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Zinc and selenium supplementation in COVID-19 prevention and treatment: a systematic review of the experimental studies

Running title: Zinc and selenium supplementation in COVID-19

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Abstract

BACKGROUND AND AIM

The COVID-19 pandemic has severely affected the world's population in the last two years. Along with non-pharmacological public health interventions, major efforts have also been made to identify effective drugs or active substances for COVID-19 prevention and treatment. These include, among many others, the trace elements zinc and selenium, based on laboratory studies and some observational human studies. However, both of these study designs are not adequate to identify and approve treatments in human medicine, and experimental studies in the form of randomized controlled trials are needed to demonstrate the effectiveness and the safety of any interventions.

METHODS

We undertook a systematic review in which we searched for published and unpublished clinical trials using zinc or selenium supplementation to treat or prevent COVID-19 in the Pubmed, Scopus and ClinicalTrials databases up to January 10th, 2022.

RESULTS

Amongst the published studies, we did not find any trial with selenium, whereas we retrieved four eligible randomized clinical trials using zinc supplementation, only one of which was double-blind. One of these trials looked at the effect of the intervention on the rate of new SARS-CoV-2 infections, and three at the COVID-19 clinical outcome in already infected individuals. The study populations of the four trials were very heterogeneous, ranging from uninfected individuals to those hospitalized for COVID-19. Only two studies investigated zinc alone in the intervention arm with no differences in the endpoints. The other two studies examined zinc in association with one or more drugs and supplements in the intervention arm, therefore making it impossible to disentangle any specific effects of the element. In addition, we identified 22 unpublished ongoing clinical trials, 19 on zinc, one on selenium and two on both elements.

CONCLUSION

No trials investigated the effect of selenium supplementation on COVID-19, while the very few studies on the effects of zinc supplementation did not confirm efficacy. Therefore, preventive or therapeutic interventions against COVID-19 based on zinc or selenium supplementation are currently unjustified, although when the results of the on-going studies are published, this may change our conclusion.

Keywords:

COVID-19; clinical trial; selenium; systematic review; supplementation; zinc.

Introduction

Coronavirus disease (COVID-19) is a severe and potentially fatal condition caused by infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), an airborne virus that spread globally after its initial outbreak in late 2019 in China [1]. The clinical spectrum of SARS-CoV-2 severity ranges from an asymptomatic condition to mild symptoms such as fever, cough, ageusia, anosmia and asthenia [2, 3], up to most severe conditions, as acute respiratory distress syndrome (ARDS) and multi organ failure [4]. When the outbreak swept across Italy, which was the first country to be seriously and extensively hit by the epidemic [5], the case-fatality rate was as high as 15% [6].

To reduce the risk of transmission of SARS-CoV-2, several public health and preventive measures have been advised, including mobility restrictions through lockdown, and hand and respiratory hygiene [7, 8]. In the last months specific vaccines have been developed, with subsequent implementation of an impressive and most effective vaccination campaign [4, 9]. For COVID-19 patients, supportive care measures, such as mechanical ventilation, and a few pharmacological therapies, such as systemic corticosteroids, remain the standard of care, in the absence of a specific antiviral therapy [3, 10, 11].

In the current situation, there is an enormous interest about the possible preventive or supportive therapies against SARS-CoV-2 infection and the related disease, COVID-19. Among these, supplementation with vitamins and minerals has been suggested to help in counteracting the COVID-19 pandemic, and it has therefore increased in some populations [12-18]. Focusing on trace elements, zinc and selenium are the two minerals that triggered most of the interest by researchers and the general population, and there is evidence that self-supplementation with these two minerals has considerably increased due to this perception in the areas characterized by a high COVID-19 prevalence [19].

Some support for the possibility that zinc and selenium may be helpful in the prevention of the SARS-CoV-2 infection and the therapy of COVID-19 comes from the antioxidant and immunomodulatory properties of these two elements or related proteins [20-22], from their antiviral activity [23, 24], as well as from some nonexperimental human studies that suggested an involvement of a 'low' zinc and selenium status in favouring COVID-19 incidence and lethality [25, 26]. It has also been noted that zinc deficiency increases IL-6 levels [27], an observation of interest given the cytokine storm characterizing COVID-19 [28]. Concerning selenium, it has been proposed that the selenium-containing antioxidant enzyme glutathione peroxidase 1 could be related to the main protease (M^{pro}) of SARS-CoV-2, and therefore selenium status might have a role in COVID-19 onset [29, 30]. In addition, the zinc supplement appears to have mild beneficial effects on acute viral respiratory tract infections [31]. Some human non-experimental studies have suggested an involvement of low zinc and selenium status in COVID-19 development, but not all studies have yielded consistent results, and the

observational design substantially weaken their capacity to demonstrate causal links [25, 32-37]. This also explains why a recent meta-analysis including both experimental (clinical trials) and non-experimental human studies on zinc and COVID-19 concluded that zinc was not proven to be effective against COVID-19 [38].

