
# SHORT REPORT

# The Potential Use of Zinc Salt in Coronavirus Diseases (COVID-19)

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**Disclosure**

The authors of this review have no competing interest in this subject.

**Disclaimer**

This review is essentially a brief report, prepared on an urgent basis, to reflect the highest level of evidence available regarding the subject at this specific time. The conclusion draws on restricted reviews from analysis of pertinent literature, on expert opinion and/or regulatory status where appropriate. All efforts have been made to ensure all relevant published material has been reviewed but this document may still not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of this review.

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## Short report on zinc salt potential in COVID-19 management

### Introduction

Zinc salt is a neutral compound formed when zinc is reacted with negatively charged elements. There are many types of zinc salt such as zinc citrate, zinc sulfates, zinc oxide, zinc nitrate, zinc chlorate, zinc phosphate, zinc molybdate, zinc chromate, zinc ricinoleate, and more. Some of them are used as a source of mineral and vitamin which is categorised under dietary supplement and some is used for topical application. For example, zinc oxide, which is not water soluble, is commonly used in topical applications but it is also used in some oral supplements such as supplements for respiratory tract infections. The water-soluble zinc salts such as zinc gluconate, zinc sulfate, zinc acetate and zinc citrate have also been reported. They are more commonly found in oral supplements in the form of dispersible tablets, syrups and lozenges due to its good bioavailability profile. (1) Aside from differences in bioavailability profile, different zinc salts also contain different elemental zinc content as illustrated in the **Table 1** below.

**Table 1:** Different elemental zinc content in common oral zinc preparations.

| Zinc preparation | Elemental zinc (mg) |
|---|---|
| Zinc acetate, 30% zinc, 25 mg | 7.5 |
| Zinc acetate, 30% zinc, 50 mg | 15 |
| Zinc gluconate, 14.3% zinc, 50 mg | 7 |
| Zinc gluconate, 14.3% zinc, 100 mg | 14 |
| Zinc sulfate, 23% zinc, 110 mg | 25 |
| Zinc sulfate, 23% zinc, 220 mg | 50 |
| Zinc oxide, 80% zinc, 100 mg | 80 |

Source: https://www.aafp.org/afp/2009/0501/p768.html

Zinc is an essential trace element which is involved in a variety of biological functions including its function as a cofactor to more than 300 enzymes, as a signaling molecule in cellular regulation and as a structural element. Zinc has shown benefits in ensuring the immune system is functioning, preventing cold, to treat and prevent zinc deficiency, for growth and for the development and health of body tissue. (2) Study showed that consuming zinc orally will reduce symptoms for respiratory infections. (3) It is also believed to have an antiviral effect towards various viruses such as respiratory syncytial virus, hepatitis C virus, herpes simplex virus, human immunodeficiency virus, vaccinia virus, and human rhinovirus. (4–11)

**Antiviral efficacy evidence**

Zinc supplement was proven beneficial to treat patients infected with many pathogenic viruses including hepatitis C virus. At the same time, zinc supplement also helps to produce an array of cytokines that can help any infectious conditions. Last but not least, zinc also inhibits replicase enzyme complexes of retroviruses that are necessary for the virus to multiply in the host cells such as pneumocytes in the case of coronavirus disease (COVID-19) patients.

- An in vitro study using swine testicle (ST) cells with transmissible gastroenteritis virus (TGEV) which were tested with zinc chloride ($ZnCl_2$) and zinc sulfate ($ZnSO_4$), demonstrated a significant reduction of viral titers at an early stage (1–4 hour post infection (hpi)) and later stage (22–24 hpi) of infections. The effects of zinc salt treatment on viral ribonucleic acid (RNA) synthesis also significantly reduced for 1–4 hpi without previous inhibition of virus penetration, which $ZnCl_2$ treatment reduce more than 40-fold and $ZnSO_4$ reduce more than 16-fold compared to the viral RNA levels in the untreated wells. The influence of zinc salt on viral protein synthesis also reduced by more than 40% for the early-stage treatment without previous inhibition of virus penetration. However, pretreatment of TGEV with zinc salt under cell-free conditions before infection did not affect the virus yield. (12)

