

REVIEW ARTICLE

## Zinc, Ionophores and Long-Haul COVID

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### ABSTRACT

*During the course of the COVID pandemic, long haul symptoms or “long COVID” has become an area of growing concern as it effects up to 30 percent of those infected with the virus. Long term loss of smell (anosmia), taste (ageusia), general fatigue and malaise are common manifestations of long COVID. These symptoms overlap with those present in many cases, both acute and chronic, of zinc and vitamin D deficiency. This suggests that repletion of these and other essential nutrients can help to minimize susceptibility to COVID and its progression. A review of zinc and its ionophores has been a piece of the acquired immunity puzzle that is in need of further attention in the context of long COVID. Thus far polyphenolic molecules with strong zinc ionophoric activity in descending order include clioquinol (CQ), pyrithione (PT), epigallocatechin galate (EGCG), quercetin, curcumin, tannic acid and luteolin. The drug Hydroxychloroquine (HCQ) is also a zinc ionophore, while ivermectin (IVM) displays some characteristics of a zinc ionophore. Zinc is able to shut down the RNA dependent RNA Polymerase or replicase enzymes, thereby preventing corona virus replication. However, it must get past the cellular membrane in order to do so. Ionophores of zinc provide this possibility, which may help to prevent both infection by SARS-CoV-2 and other viruses, as well as the post viral syndrome known as long COVID.*

Keywords: Long COVID, zinc, zinc ionophores, epigallocatechin galate, quercetin, hydroxychloroquine, ivermectin, clioquinol, pyrithione, curcumin, tannic acid, luteolin.

### INTRODUCTION

Owing to its involvement in numerous biochemical pathways and its actions in hearing, taste, cell mediated immunity, anti-oxidant activity, cell membrane stabilization, anti-inflammatory and anti-viral effects, zinc plays a pivotal role in disease pathogenesis (Gaby, 2011). Zinc is a structural element in enzymes, receptors, cytokines, growth factors and transcription factors that regulate cellular signalling and other biological activities (Fukada et al., 2011). Zinc deficiency symptoms are illustrated in Table 1.

Long COVID symptoms include many of those illustrated in the above table. However, post-viral syndrome with many of the same sequelae has been a feature of many different viruses and has been described in recent as well as past literature for many years (Stefano, 2021) (Dani et al., 2021). The extended duration of long COVID symptoms may be potentially attributed in part to compromised cell and antibody mediated immune responses, as well as lymphopenia and thymic atrophy – characteristics common to zinc deficiency (Fukada et al., 2011).

One potential reason as to why long COVID symptoms persist could be that zinc and other nutritional deficiencies are not being addressed with conventional “standard of care” medicine. This is generally defined here as isolation, palliation, masking, social-distancing, over-the-counter anti-pyretics, analgesics or antitussives and fluid administration during initial viral symptoms. Then as symptoms increase in severity, hospitalization and administration of medications such as Remdesivir, Dexamethasone and other antivirals (COVID-19 Treatment Guidelines).

**Table 1.** Zinc Deficiency Symptoms (Prasad, 1985)

Ear, nose and throat	impaired taste and smell
Psychiatric	anorexia, pica, depression, impaired concentration, jitteriness, photophobia, erectile dysfunction
Developmental	short stature, hypogonadism (males)
Dermatological	dermatitis, alopecia, white spots on fingernails
Gastroenterological	diarrhea
Ophthalmological	night blindness, blepharitis
Neurological	intentional tremor
Endocrinological	low sperm count, low serum testosterone
Hematological	anemia
Immunological	impaired wound healing, impaired immunity

Correcting zinc deficiency requires that zinc adequately penetrates into all cells. The co-administration of zinc ionophores, augments repletion and subsequent recovery, in addition to providing an auxiliary of therapeutic benefits (Celik, Gencay & Ocoy, 2021). In Chinese medicine pathophysiology, viral infection is referred to as “wind-heat invasion” with long-term post-viral symptoms referred to as “latent or smoldering heat lingering in the interior” after improperly cleared “wind-heat” (Maciocia, 1994). Chinese herbs have been used as antivirals for many years to reduce severity and sequelae of viral infections and their use in a COVID context is due in part to their quercetin and other zinc ionophore content which can increase intracellular zinc levels (Luo et al., 2020), (Bensky & Gamble, 1993).