However, in human medicine any claims of efficacy (and safety) of supplementation of substances, such as drugs or nutrients, will only be accepted if the data is derived from well-designed experimental studies, the prime choice being randomized controlled trials (RCTs) [39, 40]. COVID-19 is no exception to this general rule [41, 42]. The need to obtain experimental evidence for safety and efficacy before permitting supplementation with trace elements is important, and particularly relevant for selenium where the safety margin (between adequacy and toxicity) is narrow [43]. In the past it has been claimed that selenium could reduce the risk of cancer, cardiovascular disease and diabetes, mainly on the basis of observational epidemiologic studies and one single small trial [44]. However, experimental human studies in the form of RCTs have later shown that no such effects exist, and have even reported that adverse effects such as advanced prostate cancer and type 2 diabetes may be favoured by selenium supplementation [45, 46].

In the light of our improved understanding of the controversies surrounding nutrient supplementation studies, we reviewed published clinical trials to see if there is any evidence for possible effects of zinc or selenium on COVID-19, and therefore if there is any indication that increased intake of these trace element is warranted and appropriate to prevent the current COVID-19 pandemic. In particular, according to the PICO approach, we searched for studies which investigated subjects with a clinical diagnosis of SARS-CoV-2 infection or with developed COVID-19. The considered interventions were zinc or selenium, with the control group allocated to placebo only. Finally, we considered all possible clinical outcomes showing a potential effect of the intervention on the risk of SARS-CoV-2 infection and COVID-19 onset and progression, including, for instance, symptoms of reduction or clearance from the nasopharyngeal tract.

In addition, we wanted to determine whether the current recommendations not to use zinc supplements that exceed the recommended dietary allowance [47] should be changed. Excess intake of any nutrient, including that of these two trace elements, may lead to toxicity when the upper intake level is exceeded, therefore inappropriate reliance on these or other alleged therapeutic tools may have serious health consequence. In addition, we searched for unpublished RCTs and assessed their quality where possible, in order to predict which high quality evidence would be available for meta-analysis in the future.

Methods

To assess all the evidence on the efficiency of zinc or selenium against SARS-CoV-2 transmission and COVID-19 onset and progression, we searched for clinical trials in the Pubmed, Scopus and ClinicalTrials databases from inception until January 10, 2022, using "(zinc OR selenium) AND (COVID-19 OR SARS-CoV-2)" as MeSH terms for Pubmed and as keywords for Scopus. We filtered the research including "Clinical Trial" option on Pubmed and adding INDEXTERMS ("clinical trials") AND (LIMIT-TO (DOCTYPE , "ar")) on Scopus. On the ClinicalTrials.gov database we set COVID-19 in the "condition or disease" field and alternatively zinc or selenium in the "Intervention/treatment" field. Included clinical trials had to report results on the effects of zinc or selenium compared to no intervention or placebo, with the use of the trace element, combined or not with other treatments, being the only difference between the treated and control groups.

We assessed the risk of bias in both published and unpublished clinical trials with RoB 2 guidelines [48]. Two investigators (EB and FZ) assessed the risk of bias and any discrepancy was resolved with the help of a third coauthor (TF). Outcomes of primary interest were mortality and Intensive Care Unit admissions. Secondary outcomes were all outcomes related to SARS-CoV-2 infection and COVID-19 onset and progression, e.g. hospitalization, time after symptoms reduction or time for nasopharyngeal tract clearance.

Results

We retrieved 78 records from Pubmed and Scopus databases after removing duplicates (Figure 1). After title and abstract screening, we assessed the full-text of the remaining 13 papers. After removing duplicate studies and investigations not reporting any endpoints, we retrieved 4 trials, all of them evaluating the effect of zinc on COVID-19. Two of these four trials were registered on ClinicalTrials.gov database. No published clinical trial on selenium was found.