- An in vitro study showed that combination of zinc ion ($Zn^{2+}$) and the zinc ionophore pyrithione (PT) at low concentrations (2 μM of $Zn^{2+}$ and 2 μM of PT) inhibited the replication of severe acute respiratory syndrome coronavirus (SARS-CoV) in cell culture. Using an activity assay for replication and transcription complexes (RTCs) isolated from cells infected with SARS-CoV, the mechanism of action of $Zn^{2+}$ was through inhibition of the RNA-synthesising activity of the RTCs of SARS-CoV. Enzymatic studies using recombinant RNA-dependent RNA polymerase (RdRp) purified from *Escherichia coli* further demonstrated that $Zn^{2+}$ directly blocked the initiation step of the SARS-CoV RdRp elongation and template binding reduced. (13)

- In an in vitro study investigating the inhibitory effects of three zinc salts (zinc acetate, lactate, and sulfate) on the replication of respiratory syncytial virus (RSV). It was found that $Zn^{2+}$ completely inhibited RSV plaque formation at 1 and 10mM. At the lowest concentration tested, 10 μM, ≥ 1,000-fold reductions in RSV yield was observed when zinc was present during preincubation, adsorption, penetration, or egress of virus. The therapeutic indices, defined as ratios of 50% toxicity concentration to 50% inhibitory concentration, were 100, 150, and 120 for zinc acetate, zinc lactate, and zinc sulfate, respectively. Mechanistic studies suggested that zinc mediates antiviral activity on RSV via

alteration of ability of infected cells (using human epithelial type 2 (HEp-2) cells) to support RSV replication. (4)

- A meta-analysis compared the efficacy and dose dependent effects of zinc acetate lozenges, zinc gluconate lozenges, and placebo (seven randomised controlled trials, zinc dose was 75 mg/day.) on the common cold duration using inverse-variance random-effects method. Compared to placebo, the mean common cold duration was 33% (95% confidence interval (CI): 21% to 45%) shorter for the zinc groups. There was no significant difference between the symptom duration between the two different zinc salts, nor was there a difference between low and high doses calculated according to the total daily dose of elemental zinc. High heterogeneity was reported among the trials, $I^2 = 77\%$ ($p = 0.0003$) while studies included have various limitations including formulation issues, heterogeneity of test subjects, low quality studies of the trials using low doses of zinc, and compliance. The authors concluded that there is substantial evidence of zinc in reducing symptoms duration of the common cold, however the findings are not widely applicable to marketed zinc products, with a wide variation of formulation and commonly contain substances such as citric acid that binds zinc and hence reduces the dose effects. There was no investigation on the direct antiviral effects of zinc in this meta-analysis. (14)

- In a double-blinded, randomised controlled trial of 77 patients exhibiting common cold symptoms, it was found that zinc gluconate nasal spray (10 mmol, every 15 to 30 minutes) and zinc orotate lozenges (one every 2–3 hours) did not reduce the duration or severity of common colds compared to placebo group. (15)

- This systematic review independently extracted data and assessed trial quality from randomised, double-blind, placebo-controlled trials using zinc for at least five consecutive days to treat, or for at least five months to prevent the common cold. It has 13 therapeutic trials (966 participants) and two preventive trials (394 participants). Results show that intake of zinc is associated with a significant reduction in the duration (standardised mean difference (SMD) -0.97; 95% CI: -1.56 to -0.38) ($p = 0.001$), and severity of common cold symptoms (SMD -0.39; 95% CI: -0.77 to -0.02) ($p = 0.04$). There was a significant difference between the zinc and control group for the proportion of participants symptomatic after seven days of treatment (OR = 0.45; 95% CI: 0.2 to 1.00) ($p = 0.05$). The incidence rate ratio (IRR) of developing a cold (IRR = 0.64; 95% CI: 0.47 to 0.88) ($p = 0.006$), school absence ($p = 0.0003$) and prescription of antibiotics ($p < 0.00001$) was lower in the zinc group. Overall adverse events (OR = 1.59; 95% CI: 0.97 to 2.58) ($p = 0.06$), bad

taste (OR = 2.64; 95% CI: 1.91 to 3.64) (p < 0.00001) and nausea (OR = 2.15; 95% CI: 1.44 to 3.23) (p = 0.002) were higher in the zinc group. As for groups supplemented with zinc for at least five months, results show reduction in cold incidence, school absenteeism and prescription of antibiotics in children. The author concluded in view of differences in study populations, dosages, formulations and duration of treatment, it is difficult to make recommendations on the dose, formulation and duration that should be used. (16)

