseline zinc levels among the 249 patients were 61 mcg/dl. Among those who died, the zinc levels at baseline were significantly lower at 43 mcg/dl vs 63.1 mcg/dl in survivors.*

*Higher zinc levels were associated with lower maximum levels of interleukin-6 (proteins that indicate systemic inflammation) during the period of active infection.*

*After adjusting by age, sex, severity and receiving hydroxychloroquine, statistical analysis showed each unit increase of plasma zinc at admission to hospital was associated with a 7% reduced risk of in-hospital mortality.*

*Having a plasma zinc level lower than 50 mcg/dl at admission was associated with a 2.3 times increased risk of in-hospital death compared with those patients with a plasma zinc level of 50 mcg/dl or higher."*

## **Zinc Deficiency Linked to Poor COVID-19 Outcomes**

Another paper<sup>22</sup> reviewed by Campbell was published in the November 2020 issue of the International Journal of Infectious Diseases. Here, they found that people admitted to the hospital with COVID-19 related symptoms were more likely to be deficient in zinc than healthy controls. The median zinc level among hospitalized COVID-19 patients was

74.5 mcg/dl, compared to 105.8 mcg/dl in the control group. As reported by the authors:<sup>23</sup>

*"Amongst the COVID-19 patients, 27 (57.4%) were found to be zinc deficient. These patients were found to have higher rates of complications, acute respiratory distress syndrome (18.5% vs 0%), corticosteroid therapy, prolonged hospital stay, and increased mortality (18.5% vs 0%). The odds ratio (OR) of developing complications was 5.54 for zinc deficient COVID-19 patients."*

Importantly, while 70.4% of zinc deficient patients developed complications, only 30% of those with sufficient levels developed complications. As noted by Campbell, here we see that healthy controls had far higher zinc levels than patients with milder illness in the Spanish study.

The hospitalized patients also had higher levels on average. This raises the question as to whether the Spanish cutoff level of 50 mcg/dl might be too low still. He points out that "normal" levels of zinc are between 72 mcg/dl and 144 mcg/dl. This seems to support the findings of the Spanish study, seeing how all of the patients were on the low side.

## **Zinc Is a Key Component of MATH+ Protocol**

Among the most effective treatment protocols for COVID-19 is the [MATH+ Protocol](#),<sup>24</sup> developed by the Front Line COVID-19 Critical Care Working Group<sup>25</sup> (FLCCC).

In the interview above, Dr. Paul Marik explains how the COVID-19 critical care protocol grew out of his sepsis treatment (a core ingredient of which is vitamin C), as he and other doctors noticed there were many similarities between sepsis and severe COVID-19 infection, in particular the out-of-control inflammatory cascade.

There are also distinct differences between the two conditions, and to address those, Marik and nine other physicians founded the FLCCC and began developing a modified protocol specifically for COVID-19.

Zinc is one of the central components of this protocol. As of its July 2020 update, the protocol also includes the use of quercetin to facilitate zinc uptake. There are now MATH+ protocols<sup>26</sup> for prophylaxis, mild symptoms that can be treated at home, and a full clinical in-hospital critical care protocol.

The group has issued several updates since April 2020, so be sure to download the latest versions from the Eastern Virginia Medical School COVID Care for Clinicians site.<sup>27</sup>

## **Natural Zinc Transporters – Quercetin and EGCG**

As mentioned, quercetin<sup>28</sup> and EGCG are natural zinc ionophores that can do the same job as HCQ. According to a study<sup>29</sup> published in 2014, many of the biological actions of quercetin and EGCG actually appear to be related to their ability to increase cellular zinc uptake. As explained by the authors:<sup>30</sup>

*"Labile zinc, a tiny fraction of total intracellular zinc that is loosely bound to proteins and easily interchangeable, modulates the activity of numerous signaling and metabolic pathways. Dietary plant polyphenols such as the flavonoids quercetin (QCT) and epigallocatechin-gallate act as antioxidants and as signaling molecules.*

*Remarkably, the activities of numerous enzymes that are targeted by polyphenols are dependent on zinc. We have previously shown that these polyphenols chelate zinc cations and hypothesized that these flavonoids might be also acting as zinc ionophores, transporting zinc cations through the plasma membrane.*

*To prove this hypothesis, herein, we have demonstrated the capacity of QCT and epigallocatechin-gallate to rapidly increase labile zinc in mouse hepatocarcinoma Hepa 1-6 cells as well as, for the first time, in liposomes ... The ionophore activity of dietary polyphenols may underlay the raising of labile*

*zinc levels triggered in cells by polyphenols and thus many of their biological actions."*

Aside from increasing zinc uptake, both quercetin and EGCG also inhibit 3CL protease<sup>31</sup> – an enzyme used by SARS coronaviruses to infect healthy cells.<sup>32</sup> As explained in a 2020 paper<sup>33</sup> in Nature, 3CL protease "is essential for processing the polyproteins that are translated from the viral RNA."