The characteristics of the four eligible studies are shown in Table 1 [49-52]. The first study was a multi-center randomized clinical trial, considering a generic population of patients with a confirmed diagnosis of COVID-19 [49]. It included a total of 191 participants from Egypt with a mean age of 43 years and with possible comorbidities of hypertension, diabetes or hepatic diseases. The observation period was 28 days and the intervention consisted of 220 mg of zinc sulfate, which contained 50 mg of elemental zinc, twice a day for 15 days. Both the intervention and the placebo arms also received hydroxicloroquine, a drug which could act as a zinc ionophore. They did not evaluated baseline zinc concentration or time between zinc initiation and symptoms onset [49]. Results did not show a significant effect of zinc treatment: recovery after 28 days and death rate were 79.2% and 5.2% in the intervention group respectively, and 77.9% and 5.3% in the control group respectively.

The second study was a single-center non-randomized and apparently unblinded clinical trial [50]. It included 113 healthy exposed participants from United States, with a duration of intervention of 20 week encompassing the adminitration of 25 mg/day of zinc together with zinc ionophores (quina plant bark extract and quercetin), vitamins C, D3 and E, and l-lysine. Population age mode was 59 years and considered comorbidities were hypertension, coronary artery disease and type 2 diabetes mellitus. Also, in this case, zinc baseline concentration was not considered. This non-randomized trial suggested possible differences between the intervention arm and the control arm (apparently not given placebo), as it reported a lower infection rate in the intervention arm (15% were diagnosed with SARS-CoV-2 infection in the control group after 20 weeks, 0% in intervention group).

The third study was a single-center double-blind randomized clinical trial on 33 COVID-19 confirmed hospitalized adults with oxigen saturation of 94% or less, having a mean age of 60 years [51]. The population was from Australia and it included participants with hypertension, diabetes, chronic cardiovascular disease, chronic respiratory disease, cirrhosis and hepathic failure. The period of intervention (0.24 mg elemental zinc/kg body weight/day) was 7 days and the period of observation of both intervention and placebo arms was 28 days. In contrast to other studies, serum baseline zinc concentration was assessed. The study did not reach the enrolment target because public health measures reduced the number of people eligible for enrolment [51]. As the only conclusion of the study, the authors reported the increased serum zinc levels induced by intravenous zinc supplementation, and the capaciity of zinc supplementation to restore adequate zinc status in the supplemented participants. Additional results reported a worse outcome concerning hospitalization in the first 7 days in the intervention arm (85% of patients hospitalized versus 67% in the placebo arm), while no differences between the two arms was observed at 28 days.

The last study was a multi-center and apparently unblinded randomized clinical trial carried out in the US, with 214 participants with SARS-CoV-2 infection who were receiving outpatient care in Ohio and Florida [52]. The mean age of the population was 45 years, and a substantial part of it reported comorbidities such as diabetes, hypertension, dyslipidemia, asthma, anxiety and depression. The intervention arm received a daily supplementation of 50 mg gluconate zinc for 10 days, while the control group received a standard ‘usual care’ for COVID-19 without further specification. The time between symptom onset and zinc intervention was assessed. The trial was stopped early for futility. A 50% reduction in symptoms occurred in a mean period of 6.7 days after the start of the trial in the standard care group, while the corresponding period in the zinc-only group was 5.9 days. Additionally, hospitalization occurred in 8.6% of the intervention group and 6.0% of the control group, while death fate was 0% for both.

Risk of bias evaluation of clinical trials with published results is shown in Table 2. All the studies had at least one source of high risk of bias: all studies analyzed, except one [51], have high

risk of bias in the deviation from the intendeed interventions. It should be noted that only two out of four trials were registered on ClinicalTrial.gov [49, 52], one [51] had published its protocol in a previous study [53], and one not neither [50].