- Various zinc salts have been used against the common cold syndrome, which is known to be initiated by respiratory viruses, particularly rhinoviruses. Using rhinovirus as the challenge virus, zinc salts (Zn) potentiate the antiviral action of native human leukocyte interferon (HuIFN-*α*) and rHuIFN-*γ*. In accordance with that, HuIFN-*α* was potentiated 10-fold at rather low levels of IFN activity (0.6–0.8 U/ mL), resulting in 100% protection. In contrast to HuIFN-*α*, rHuIFN-*γ* directly increased the cytopathic effect of rhinovirus at low levels (<2 U/mL) but protected the cells at higher IFN levels (5–20 U/ mL). However, no potentiation was seen with Zn. The HuIFN-β is protected against rhinovirus at the same doses as used with HuIFN-*α*, but in contrast to HuIFN-*α*, no potentiation was noted. The paper concluded further investigation required to determine the use of zinc gluconate or other zinc complexes together with IFN-α in oral administration of low-dose IFN for patients with common cold. (17)

- Free ionic zinc ($Zn^{2+}$) in saliva shortens duration and severity of common cold (CC) symptoms. The mechanism of $Zn^{2+}$ complexes with proteins of critical nerve endings and surface proteins of human rhinovirus (HRV) is proposed by interrupting nerve impulses and block docking of HRV on intercellular adhesion molecule-1 (ICAM-1) on somatic cells, thereby interrupting HRV infection. Since leukocyte function associated antigen (LFA) 1 binds leukocytes to cells through intercellular adhesion molecule (ICAM) 1, initiating inflammation, $Zn^{2+}$ is expected to block LFA-1/ICAM-1 binding and thereby suppress inflammation. This explains reduction of inflammation experienced by persons taking zinc gluconate/glycine (ZGG) lozenges for CC. Allergic rhinitis and CC share many common symptoms, and ZGG also mitigates the allergic symptoms. Focal irritation, increased ICAM-1 expression, and recruitment of leukocytes to epithelial foci are the common elements. Zinc ions may be an important anti-inflammatory factor because they can block docking of both HRV and LFA-1 with ICAM-1. (18)

- Zinc gluconate lozenges were tested in a double-blind, placebo controlled, clinical trial. The initial (loading) dose for all subjects was two tablets, one followed by the other, dissolved in the mouth as lozenges (about 10 to 20 min

each). Thereafter, adults and youths dissolved one tablet every two wakeful hours, not exceeding 12 and nine tablets per day, respectively. Children under 25 kg received one-half tablet every two wakeful hours, not exceeding six tablets per day. Subjects were instructed to treat their cold until all symptoms had been absent for six hours and then to stop all treatment. They were instructed to treat the cold during the night only if they were already awake. Other common cold treatments were not permitted. Emphasis was placed on the necessity of dissolving the tablets in the mouth as lozenges. One 23-mg zinc lozenge or matched placebo was dissolved in the mouth every two wakeful hours after an initial double dose. After seven days, 86% of 37 zinc-treated subjects were asymptomatic, compared with only 46% of 28 placebo-treated subjects ($p = 0.0005$). Side effects or complaints were usually minor and consisted mainly of objectionable taste and mouth irritation. Zinc lozenges shortened the average duration of common colds by about seven days. (19)

