Zinc Ionophores: Optimism for the Immune System

Vladimir Zelenko, M.D.

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Summary

Zinc Ionophores have broad spectrum antiviral properties against RNA viruses such as COVID-19. The emerging scientific data from peer reviewed journals and clinical trials show that zinc ionophores, including Quercetin, may have significant effects against COVID-19. Zinc ionophores transport extracellular Zinc (Zn^{2+}) ions across a cell membrane, and have been studied for their antiviral and anti-cancer activities. Studies show Quercetin is a natural antioxidant and anti-inflammatory compound contained in abundance fruits and vegetables - it can be purchased over the counter in supplement form.[1] Optimizations to Quercetin as a supplement can likely provide an even stronger effect against COVID-19 by including Zinc, Vitamin C and Vitamin D. This paper outlines the scientific research that provides the justification for bringing these four (4) molecules together in one capsule to optimize the immune system to fight COVID-19.

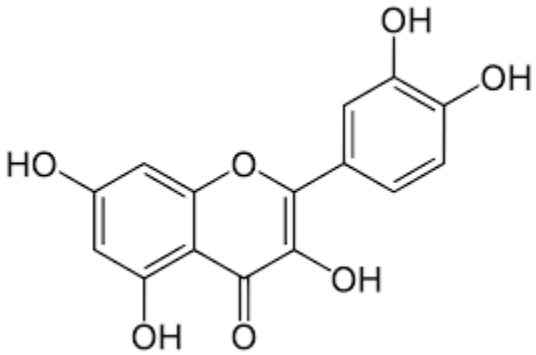
1. Quercetin (Zinc Ionophore)
2. Zinc
3. Vitamin C
4. Vitamin D

Recent data, from peer reviewed studies, scientific data and clinical trials show that synergistic supplement combinations involving zinc and the zinc ionophore quercetin may be effective antiviral prevention and therapeutic agents against COVID-19. An ionophore transports molecules inside cell membranes. COVID-19 viral entry and replication in cells is inhibited by zinc - significantly

[1] https://www.sciencedirect.com/topics/neuroscience/quercetin

reducing COVID-19 infection and mortality.[2] Generally, the more zinc that can be brought into respiratory cells, the better off a COVID-19 patient will be.

Quercetin



Quercetin, a natural anti-oxidant and anti-inflammatory compound contained in abundance in various fruits and vegetables, is a zinc ionophore. Zinc ionophores help transport zinc inside the cells COVID-19 attacks - respiratory cells, providing significant antiviral action against COVID-19.[3] Additionally, Quercetin has been shown to be a potent inhibitor of coronaviruses by inhibiting cellular entry as well as inhibiting proinflammatory cytokines.[4] One of the hallmarks of COVID-19 is

[2] R. Derwand, M. Scholz, "Does zinc supplementation enhance the clinical efficacy of chloroquine/hydroxychloroquine to win today's battle against COVID-19?", Med. Hypoth. 142 (2020), 109815 https://doi.org/10.1016/j.mehy.2020.109815 R. Derwand, M. Scholz, V. Zelenko. COVID-19 outpatients: early risk-stratified treatment with zinc plus low-dose hydroxychloroquine and azithromycin: a retrospective case series study Int. J. Antimicrob. Agents 56 (2020), 106214 https://doi.org/10.1016/j.ijantimicag.2020.106214 I. Wessels, B. Rolles, L. Rink1. The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis, Front. Immunol. 11 (2020), 1712 https://doi.org/10.3389/fimmu.2020.01712 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7365891/

[3] H. Dabbagh-Bazarbachi, G. Clergeaud, I.M. Quesada, M. Ortiz, C.K. O'Sullivan, J.B. Fernández-Larrea. Zinc ionophore activity of quercetin and epigallocatechin-gallate: from Hepa 1-6 cells to a liposome model. J. Agric. Food. Chem. 62(32) (2014) 8085-8093. https://doi.org/10.1021/jf5014633 http://www.ncbi.nlm.nih.gov/pubmed/25050823

[4] L. Yi, Z. Li, K. Yuan et al. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J. Virol. 78 (20) (2004), 11334-11339.

an imbalanced immune response cascading to cytokine storms and then hyper inflammation which then can lead to acute respiratory distress syndrome (ARDS).