Ongoing Trials

For currently unpublished clinical trials searched on ClinicalTrials.gov database, we retrieved 82 records, 22 of which were included even if they did not upload results (Table 3): five clinical trials are completed but the results are not yet published; ten clinical trials are in the recruitment phase. The main reason for excluding a study was the fact that the effects of trace elements were not tested, as they were administrated to both the control and case group. Nineteen ongoing trials evaluate the administration of zinc, fourteen ongoing trials specify the dose in various zinc coumpounds. The minimum daily dose of zinc was 10 mg and the maximum was 220 mg. One study analyzed selenium through administering a dose of 1000 mcg daily intravenously. In other two ongoing trials, zinc and selenium together were administered at daily doses of 7.5 mg and 15 mcg and of 10 mg and 110 mg, respectively. The risk of bias assessment was performed without considering the two domains referred to result reporting (Table 4). Most of unpublished clinical trials performed a randomized allocation for the interventions but did not provide any information about allocation concealment. Twenty ongoing trials performed a randomization, one is not randomized and another had no information available. Some studies did not blind all the participants, trial personnel and outcome assessors e.g. analysts: five studies were open label, two had a single masking: in one of the two the evaluators are blinded, in the other the participants are blinded. The remaining studies were at least double-blind.

Discussion

The relation between zinc, selenium and SARS-CoV-2 infection and COVID-19 has been discussed in the biomedical literature [49-52], and the possibility of beneficial effects of supplementation with these two trace elements has been proposed based on the purported effects of

zinc and selenium on the immune system, the capacity of these elements to counteract viral infections and diseases [24, 54, 55], and, finally, on the results of a few nonexperimental human studies [56-58]. The hypothesis arises from mechanistic evidence generated from biochemical and toxicological studies *in vitro* or in laboratory animals, showing that zinc and selenium support the immune system [13, 20] and can have effects against viral pathologies and viral replication [24, 54]. Indeed, zinc and selenium are involved in both the innate and cell-mediated immune response [20, 59-65], and zinc supplementation has been proposed to enhance the immune response [13, 66, 67].

However, in order to establish causal connections between these two trace elements and both SARS-CoV-2 infection and COVID-19 disease, randomized controlled trials are needed. In fact, this is the only reliable study design, and the gold standard for clinical research, human medicine and pharmacology to assess and confirm the efficacy and safety of any intervention [68-70]. For zinc and selenium, safety is also an issue and an endpoint of major relevance, due to the potential toxicity of high doses of these two elements, particularly of selenium, an element known to have a narrow safe range of intake [71, 72]. In this review, we were unable to retrieve any trials on selenium supplementation and COVID19-related endpoints, and therefore the current evidence does not justify selenium supplementation to prevent and treat COVID-19, especially given potential safety issues. The RCTs on zinc were characterized by substantially null and non-conclusive findings, and, in addition, several methodological issues that hampered the interpretation of results. In particular, one study did not implement any randomization, since allocation to the treatment was on a voluntary basis [50]. The results were interpreted independently from the comments and conclusions of the authors of the corresponding studies, and from the implementation of any statistical analysis.

Two of the eligible studies evaluated the effect of zinc in monotherapy supplementation, both showing lack of effect against COVID-19 severity [51, 52]. Conversely, one trial suggested possible differences between the control and intervention groups, but it was not randomized, and, in addition, zinc was part of a multi-pharmacological intervention, so the effect of zinc itself could not be disentangled. The included studies showed high heterogeneity also in terms of employed elemental

zinc doses, ranging from 7 mg/day to 100 mg/day, as well as mode of administration, i.e. intravenous or oral. In addition, the study populations in these trials were heterogeneous, since they included both participants uninfected and infected by SARS-CoV-2, and without COVID19 or with very different severity of the disease (mild, moderate, severe and critical COVID19, or unknown severity). Three studies were unblinded, thus being exposed to very serious risk of bias for possible difference in behaviour among participants based on the allocation arm, and no RCTs with low risk of bias appear to have been carried out so far. An aspect that can mislead is the lack of baseline zinc measurement at the time of enrolment, especially if no randomization has been done. Only one study performed this measurement at baseline [51].

Zinc status is notoriously difficult to assess, except for severe deficiency, and plasma zinc concentration changes in the presence of infection, so it would be difficult to determine zinc status in patients infected with COVID-19 [73, 74]. For all these reasons, any utility of zinc supplementation in COVID-19 prevention and treatment has not been proven so far, thus supporting the recommendation not to rely on zinc supplementation in COVID-19 therapy [47, 75].