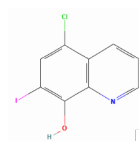
### METHODS

A search of the existing literature using the keywords: Long COVID, COVID-19, zinc, zinc ionophores, epigallocatechin galate, quercetin, hydroxychloroquine, ivermectin, clioquinol, pyrithione, curcumin, tannic acid, and luteolin was performed utilizing PubMed, Web of Science and PubChem internet databases. Articles for review were confined to meta-analyses, review articles and clinical trials discussing ionophoric activity of the aforementioned molecules, or mechanisms in which they work. Evidence and information regarding the functions and applications

of each molecule was consolidated and presented, followed by our professional opinions on their potential use in research and practice. While this is only a general review, we feel it worth mentioning in order to stimulate further inquiry into their possible use as therapeutics in conjunction with existing protocols of treatment.

### POLYPHENOLIC MOLECULES WITH STRONG ZINC IONOPHORIC ACTIVITY

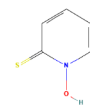
#### Clioquinol



(PubChem Clioquinol: <https://pubchem.ncbi.nlm.nih.gov/compound/Clioquinol>)

Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) was used in the past as an oral anti-parasitic agent until the discovery that it induced mitochondrial and neurotoxicity in the presence of zinc when orally administered (Arbiser et al., 1998). While it can be used topically to treat prostate cancer (Costello & Franklin, 2019), it would be of dubious benefit in the short term treatment of long covid if given internally due to these toxicity concerns.

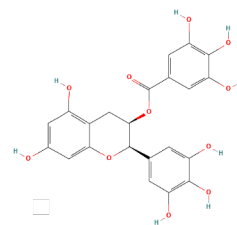
#### Pyrithione



(PubChem Pyrithione: <https://pubchem.ncbi.nlm.nih.gov/compound/Pyrithione>)

Zinc Pyrithione finds use in medicine as a topical anti-fungal for seborrheic dermatitis (Barak-Shinar & Green, 2018). However, it is toxic via any other route of administration and therefore of no benefit for long COVID treatment (Scientific Committee on Consumer Safety, Opinion in Zinc Pyrithione, 2013).

#### Epigallocatechin Galate (EGCG)

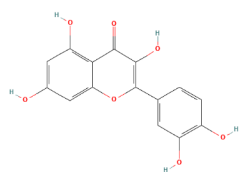


(PubChem Epigallocatechin Gallate: <https://pubchem.ncbi.nlm.nih.gov/compound/Epigallocatechin-gallate>)

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Epigallocatechin Galate (EGCG) is a water soluble polyphenolic catechin found most abundantly in green tea that exhibits strong zinc ionophoric activity (Dabbagh-Bazarbachi et al., 2014). In cancer treatment and prevention it has been shown to down-regulate both COX-2 and NFkB, lower inflammation, and up-regulate TNFa, which increases cancer cell apoptosis (Ramos, 2008). EGCG has also been shown to have potent antiviral activity to a number of viruses including HCV, HIV-1, influenza, zika and others via viral binding interference, inhibition of reverse transcriptase and other mechanisms (Steinmann et al., 2013; Mhatre et al., 2021). When combined with theaflavin (an active ingredient of black tea), there is a dose-dependent inhibition of SARS-CoV-2 3CL-protease, an enzyme critical to viral replication (Jang et al., 2020). During viral infection with H5N1, early administration of EGCG has been demonstrated to inhibit membrane fusion and viral entry into cells, subsequently lowering the viral titre (Saadh & Aldalaen, 2021). Co-administration of EGCG with zinc strengthens this inhibition (Saadh & Aldalaen, 2021). A common theme to long COVID syndrome is the chronic inflammation that remains in the wake of the initial infection. The inflammatory mechanism of long COVID is comparable to that of rheumatoid arthritis in that the increased amounts of inflammatory cytokine IL-1b cause down-stream increases in IL-6 and IL-8 which add to the overall inflammatory burden (Singh et al., 2016). When deployed early or prophylactically, EGCG may help to curb the length of time that this inflammation persists (Chourasia et al., 2021).