And, according to another 2020 study,<sup>34</sup> the ability of quercetin, EGCG and certain other flavonoids to inhibit SARS coronaviruses "is presumed to be directly linked to suppress the activity of SARS-CoV 3CLpro in some cases."

Niacin (vitamin B3) and selenium also improve the absorption and bioavailability of zinc. For example, a study<sup>35</sup> published in 1991 demonstrated that when young women were on a vitamin B6-deficient diet, their serum zinc declined, suggesting B6 deficiency affected zinc metabolism such that "absorbed zinc was not available for utilization."

A more in-depth exploration and explanation of both niacin and selenium's relationship to zinc is provided in the 2008 paper, "Zinc, Metallothioneins and Longevity: Interrelationships With Niacin and Selenium."<sup>36</sup>

## **More Support for Quercetin**

Support for the use of quercetin against COVID-19 has also been reported by the Green Stars Project.<sup>37</sup> Using the supercomputer SUMMIT, Oak Ridge National Lab researchers looked for molecules capable of inhibiting the COVID-19 spike protein from interacting with human cells. Quercetin is fifth on that list.<sup>38</sup>

Quercetin is also a potent antiviral in general. As detailed in "[Quercetin Lowers Your Risk for Viral Illnesses](#)," mechanisms of action that can make it useful against COVID-19 include:

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Inhibiting virus' ability to infect cells<sup>39</sup>

Inhibiting replication of already infected cells

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Reducing infected cells' resistance to treatment with antiviral medication

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Inhibiting lipopolysaccharide (LPS)-induced tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) production in macrophages.<sup>40</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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Inhibiting release of proinflammatory cytokines and histamine by modulating calcium influx into the cell<sup>41</sup>

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Stabilizing mast cells<sup>42</sup>

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Regulating the basic functional properties of immune cells<sup>43</sup>

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Down-regulating or suppressing inflammatory pathways and functions<sup>44</sup>

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## Zinc-to-Copper Ratio Can Impact Immune Function

When it comes to zinc supplementation, more is not necessarily better. In fact, it can frequently backfire if you do not also maintain a healthy zinc-to-copper ratio. As explained by Chris Masterjohn, who has a Ph.D. in nutritional sciences,<sup>45</sup> in an article<sup>46</sup> and series of Twitter posts:<sup>47</sup>

*"In one study, 300mg/day of zinc as two divided doses of 150 mg zinc sulfate decreased important markers of immune function, such as the ability of immune cells known as polymorphonuclear leukocytes to migrate toward and consume bacteria.*

*The most concerning effect in the context of COVID-19 is that it lowered the lymphocyte stimulation index 3 fold. This is a measure of the ability of T cells to increase their numbers in response to a perceived threat. The reason this is so*



*concerning in the context of COVID-19 is that poor outcomes are associated with low lymphocytes ...*

*The negative effect on lymphocyte proliferation found with 300 mg/day and the apparent safety in this regard of 150 mg/d suggests that the potential for hurting the immune system may begin somewhere between 150-300 mg/d ...*

*It is quite possible that the harmful effect of 300 mg/d zinc on the lymphocyte stimulation index is mediated mostly or completely by induction of copper deficiency ...*

*The negative effect of zinc on copper status has been shown with as little as 60 mg/d zinc. This intake lowers the activity of superoxide dismutase, an enzyme important to antioxidant defense and immune function that depends both on zinc and copper ...*

*A study done with relatively low intakes of zinc suggested that acceptable ratios of zinc to copper range from 2:1 to 15:1 in favor of zinc. Copper appears safe to consume up to a maximum of 10 mg/d.*

*Notably, the maximum amount of zinc one could consume while staying in the acceptable range of zinc-to-copper ratios and also staying within the upper limit for copper is 150 mg/d."*

Another factor to keep in mind is that certain additives can inhibit zinc absorption, which is the complete opposite of what you're looking for. For instance, research has shown citric acid, glycine, mannitol and sorbitol can reduce zinc absorption,<sup>48</sup> so zinc lozenges containing these ingredients may be less useful.

## **How Much Zinc Do You Need?**

That said, the recommended dietary allowance for zinc in the U.S is 11 mg for adult men and 8 mg for adult women, with slightly higher doses recommended for pregnant and breastfeeding women.<sup>49</sup>

As a prophylactic against COVID-19 and other viral infections, Masterjohn recommends taking 7 mg to 15 mg of zinc four times a day, ideally on an empty stomach, or with a phytate-free food. He also recommends getting at least 1 mg of copper from food and supplements for every 15 mg of zinc you take.

Last but not least, remember there are many food sources of zinc, so a supplement may not be necessary. I eat about three-quarters of a pound of ground bison or lamb a day, which provides 20 mg of zinc. I personally don't take any zinc supplement other than what I get from my food.

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