For the prevention and therapy of COVID19, as more generally with any human disease, it is mandatory to use only treatments and drugs with scientifically established efficacy, and these may only be identified through randomized controlled trials adequately testing the efficacy and safety of an intervention in the target populations [69, 70]. Claims based on observational studies or laboratory studies are insufficient and may be misleading and therefore have serious consequences, such as false expectations of protection, choice of ineffective treatment, and decrease in the use of the appropriate measures to prevent the infection (starting from the specific vaccination). Finally, in some cases, mineral supplementation may lead to intakes that exceed the upper safe level (UL), a serious instance particularly for selenium given its uncertain but narrow safe range of intake [46, 72, 76]. The intake of zinc exceeded the UL derived by various agencies [77, 78] in one analyzed trial [49]. As things stand, in the absence of data from clinical trials to support zinc and selenium supplementation in COVID19 prevention and therapy, supplementation of these trace elements for these goals should

be avoided. It should also be noted that the use of zinc and selenium has not been supported or authorized by Drug Regulatory Agencies and by bodies as the World Health Organization and the Center for Disease Control [47, 75]. Nevertheless, the presence of so many ongoing trials compared to those published until now could in future modify the indications that emerge from our review.

Declarations of interest: none.

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Table 1. Description of eligible studies on clinical trials on the effects of zinc and selenium against COVID-19.

Study	Trial type and duration	Population	Population characteristics	Location	Interventions	Conclusions of the study
Abd-Elsalam 2021 [49]	RCT 23 June 2020-23 August 2020 28 days	Confirmed diagnosis of COVID-19 infection N=191	Female: 44 IG group-31 CG; Male: 52 IG-64 CG Excluded: patients with hypokalemia or hypomagnesemia, porphyria, neutrophilia, myasthenia gravis, maculopathy or changes in the visual field, heart failure, prolonged QT interval in ECG, liver cirrhosis, psoriasis, epilepsy, anemia from pyruvate kinase and G6PD deficiencies, chronic kidney disease, and pregnant or lactating females	Egypt	Combination of: - CQ/HCQ - 220 mg of Zinc Sulfate twice daily (50 mg of Elemental Zinc twice daily)	Zinc supplements did not modify the clinical efficacy of HCQ: recovery after 28 days and death fate were 79.2% and 5.2% in intervention group respectively, and 77.9% and 5.3% in control group

							respectively.
Margolin 2021 [50]	Non-randomized clinical trial March 2020-July 2020 20 weeks	Healthy exposed population N=113	53 IG-60 CG Female/male:60/40 Excluded: Oxygen saturation<94%, afebrile temperature	United States (Ohio)	Combination of: - Zinc 25 mg once a day - Vitamin C - Vitamine D3 - Vitamine E -l-lysine - Quercetin - Quina™	15% were diagnosed with SARS-CoV-2 infection in the contrl group after 20 weeks, 0% in intervention group.
Patel 2021 [51]	Phase IIa pilot double-blind RCT From May 2020 28 days	COVID-19 confirmed hospitalized adults with oxygen saturation (SpO2) of 94% or less N=33	Female: 4 IG-8 CG Male: 11 IG-10 CG Exclusion: age<18, pregnant, lactating female, allergy to zinc, severe hepatic impairment, history of organ transplant which requires immunosuppressive treatment which can interfere with kidney function, HIV infection, patient required cardiopulmonary resuscitation, imminent or inevitable death, eGFR<60mL/min/1,73m^2 or patient requiring dialysis, haemochromatosis	Australia	- 0.5 mg/kg/day of Zinc Chloride (0.24 mg/kg/day elemental zinc)	The primary outcome in non-ventilated patients was oxygen flow required to maintain blood oxygen levels above 94%.

					by intravenous infusion	Did not reach its target enrollment. Same clinical results in the two groups. HDIV Zn increased serum zinc levels above the deficiency cutoff of 10.7 µmol/L in the intervention arm.
Thomas 2021 [52]	RCT 27 April 2020-14 October 2020 10 days	Diagnosis of SARS-CoV-2 infection confirmed with a polymerase chain reaction assay N=214	Female: 37 only zinc intervention group -31 control group Male: 0 Excluded: hospitalized, resided outside of Ohio or Florida, pregnant, actively lactating, had advanced chronic kidney disease, liver disease awaiting transplantation, or history of calcium oxalate kidney stones	United States (Ohio and Florida)	Separately: -50 mg of Zinc Gluconate once a day (7 mg of Elemental Zinc once a day	Study was stopped. Treatment had no effect on SARS-CoV-2 symptoms. 50% reduction in symptoms occurred in a mean of 6.7 days in standard care group and 5.9

						[79]) - Ascorbic acid - Combination of both treatment	days in zinc only group.