### Quercetin



(PubChem Quercetin: <https://pubchem.ncbi.nlm.nih.gov/compound/Quercetin>)

Quercetin (QCT) is a water insoluble bioflavonoid that is found in many fruits, vegetables and herbs, with concentrations in typical foods as listed in Table 2.

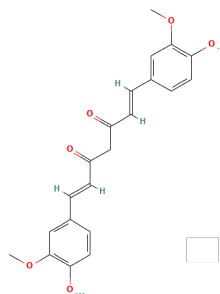
Quercetin has desirable therapeutic characteristics which include immunomodulation, anti-inflammatory and antiviral capabilities, thrombin-inhibitory actions and strong antioxidant capacity (Di Pierro et al., 2021). Many of the Chinese medicinal herbs that are currently being employed as part of multimodal treatments for COVID-19 in China also contain quercetin in beneficial amounts (Luo et al., 2020), (Bensky & Gamble, 1993). When quercetin is

combined with very large doses of vitamin C, its anti-inflammatory effects are increased, and with zinc added, the immunomodulatory effect may be strengthened via inhibition of RNA dependant RNA polymerase, which prevents covid viral replication (Pal et al., 2021). In addition to being well tolerated and lacking in any side effects, quercetin has also been shown to help ameliorate chronic fatigue and poor appetite, which may help to improve long COVID outcomes (Di Pierro et al., 2021).

**Table 2.** Common Sources of Quercetin (Cione et al., 2019)

Apples	4.7 mg/100g
Berries	3.5 8mg/100g
Grapes	2.17 mg/100g
Broccoli	1.8 mg/100g
Onions	1.8 mg/100g
Black tea	1.13 mg/100g

### Curcumin



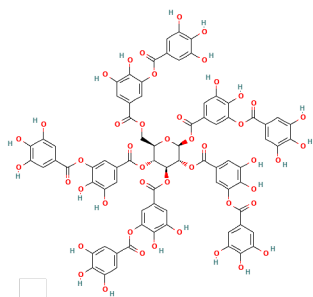
(PubChem Curcumin: <https://pubchem.ncbi.nlm.nih.gov/compound/Curcumin>)

Curcumin is a phenolic compound coming from turmeric (*curcuma longa*) and part of the ginger family of plants (Zingiberaceae) that has widespread use in East Asia as a food ingredient, additive, Chinese medicinal (Jiang Huang – blood invigorator), Ayurvedic medicinal and anti-inflammatory (Cione et al., 2019; Bensky & Gamble, 1993). Curcumin exhibits antiviral activity against enveloped viruses such as dengue and hepatitis C by interfering with the binding of viruses to cell receptors (Keflie & Biesalski, 2021). However, due to its low solubility, other methods of increasing its bioavailability should be explored. Many polyphenols, including curcumin, form chelates with various transition metals such as zinc cations (Celik, Gencay & Ocsoy, 2021). This curcumin-zinc (II) complex may increase the bioavailability and effectiveness of zinc (Sareen, Jain &

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Dhar, 2016). There have not been any studies examining curcumin as a zinc ionophore in the context of SARS-CoV2 infection; thus zinc and curcumin co-supplementation may be of interest in future trials.

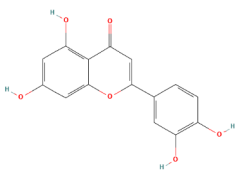
### Tannic Acid



(PubChem Tannic Acid: <https://pubchem.ncbi.nlm.nih.gov/compound/Tannic-acid>)

Tannic acid (or Chinese tannin) is one of the polyphenols in tea which has similar zinc ionophoric actions. Similar to quercetin and EGCG, tannic acid also binds and inactivates the viral cysteine proteases PLpro (papain-like protease) and 3CLpro (chymotrypsin-like protease), which blocks viral replication in the host cell cytosol (Kaul et al., 2021). In addition, tannic acid and other polyphenols exhibit broad spectrum antibacterial and antifungal characteristics (Chung et al, 1998). These anti-microbial functions can help to prevent bacterial superinfection in at-risk patients suffering from long COVID.