- Zinc ions rapidly inhibit virus production in HeLa cells infected with human rhinovirus type 1A and lead to the accumulation of human rhinovirus type 1A precursor polypeptides. The degree to which cleavage of these precursors is inhibited is directly dependent on the quantity of cell-associated zinc. Proteolysis resumes after the removal of the zinc-containing medium, and the accumulated viral precursors are cleaved predominantly to stable virus polypeptides. The precursors stabilized at the lowest zinc levels are those that contain capsid protein sequences. Furthermore, added zinc is bound to human rhinovirus type 1A capsids and prevents them from forming crystals. Zinc-resistant mutants display antigenic alterations in coat proteins. These results suggest that zinc complexes with rhinovirus coat proteins and alter them so that they cannot function as substrates for proteases or as reactants in the assembly of the virus. (10)

- A meta-analysis evaluated the role of zinc supplementation in the management of chronic liver diseases (13 randomised controlled trials). Among these 13 trials, six assessed chronic hepatitis C treatment (relative risk 0.83; CI: 0.64–1.07; $I^2 = 26\%$) comparing treatment of chronic hepatitis C with interferon plus ribavirin associated with zinc supplementation vs placebo, indicating no protective effect of zinc supplementation on the improvement of sustained virological response. (20)

- Zinc deficiency in humans may impaired immunity including through imbalance between Th1 and Th2 cells, CD4+/CD8+ ratio, and percentage of CD73+ cells in the CD8+ population (21,22). Gathering evidence from various in vitro and in vivo studies, in addition to clinical symptoms of zinc deficiency documented since decades ago, it is believed that zinc homeostasis is

important in maintaining immune function in the human body (23,24). There is limited evidence to directly link zinc's potential immune modulation properties and its antiviral effects in COVID-19 currently. However, as the pathogenesis, role, and timeline of immune cells activation, under activation, over activation in COVID-19 is yet to be clearly elucidated with much to be investigated, it remains a challenge to target an unknown and unclear therapeutic target i.e. the immune system.

- Apart for respiratory viruses, zinc salts have shown direct viral inhibitory activities against other viruses in vitro, including hepatitis C virus, human immunodeficiency virus, Human papillomavirus, herpes simplex virus, foot and mouth virus, and encephalomyocarditis virus at various concentrations. (25)

**Mechanism**

Animal study have shown the effect of zinc supplementation on improving thymic size and increasing the levels of active thymulin in aging mice which is important for T-cell development and maturation (26).

An in vivo study in aging male C57BL/6 mice (12-month-old) given a zinc salt diet (117 mg/kg zinc) for three months showed significant ($p < 0.005$) increase in thymus weight and viable thymocytes compared to the control group. The study also showed zinc supplementation significantly increased thymulin levels via activation of preexisting inactive thymulin molecules in aging mice. (27)

Similarly, an in vivo study conducted in male Balb/c mice (22-month-old) administered with oral zinc supplementation in the form of zinc sulfate dissolved in water (22 mg/L) also showed that oral supplementation of zinc for one month in old mice induced a recovery of both the active thymulin plasma levels and the number of thymulin-secreting cells on the 15th day of treatment compared with the values observed in age-matched zinc-untreated old mice ($p < 0.001$). Then, a slow increase in total thymulin concentrations was also present after the 15-day treatment, reaching the same values observed in young animals in 30-day treatment. The total thymulin level was maintained if zinc supplementation is continued for three months. However, the total thymulin levels and the number of thymulin-secreting cells decreased to pretreatment values by the 60th day of observation if zinc supplementation is discontinued after one month of treatment. (28)

Two clinical studies in healthy elderly subjects also showed that moderate zinc supplementation is helpful for improving delayed type hypersensitivity (DTH) reaction

response to vaccination and decreasing rate of infections in elderly (29,30). However, benefits of zinc supplementation in acute infection such as COVID-19 infection in elderly patients have not been studied.