Abbreviations: CG, control group; CQ, chloroquine; eGFR, estimated glomerular filtration rate; HCQ, hydroxychloroquine; HDIVZn, high-dose intravenous zinc; IG, intervention group; RCT, randomized controlled trial.

Table 2. Risk of bias of the eligible clinical trials evaluated with RoB 2 tools. Red, yellow and green marks correspond to high, medium and low risk of bias respectively.

Study	Bias arising from randomization process	Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result
Abd-Elsalam 2021 [49]						
Margolin 2021 [50]						
Patel 2021[51]						
Thomas 2021 [52]						

Table 3. Description of unpublished clinical trials on the effects of zinc and selenium against COVID-19.

NCT Number	Interventions	Enrollment	Study Designs	Locations	Status
NCT04323228	Dietary Supplement: Oral supplement enriched in antioxidants (15 mcg Selenium and 7.5 mg Zinc once a day) Dietary Supplement: cellulose-containing placebo capsules	40	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Care Provider) Primary Purpose: Supportive Care	Saudi Arabia	Recruiting
NCT04334512	Drug: Hydroxychloroquine Drug: Azithromycin Dietary Supplement: Vitamin C Dietary Supplement: Vitamin D Dietary Supplement: Zinc (not	600	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment	California, United States	Recruiting

	specified)				
NCT04335084	Drug: Hydroxychloroquine Dietary Supplement: Vitamin C Dietary Supplement: Vitamin D Dietary Supplement: Zinc (not specified)	600	Allocation: Randomized Intervention Model: Single Group Assignment Masking: Double (Participant, Investigator) Primary Purpose: Prevention	California, United States	Recruiting
NCT04435587	Drug: Ivermectin Pill/ Zinc sulfate (100 mg two times a day for three days) Drug: Combined ART/hydroxychloroquine/Zinc sulfate (23 mg two times a day for five days)	80	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor) Primary Purpose: Treatment	Thailand	Recruiting
NCT04446104	Drug: Hydroxychloroquine Sulfate Tablets Drug: Ivermectin 3 mg Tab Drug: Zinc (80 mg once a day) Drug: Povidone-Iodine Dietary Supplement: Vitamin C	4257	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Prevention	Singapore	Completed
NCT04468139	Drug: Quercetin Dietary Supplement: bromelain Drug: Zinc (50 mg once a day) Drug: Vitamin C	60	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Saudi Arabia	Recruiting
NCT04472585	Drug: Ivermectin Injectable Solution Other: Injectable Placebo Drug: Zinc (20 mg three times a day) Drug: Placebo empty capsule Drug: Oral Ivermectin	180	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Pakistan	Recruiting
NCT04542993	Dietary Supplement: Zinc Picolinate (50 mg three times a day) Dietary Supplement: Resveratrol Dietary Supplement: Zinc Picolinate Placebo Dietary Supplement: Resveratrol Placebo	60	Allocation: Randomized Intervention Model: Single Group Assignment Masking: Single (Participant) Primary Purpose: Supportive Care	Washington, United States	Active, not recruiting
NCT04558424	Dietary Supplement: Zinc gluconate (220 mg once a day) and ascorbic acid	50	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Supportive Care	Bangladesh	Not yet recruiting
NCT04621149	Other: chlorine dioxide Dietary Supplement: zinc acetate (not specified) Drug: Famotidine Other: placebo Dietary Supplement: lactoferrin, green tea extract	120	Allocation: Randomized Intervention Model: Factorial Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Arizona, United States	Recruiting
NCT04621461	Dietary Supplement: Zinc	3	Allocation: Randomized	New York,	Completed