### Luteolin

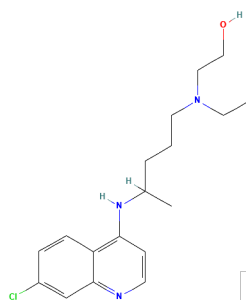


(PubChem Luteolin: <https://pubchem.ncbi.nlm.nih.gov/compound/Luteolin>)

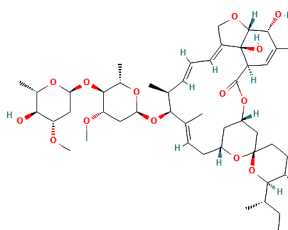
Luteolin is a bioactive flavone present in many medicinal herbs, common fruits and vegetables such as onions, cabbage, peppers, apple skins, lemongrass, dandelion, perilla leaf and chrysanthemum (Aziz, Kim & Cho, 2018). Its therapeutic properties include anti-inflammatory, antimicrobial, antioxidant and neuroprotective functions, and it is non-toxic (Aziz, Kim & Cho, 2018). As with other bioflavonoids like quercetin, luteolin may inhibit a variety of inflammatory cytokines including interleukins (IL) 1b,2,4,5,6,8,12, 13,17 and TNF- $\alpha$ , inhibit COX-2 enzyme, as well as stimulate the release of IL10, an anti-inflammatory cytokine, and inhibit histamine release from mast cells (Seelinger, Mersfort & Schempp, 2008). There is speculation that long

COVID symptoms could be related to abnormal hyperactivation of dysfunctional mast cells (Afrin, Weinstock & Molderings, 2020), and thus downregulation of mast cell activation or mast cell mediated inflammation may aid with long COVID symptomatology.

### Hydroxychloroquine and Ivermectin



(PubChem Hydroxychloroquine: <https://pubchem.ncbi.nlm.nih.gov/compound/Hydroxychloroquine>)



(PubChem Ivermectin: <https://pubchem.ncbi.nlm.nih.gov/compound/Ivermectin>)

Both hydroxychloroquine and ivermectin have been at the center of controversy surrounding SARS-CoV-2 treatment since nearly the beginning of the pandemic. While it is beyond the scope of this paper to comment on the possible reasons for this, it is important to mention that both drugs originated from natural sources, and display zinc ionophoric activity (Butters & Whitehouse, 2021). Although previously mentioned ionophores display affinities for other transition metals such as iron and copper to some degree as well, hydroxychloroquine appears to be specific to zinc which may be advantageous as zinc deficiency is of the utmost concern in the context of both acute SARS-CoV-2 and subsequent long COVID treatment (Xue et al., 2014).

Ivermectin was first discovered by professor Satoshi Omura in 1975 from a soil sample containing fermentation products from *Streptomyces avermitilis* bacteria. Due to its versatility and benefit in treating parasitosis, viruses and some cancers, Dr. Omura was awarded the 2015 Nobel Prize in physiology or medicine for this discovery (Crump, 2017). While ivermectin was initially used to treat onchocerciasis and strongyloidiasis, it has found off label



uses in treating cancer, asthma and viral infections from dengue, encephalitis, HIV and several RNA viruses (including SARS-CoV-2) by the blockade of nuclear trafficking of viral proteins (Crump, 2017). It has also been postulated to be a zinc ionophore via two ivermectin molecules reacting in a head to tail orientation which would aid in escorting zinc ions into the cell cytoplasm (Zaidi & Dehgani-Mobaraki, 2022). Being a zinc ionophore would account for one of its many reasons for inclusion into doctor led clinical protocols and trials such as the Front Line Covid Critical Care Alliance (FLCCC) and the Canadian Covid Care Alliance (CCCA) (Rizzo, 2020).