**Safety of zinc salt**

- The review covers three different consequences which are acute toxicity intakes (1 to 2 g of zinc sulfate which equals to 225 to 450 mg of elemental zinc showed symptoms of nausea and vomiting, epigastric pain, abdominal cramps, and diarrhea (frequently bloody); pharmacological intakes (dose of zinc in the range of 100–300 mg to treat various medical problems developed severe copper deficiency and alterations in immune response and in blood lipid profiles); and moderately excessive intakes (ranging from 15 mg daily to 100 mg daily, it was shown to interfere with the utilization of copper and iron and to adversely affect high-density lipoprotein (HDL) cholesterol concentrations). (31)

- A review study that covers both zinc excessive and zinc deficiency effects. But toxicity relating to zinc excessive oral intake has shown gastrointestinal problems (abdominal pain, nausea, and vomiting with additional effects including lethargy, anemia, and dizziness (150 mg intake of elemental zinc for six weeks)); zinc-induced copper deficiency (approximately 150 mg of zinc daily for long term); prostate cancer (long-term supplementation with higher doses increased the relative risk 2.9-fold) and immunological effects (330 mg zinc/day in three doses for a month affected lymphocyte function). (32)

- ICR mice and Wistar rats of both sexes (n = 12/sex/group) were fed a diet containing zinc sulphate ($ZnSO_4$) at 0, 300, 3, 000 and 30,000 ppm for 13 weeks. Animals in the 30,000-ppm group showed retarded growth along with low food intake, abnormal values in a few hematological parameters and regressive changes of the pancreatic exocrine gland. In addition, mice had decreased water intake and significant deviations in biochemical parameters, toxic lesions appeared in the stomach, intestine and spleen of both sexes and in the kidney of females. Four males and one female mouse were found dead or moribund during the study. The maximum no-effect level of $ZnSO_4$ was determined to be 3,000 ppm, which is approximately equivalent to the following doses: mice; male 458 mg/kg/day, female 479 mg/kg/day, rats; male 234 mg/kg/day, female 243 mg/kg/day. (33)

- In a one-year study, an unspecified number of newborn Chester Beatty stock mice (sex not reported) were administered 0, 1,000, or 5,000 ppm zinc

(approximately 0, 170, or 850 mg/kg/day) as $ZnSO_4$ in drinking water. There was no difference in body weight gain between control and treated groups, except for the dietary zinc group which became anemic. Survival was not reported in the treated group compared with control groups. An apparent increase in the incidence of hepatomas was observed in treated mice surviving for 45 weeks or longer relative to controls. The incidence of hepatoma was slightly increased in the 850 mg/kg/day group (7/23; 30.4%) compared to controls (3/24, 12.5%). (34)

- Twelve healthy adult men ingested 440 mg of $ZnSO_4$ per day for five weeks. The HDL concentration decreased 25% below baseline values (40.5 to 30.1 mg/dL). Total cholesterol, triglyceride, and low-density lipoprotein cholesterol levels did not change throughout the study. (35)

- A study observed decreased concentrations of HDL cholesterol when male subjects consumed either 50 or 75 mg Zn/day for 12 weeks. With the higher amount of supplementation, HDL cholesterol was also significantly depressed at six weeks of supplementation. (36)

- High concentrations of zinc in drinks, up to 2,500 mg/L with an estimated dose of 325–650 mg, have been linked to poisoning of individuals, causing nausea, abdominal cramping, vomiting, tenesmus, and diarrhea with or without bleeding (37,38).

- A clinical trial observed that elderly men taking 80 mg daily were hospitalised for urinary complications more often than those taking a placebo (39).

- Case report: Acute exposure to 440 mg/day $ZnSO_4$ (2.6 mg elemental zinc/kg/day) for one week resulted in anaemia for a 13-year-old girl treated for acne. The patient experienced epigastric discomfort and fainted prior to admission. It was noted that the anemia may have been secondary to the gastrointestinal haemorrhages. (40)

- Case report: The patient described was a 30-year-old quadriplegic man who was receiving oral $ZnSO_4$ 660 mg/day) to promote the healing of and prevention of decubitus ulcers. In the gut, dietary zinc interacts with copper in a competitive manner, and high levels of zinc lead to copper deficiency. Zinc-induced copper deficiency anaemia can be morphologically identified in the bone marrow preparations by cytoplasmic vacuolisation of both myeloid and erythroid precursor elements. His zinc therapy was discontinued and was treated with intravenous copper for seven days before being discharged. His

haematological parameter was back to normal 22 days post copper replacement therapy. (41)

- Case report: A woman given 440–660 mg $ZnSO_4$ (110–165 mg Zn) daily for 10 months for aphthaus ulcers of her mouth and tongue developed copper deficiency with anaemia and neutrapenia (42).