Quercetin has been shown to inhibit proinflammatory cytokine production as well as inflammation due to its antioxidant properties, amongst others. By inhibiting destructive inflammation and potentially the entire cascade, quercetin may prevent severe damage to the respiratory system amongst other organs.[5]

Specifically with respect to respiratory infections:

- A randomized, double-blinded, placebo-controlled trial suggested Quercetin significantly lowered upper respiratory tract infection (URTI) severity (36% reduction, $P = 0.020$) and URTI total sick days (31% reduction, $P = 0.048$) in individuals (>40 years) compared with placebo.[6]

- With respect to influenza, an RNA respiratory virus like COVID-19, treatment with quercetin produced significant increases in the pulmonary concentrations of various antioxidants and a protective effect on lung morphology and a significant decrease in the number of infiltrating cells.[7]

Recent clinical trial data shows that the combination of Vitamin C and Quercetin provided strong preventative protection against COVID-19 infection of

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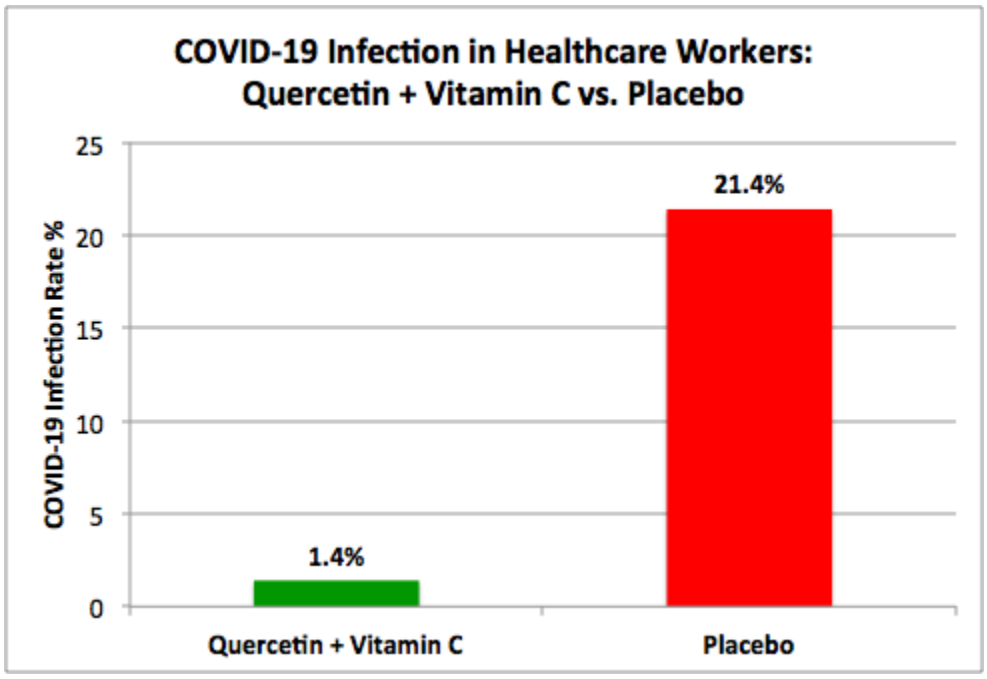
https://doi.org/10.1128/JVI.78.20.11334-11339.2004
http://www.ncbi.nlm.nih.gov/pubmed/15452254

[5]A. Saeedi-Boroujeni, M.R. Mahmoudian-Sani. Anti-inflammatory potential of Quercetin in COVID-19 treatment. J. Inflamm. 18 (3) (2021), https://doi.org/10.1186/s12950-021-00268-6

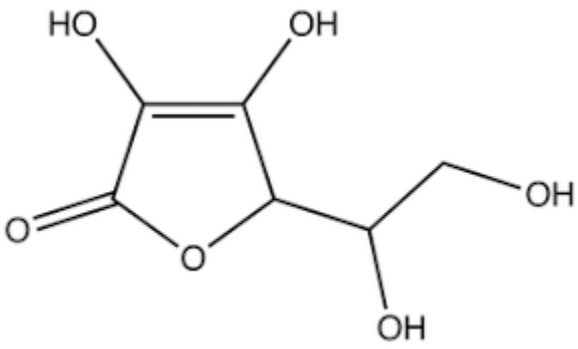
[6] S.A. Heinz, D.A. Henson, M.D. Austin, F. Jin, D.C. Nieman. Quercetin supplementation and upper respiratory tract infection: a randomized community clinical trial. Pharmacol Res. 62 (3) (2010), 237-242. https://doi.org/10.1016/j.phrs.2010.05.001 http://www.ncbi.nlm.nih.gov/pubmed/20478383