### DISCUSSION

Molecules that have ionophoric characteristics are usually described as having a hydrophilic pocket that allow for one or more binding sites for cations, yet the outer surface of the molecule is hydrophobic. This allows a complex to form around the ions, making them able to transport across cell membranes, which alters electrolyte balance (Freedman, 2012). The rationale for concentrating on zinc and its repletion in this paper is due to both the symptoms of long COVID converging with many of the symptoms of zinc deficiency as illustrated in Table 1, as well as widespread zinc deficiency in many global elderly and vulnerable populations (Mocchegiani et al., 2013). There are various causes of zinc deficiency which include genetics, nutrition, iatrogenic factors and chronic diseases such as ulcerative colitis and alcoholism (Saper & Rash, 2009). However, the most effective method of treatment for long COVID in our opinion is preventative/ prophylactic in nature or one which reduces the symptom severity should COVID-19 infection occur.

Although zinc status is usually checked via plasma zinc values (morning fasting lower limit: 10.7mmol/L), plasma does not indicate cellular zinc concentrations (Maret & Sandstead, 2006). The total body pool of zinc is between 2-3g in adults, yet this pool is not uniformly distributed across all tissues. Those tissues with high rates of cellular turnover, such as the liver and blood cells (granulocytes, lymphocytes and platelets) are likely more sensitive to mild or moderate deficiencies in zinc. For example, it has been demonstrated that elderly subjects can have normal plasma zinc levels, yet low leukocyte zinc which reflects immune impairment (low thymulin activity) (Prasad et al., 1988).

The antiviral mechanisms of zinc appear to vary with virus type. For example, intracellular Zn<sup>2+</sup> ions have been shown to inhibit SARS CoV-1 RNA dependent RNA Polymerase (RdRp) template binding and elongation (Read et

al., 2019), whereas free zinc binds to HSV virions, preventing infection by inhibition of viral membrane fusion (Arens & Travis, 2000).

Although zinc deficiency is far more common globally than its excess (Pal et al., 2021), a word about potential zinc toxicity with over-supplementation is also required as it can lead to immunosuppression (Chandra, 1984). Excessive zinc supplementation can induce copper deficiency, which can impair antibody production by T-lymphocytes (Blakley & Hamilton, 1987). However, the induction of copper deficiency due to excessive zinc supplementation is an issue that most nutritionally minded clinicians are aware of, and mitigate via concurrent copper supplementation and zinc level monitoring.

Zinc supplementation on its own takes time to be effective due to slow fractional absorption (Maares & Haase, 2020), highlighting the need for co-supplementation with zinc ionophores.

In theory, if total body cellular zinc levels can be brought up quickly during or soon after acute SARS COV-2 infection, there may be reduced risk of developing long COVID or the symptom severity and disease progression may be lessened. The two readily available, over-the-counter and non-toxic bioflavonoids quercetin (QCT) and epigallocatechin galate (EGCG), are both strong zinc ionophores (Dabbagh-Bazarbachi et al., 2014). Both are found in abundance in the Japanese diet (QCT in vegetables and EGCG in green tea) in addition to zinc rich foods such as oysters. This may help to explain why, despite the population density of Japan, the lower case loads of COVID-19 are being observed. Both quercetin and zinc are a part of doctor led recommended treatment protocols that have been developed and adopted by organizations such as the Front Line COVID-19 Critical Care Alliance (FLCCC) and Canadian COVID Care Alliance (CCCA) as part of multi-drug/ nutrient treatment and preventative regimens such as I-MASK+, MATH+ and I-RECOVER protocols which also include key nutrients such as vitamin C, vitamin D and thiamine. I-RECOVER protocol in particular is being used for long COVID.

### CONCLUSION

While current measures such as vaccination, social distancing, masking and lockdowns are a part of the solution to the global pandemic, none of them will enhance nutrient repletion needed to reduce susceptibility to, or symptomatology of, COVID-19. In China, the pharmacological properties of combined Chinese herbal prescriptions are well recognized and are helping to treat COVID-19. Likewise, poly-modal approaches to this complex pandemic

that include the use of zinc and its ionophores must also be employed in order to help reduce the overall burden to global society that this pandemic has created.

### FUNDING

This research received no external funding.

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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