- Case report: Sideroblastic anaemia and leukopenia associated with copper deficiency in a young man consuming large amounts of supplemental zinc for two years (42).

**Synergistic effect with hydroxychloroquine**

- A review paper indicates that chloroquine (CQ) and hydroxychloroquine (HCQ), which are metal ionophores, exert over antiviral and anticancer properties, especially when coupled with enough doses of metal ion additives (such as zinc) that will galvanise their functions in living tissues. Although there is a variety of compelling evidence that has been published from early clinical trials in China that showed the efficacy of CQ and HCQ, none of these clinical trials so far considered using a combination of dose dependent zinc supplements with HCQ and CQ administration. (43)

- Possible mechanism: The CQ can induce the uptake of zinc into the cytosol of the cell, which is capable of inhibiting RdRp and ultimately halting the replication of coronavirus in the host cell. (13,43)

- There is an on-going clinical trial with identifier number NCT04370782, title ‘Hydroxychloroquine and Zinc with Either Azithromycin or Doxycycline for Treatment of COVID-19 in Outpatient Setting’ in United States. This trial is estimated to have a sample size of 750 participants to assess the safety and efficacy of hydroxychloroquine and zinc in combination with antibiotic drug. (44)

Although there is evidence that shows CQ and HCQ acting as metal ionophores, which allows zinc as metal ion additives to exert its pharmacological action, most of the studies are in vitro. Currently, clinical trials are still on-going to determine the synergistic administration of zinc supplement with CQ or HCQ against the novel SARS-CoV-2 virus. It is important to determine the dosage needed by CQ or HCQ to allow zinc to penetrate the cell and inhibit coronavirus RNA polymerase activity as

well as its safety because CQ and HCQ is known to cause gastrointestinal side effects. Refer **Appendix 1** for more related on-going clinical trials.

**Recommended dosage**

- Zinc sulfate: Depending on the disease, the recommended dosage can range from 220–600 mg (50–36 mg elemental zinc) (45)

- Zinc gluconate: Depending on the disease, the recommended dosage can range from 4.5–450 mg (0.64–64.35 mg) (45)

## Conclusion

Based on the available evidence, zinc has the ability to inhibit the replication of SARS-CoV from in vitro studies, while there is no published scientific evidence on its activity in the SARS-CoV-2 virus yet. It is also found that for zinc to exert its pharmacological antiviral effects, zinc ionophores such as hydroxychloroquine or pyrithione can be used in combination. Zinc homeostasis is important to maintain immune function. However, based on available data and current understanding of the immune related pathogenesis of COVID-19, it is still too early to conclude its efficacy on human use in COVID-19 as few clinical trials are still on-going. When optimising zinc dose, several factors need to be taken into account including type of zinc salt used, amount of elemental zinc, dosage of the zinc ionophore used in combination, and safety data (ensuring no excessive zinc administered and side effects from zinc ionophores used). Zinc supplementation seems to play more of a preventative role, especially in deficiency cases, rather than as a treatment since there is human evidence of routine zinc supplementation (> three months) having positive effect in reducing the duration of respiratory tract infections.

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**Appendix 1**

On-going clinical trials on zinc supplementation in COVID-19 management

| No. | Trial Name | Identifier | Phase & sample size | Intervention | Primary Outcome |
|---|---|---|---|---|---|
| 1 | Impact of Zinc and Vitamin D3 Supplementation on the Survival of Aged Patients Infected With COVID-19 (ZnD3-CoVici) | NCT04351490 | Phase: Unspecified<br><br>Enrollment size: 3140 | **Group 1**<br>Dietary supplement with<br>Zinc gluconate capsule 15 mg x 2 per day during 2 months<br>AND<br>25-OH cholecalciferol drinkable solution 10 drops (2000 IU) per day during 2 months<br><br>**Group 2**<br>No dietary supplement<br><br>Unclear details given on other conventional therapy | 2 months survival rate in asymptomatic subjects at inclusion |
| 2 | A Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection | NCT04335084 | Phase: II<br><br>Enrollment size: | Single group given:<br><br>**Drug:** Hydroxychloroquine | Prevention of COVID-19 symptoms and safety as adverse effects as recorded in a |