[7] P. Kumar, M. Khanna, V. Srivastava, et al. Effect of quercetin supplementation on lung antioxidants after experimental influenza virus infection. Exp. Lung Res. 31(5) (2005), 449-459. https://doi.org/10.1080/019021490927088 http://www.ncbi.nlm.nih.gov/pubmed/16019982. P. Kumar, S. Sharma, M. Khanna, H.G. Raj. Effect of quercetin on lipid peroxidation and changes in lung morphology in experimental influenza virus infection. Int. J. Exp. Pathol. 84(3) (2003) 127-134. https://doi.org/10.1046/j.1365-2613.2003.00344.

healthcare workers when compared to the control group as shown below.[8] Specifically, 1.4% (1 out of 71 healthcare workers) of healthcare workers using Quercetin and Vitamin C combination were infected with COVID-19 vs. 21.4% (9 out of 42 healthcare workers) of healthcare workers in the control group were infected with COVID-19 (Total Subjects, n = 113).



Vitamin C



[8]B. Arslan, N.U. Ergun, S. Topuz, et al. Synergistic Effect of Quercetin and Vitamin C Against COVID-19: Is a Possible Guard for Front Liners. https://europepmc.org/article/ppr/ppr239932; 2020.

Vitamin C is a potent antioxidant, likely immune system optimizer and has been shown to work synergistically with quercetin, likely increasing quercetin's bioavailability.[9] As per Integrative Medicine's 4th edition, quercetin is a poorly absorbed nutrient but Vitamin C increases the absorption of quercetin and recommends that Quercetin should be blended with Vitamin C.[10] Specifically, 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.[11] It has been shown that Quercetin and Vitamin C markedly inhibited mRNA expression of pro-inflammatory cytokines - as the release of inflammatory cytokines are behind acute respiratory distress syndrome.[12] The quercetin and vitamin C combination can prevent the exacerbation of inflammation.

Zinc[13] is a well known supplement that is generally contained in standard multivitamins. It provides immune support amongst other functions. Zinc inhibits

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[9]D. Jafari, A. Esmaeilzadeh, M. Mohammadi-Kordkhayli, N. Rezaei (2019) Vitamin C and the Immune System. In: Mahmoudi M., Rezaei N. (eds) Nutrition and Immunity. Springer, Cham. https://doi.org/10.1007/978-3-030-16073-9_5
F. Jin, D. Nieman, R. Shanely, et al. The variable plasma quercetin response to 12-week quercetin supplementation in humans. Eur. J. Clin. Nutr. 64 (2010), 692-697 https://doi.org/10.1038/ejcn.2010.91

[10] https://www.sciencedirect.com/topics/neuroscience/quercetin

[11] C.B.R M. Luciano, B. Max, J.D. Catravas, P.E. Marik. Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19)., Front. Immunol. 11 (2020), 1451 https://dx.doi.org/10.3389%2Ffimmu.2020.01451 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7318306/

[12] J.Y. Choe, S.K. Kim. Quercetin and Ascorbic Acid Suppress Fructose-Induced NLRP3 Inflammasome Activation by Blocking Intracellular Shuttling of TXNIP in Human Macrophage Cell Lines. Inflammation 40 (2017), 980-994 https://doi.org/10.1007/s10753-017-0542-4 https://link.springer.com/article/10.1007%2Fs10753-017-0542-4

[13] I. Wessels, B. Rolles, L. Rink1. The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis, Front. Immunol. 11 (2020), 1712 https://doi.org/10.3389/fimmu.2020.01712 https://www.frontiersin.org/articles/10.3389/fimmu.2020.01712/full . All statements from this section without a citation come from this article, either directly or paraphrased.

coronavirus replication and is a general stimulant of antiviral immunity.[14] Higher levels of intracellular zinc showed to increase intracellular pH; which affect on RNA-dependent RNA polymerase and decreases the replication mechanism of RNA viruses (e.g. COVID-19).[15] Therefore, zinc ionophores (e.g. Quercetin) can likely be used with zinc supplement to act as antiviral against many RNA viruses including influenza and COVID-19. Suggested benefits of zinc supplementation along with zinc ionophores to prevent and treat COVID-19 and other respiratory tract infections are supported by countless studies.[16] In most cases, prophylactic and early use of zinc supplementation was more effective than late therapeutic proceedings. Up to 30% of the everyday respiratory infections, briefly named "common cold," are due to infections with coronaviruses. Studies showed reduced symptom severity, reduced frequency, and duration of the common cold after zinc administration depending on dosage, zinc compound and the start time after initial symptoms.[17]

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[14] I. Wessels, B. Rolles, L. Rink1. The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis, Front. Immunol. 11 (2020), 1712 https://doi.org/10.3389/fimmu.2020.01712 https://www.frontiersin.org/articles/10.3389/fimmu.2020.01712/full .