| No. | Trial Name | Identifier | Phase & sample size | Intervention | Primary Outcome |
|---|---|---|---|---|---|
| | (HELPCOVID-19) | | 600 | **Dietary Supplement**: Vitamin C, Vitamin D, Zinc<br><br>Dose and duration unspecified | daily diary [Time Frame: 24 weeks] |
| 3 | A Study of Quintuple Therapy to Treat COVID-19 Infection (HAZDpaC) | NCT04334512 | Phase: II<br><br>Enrollment size: 600 | Single group given:<br><br>**Drug:** Hydroxychloroquine and azithromycin<br><br>**Dietary Supplement**: Vitamin C, Vitamin D, Zinc<br><br>Dose unspecified<br><br>Duration: 24 weeks | Successful treatment as determined by Negative Test and resolution of symptoms and safety (side effects) after 24 weeks |
| 4 | Proflaxis Using Hydroxychloroquine Plus Vitamins-Zinc During COVID-19 Pandemia | NCT04326725 | Case-control, prospective observational<br><br>Enrollment size: 80 | Hydroxychloroquine 200mg single dose repeated every three weeks plus vitamin C including zinc once a day | Protection against COVID-19 [ Time Frame: 4 months] |

| No. | Trial Name | Identifier | Phase & sample size | Intervention | Primary Outcome |
|---|---|---|---|---|---|
| | | | | Unclear dose for Vitamin C and Zinc<br><br>Duration unclear | |
| 5 | Hydroxychloroquine and Zinc with Either Azithromycin or Doxycycline for Treatment of COVID-19 in Outpatient Setting | NCT04370782 | Phase:<br>IV (QUESTIONABLE to be PHASE IV)<br><br>Enrollment size:<br>750 | **Group 1:**<br>Hydroxychloroquine 400mg twice a day (BID) on day 1, followed by 200mg BID for days 2-5<br>AND<br>Azithromycin 500mg on day 1, followed by 250mg once daily for days 2-5<br>AND<br>Zinc sulfate 220mg once daily for 5 days<br><br>**Group 2:**<br>Hydroxychloroquine 400mg twice a day (BID) on day 1, followed by 200mg BID for days 2-5<br>AND<br>Doxycycline 200mg once | Time to resolution of symptoms relative to baseline<br><br>Number of participants hospitalized and/or requiring repeat emergency room visits<br><br>ICU length of stay<br><br>number of days on ventilator |

| No. | Trial Name | Identifier | Phase & sample size | Intervention | Primary Outcome |
|---|---|---|---|---|---|
| | | | | daily for 5 days<br>AND<br>Zinc sulfate 220mg once daily for 5 days | |
| 6 | A Randomised Controlled Trial of Early Intervention in COVID-19: Favipiravir Verses HydroxycholorquiNe & Azithromycin & Zinc vErsEs Standard CaRe (PIONEER) | NCT04373733 | Phase:<br>III<br><br>Enrollment size:<br>450 | **Group 1:**<br>Favipiravir: Day 1 1800mg twice per day, Days 2-10 800mg twice per day<br><br>**Group 2:**<br>Hydroxychloroquine: Day 1 400mg twice per day, Days 2-10 200mg twice per day<br>AND<br>Azithromycin: Day 1-3 250mg once per day<br>AND<br>Zinc-sulfate: Days 1-10 125mg twice per day<br><br>**Group 3:**<br>No intervention | Time to improvement by two points on a seven-category ordinal scale [up to 28 days from randomisation] |

In summary, for registered trials, in which most are either newly registered or recruiting while none have been completed yet, zinc salt is mainly investigated as a dietary supplement or add-on therapy to standard conventional drugs such as hydroxychloroquine, azithromycin, doxycycline, and favipiravir.