[15] A. Ahmed, A. Alqattan. The Study of Quadruple Therapy Zinc, Quercetin, Bromelain and Vitamin C on the Clinical Outcomes of Patients Infected With COVID-19, Ministry of Health, Saudi Arabia, https://clinicaltrials.gov/ct2/show/NCT04468139?term=NCT04468139&rank=1

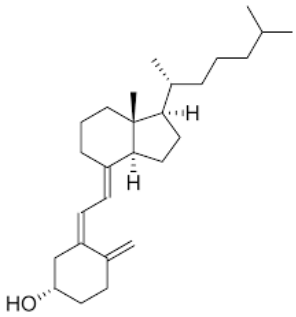
[16]P.M. Carlucci, T. Ahuja, C. Petrilli, H. Rajagopalan, S. Jones, J. Rahimian. Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. J Med Microbiol. 69(10) 2020, 1228-1234. https://doi.org/10.1099/jmm.0.001250 https://pubmed.ncbi.nlm.nih.gov/32930657/ , R. Derwand, M. Scholz, V. Zelenko. COVID-19 outpatients: early risk-stratified treatment with zinc plus low-dose hydroxychloroquine and azithromycin: a retrospective case series study Int J Antimicrob Agents 56 (2020), 106214 https://doi.org/10.1016/j.ijantimicag.2020.106214 G. Dubourg, J.C. Lagier, Ph Brouqui, J.P. Casalta, V. Jacomo, B. La Scola, J.M. Rolain, D. Raoult. Low blood zinc concentrations in patients with poor clinical outcome during SARS-CoV-2 infection: is there a need to supplement with zinc COVID-19 patients?, J. Microbiol. Immunol. Infec. (2021), in press https://doi.org/10.1016/j.jmii.2021.01.012 https://www.sciencedirect.com/science/article/pii/S1684118221000268 I. Wessels, B. Rolles, L. Rink1. The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis, Front. Immunol. 11 (2020), 1712 https://doi.org/10.3389/fimmu.2020.01712 https://www.frontiersin.org/articles/10.3389/fimmu.2020.01712/full (Table 1).

[17] https://www.vladimirzelenkomd.com/ ; A.J. te Velthuis, S.H. van den Worm, A.C. Sims, R.S. Baric, E.J. Snijder, N.J. van Hemert. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog. 6(11) (2010), e1001176. https://doi.org/10.1371/journal.ppat.1001176 https://pubmed.ncbi.nlm.nih.gov/21079686/

Zinc deficiency is very common especially in the elderly, diabetics, cancer patients, asthma, immunosuppressed and obese - all of which have higher levels of mortality for COVID-19. Furthermore, zinc deficiency is associated with increased risk of infectious disease, pneumonia and severity of COVID-19. Conversely, zinc supplementation is associated with a significant decrease in COVID-19 mortality as long as it is delivered with a zinc ionophore.[18]

In short, a balanced zinc homeostasis is essential. Zinc supplementation improves the mucociliary clearance, strengthens the integrity of the epithelium, decreases viral replication, preserves antiviral immunity, attenuates the risk of hyper-inflammation, supports anti-oxidative effects and thus reduces lung damage and minimizes secondary infections. Especially older subjects, patients with chronic diseases and most of the remaining COVID-19 risk groups would most likely benefit.

Vitamin D-3[19]



[18] P.M. Carlucci, T. Ahuja, C. Petrilli, H. Rajagopalan, S. Jones, J. Rahimian. Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. J. Med. Microbiol. 69(10) 2020, 1228-1234. https://doi.org/10.1099/jmm.0.001250 https://pubmed.ncbi.nlm.nih.gov/32930657/ R. Derwand, M. Scholz, V. Zelenko. COVID-19 outpatients: early risk-stratified treatment with zinc plus low-dose hydroxychloroquine and azithromycin: a retrospective case series study Int. J. Antimicrob. Agents 56 (2020), 106214 https://doi.org/10.1016/j.ijantimicag.2020.106214

[19] J.P. Bilezikian, D. Bikle, M. Hewison, M. Lazaretti-Castro, A.M. Formenti, A. Gupta, M.V. Madhavan, N. Nair, V. Babalyan, N. Hutchings, N. Napoli, D. Accili, N. Binkley, D.W. Landry, and A. Giustina. Vitamin D and COVID-19, Eur. J. Endocrinol. 183 (2020), R133-R147 https://doi.org/10.1530/EJE-20-0665 https://eje.bioscientifica.com/view/journals/eje/183/5/EJE-20-0665.xml

Vitamin D is essential to a healthy immune system as it initiates the adaptive immune response. Clinical trial data shows that Vitamin D supplementation is safe and protects against acute respiratory tract infection mortality whereas low levels of vitamin D are associated with higher risk for infection and mortality.[20] In addition, a meta-analysis of COVID-19 studies shows that over 90% of studies report positive effects of Vitamin D against COVID-19.[21]

Vitamin D promotes the expression of a protein called cathelicidin which is crucial to antiviral immunity via the induction of cathelicidin and defensins, which can block viral entry into cells as well as suppress viral replication. Additionally, Vitamin D via cathelicidin promotes antimicrobial function as well as other functions including the stimulation of T cells into the site of infection which inhibit the proinflammatory processes, and promotion of the clearance of respiratory pathogens by inducing apoptosis and autophagy of infected epithelial cells. In addition vitamin D promotes the killing of pneumococcus by stimulating neutrophils via a range of mechanisms. Over the last 10 years, vitamin D deficiency has also been linked to a wide range of common infectious diseases, such as pneumonia, influenza, amongst others.

The link between vitamin D and viral infections arose from the observation of the seasonality of vitamin D with lower levels in the winter and concomitant increases in influenza. Conversely, in summer, serum levels of Vitamin D increase and influenza virtually disappears, except during pandemics. Even in pandemics, most deaths occur during cold months.

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[20] A.R. Martineau, D.A. Jolliffe, R.L. Hooper, L. Greenberg, J.F. Aloia, P. Bergman, G. Dubnov-Raz, S. Esposito, D. Ganmaa, A.A. Ginde, E.C. Goodall, C.C. Grant, C.J. Griffiths, W. Janssens, I. Laaksi, S. Manaseki-Holland, D. Mauger, D.R. Murdoch, R. Neale, J.R. Rees, S. Simpson Jr, I. Stelmach, G.T. Kumar, M. Urashima, C.A. Cam. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data, BMJ 356 (2017), i6583 https://doi.org/10.1136/bmj.i6583 https://www.bmj.com/content/356/bmj.i6583

[21] https://vdmeta.com/

The Zelenko Protocol[22]

Since March 2020, my team has successfully treated over 3,000 patients with Covid-19 with the Zelenko Protocol. Our high-risk patient survival rate was >99.3% (0.7% mortality) which represents a radical improvement when compared to national data of high-risk patients with a survival rate of 92.5% (7.5% mortality). My team has successfully prophylaxed (prevention) a similar number of patients against COVID-19 with the Zelenko Protocol, with a patient survival rate of 100%. I have provided counsel to governments, physicians and hospital networks regarding prophylaxis and prehospital care of Covid-19 and I am fully familiar with their results.

Based on this real world experience, peer reviewed literature and clinical trial data, this supplement combination has significantly improved patient outcomes and should be considered as part of the armamentaria against Covid-19. As part of the Zelenko Protocol for COVID-19, I recommend the following for the prophylaxis of low and moderate risk patients:

- Elemental Zinc 25mg 1 time a day[23]
- Vitamin D 5000iu 1 time a day
- Vitamin C 800mg 1 time a day[24]
- Quercetin 500mg 1 time a day

Treatment of low risk patients:

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[22] https://www.vladimirzelenkomd.com/

[23] I. Wessels, B. Rolles, L. Rink1. The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis, Front. Immunol. 11 (2020), 1712 https://doi.org/10.3389/fimmu.2020.01712

[24] C.B.R M. Luciano, B. Max, J.D. Catravas, P.E. Marik. Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19)., Front. Immunol. 11 (2020), 1451 https://dx.doi.org/10.3389%2Ffimmu.2020.01451 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7318306/

- Elemental Zinc 50mg 1 time a day for 7 days[25]
- Quercetin 500mg 2-3 times a day for 7 days[26]
- Vitamin C 800mg 1 time a day for 7 days
- Vitamin D3 5000iu 1 time a day for 7 days

[25] I. Wessels, B. Rolles, L. Rink1. The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis, Front. Immunol. 11 (2020), 1712 https://doi.org/10.3389/fimmu.2020.01712 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7365891/

[26] C.B.R M. Luciano, B. Max, J.D. Catravas, P.E. Marik. Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19)., Front. Immunol. 11 (2020), 1451 https://dx.doi.org/10.3389%2Ffimmu.2020.01451 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7318306/

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