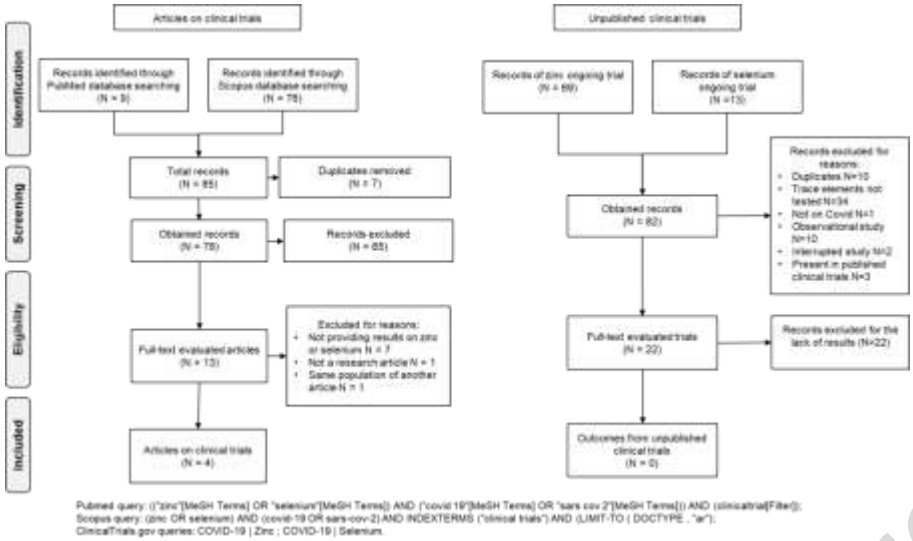
	Sulfate (220 mg once a day) Drug: Placebo		Intervention Model: Single Group Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment	United States	
NCT04641195	Dietary Supplement: Vitamin D3 (cholecalciferol) Dietary Supplement: Zinc gluconate (40 mg once a day) Dietary Supplement: Zinc gluconate (40 mg once a day) & Vitamin D (cholecalciferol) Other: Placebo	700	Allocation: Randomized Intervention Model: Factorial Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	India	Recruiting
NCT04751669	Dietary Supplement: Vitamin and trace elements (Zinc 10 mg once a day and Selenium 110 mg once a day) Dietary Supplement: Placebo	300	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Spain	Not yet recruiting
NCT04828538	Dietary Supplement: Vitamin D Dietary Supplement: Omega DHA / EPA Dietary Supplement: Vitamin C, Vitamin B complex and Zinc Acetate (100 mg once a day)	3600	Allocation: Randomized Intervention Model: Factorial Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Other	Mexico	Active, not recruiting
NCT04869579	Drug: Selenious Acid (first day 2000 mcg, following days 1000 mcg) Other: Placebo	100	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment	Texas, United States	Not yet recruiting
NCT04935515	Drug: Oral Antibiotic, Antihistamine, Anti-inflammatory, Multivitamins and Zinc (not specified) Drug: Oral low dose steroid Drug: Intravenous Antibiotics with Low dose steroid. Drug: Oral anti-coagulant	25	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Supportive Care	India	Completed
NCT04937556	Dietary Supplement: Probiotic: Lactobacillus salivarius + Vit D + Zinc (not specified) Dietary Supplement: Placebo	60	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment	Spain	Recruiting
NCT05003492	Combination Product: Combination therapy with Zinc (15 mg twice daily) plus Standard therapy Radiation: Photodynamic therapy Drug: Standard therapy	2	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Saudi Arabia	Not yet recruiting
NCT04377646	Drug: Hydroxychloroquine Drug: Hydroxychloroquine (placebo) Drug: Zinc (15 mg once a day) Drug: Zinc (Placebo)	660	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Prevention	Tunisia	Not yet recruiting
NCT04551339	Dietary Supplement: PreserVision AREDS	2700	Allocation: Randomized Intervention Model: Parallel	Minnesota, United	Completed

	formulation soft gels or tablets (69,6 mg/day of zinc) Dietary Supplement: Multivitamin with 11mg of zinc		Assignment Masking: None (Open Label) Primary Purpose: Other	States	
NCT04584567	Drug: Doxycyclin + Placebo Drug: Doxycyclin + Zinc (15 mg once a day) Drug: Placebo	194	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Prevention	Tunisia	Completed
NCT04780061	Drug: Vitamin D3 50,000 IU Dietary Supplement: Vitamin C/Zinc (8,3 mg three times a day) Dietary Supplement: Vitamin K2/D Other: Microcrystalline Cellulose Capsule Other: Medium Chain Triglyceride Oil	200	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Canada	Recruiting

Table 4. Risk of bias evaluation of the ongoing clinical trials having used RoB tools. Red, yellow and green marks correspond to high, medium and low risk of bias, respectively. The last two domains have not been evaluated as no result was presented.

Trial	Bias arising from randomization process	Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias in measurement of the outcome
NCT04468139	✗	✗	−	−
NCT05003492	−	✗	✗	−
NCT04446104	−	✗	✗	−
NCT04935515	✗	✗	✗	−
NCT04435587	−	✗	✗	−
NCT04542993	−	✗	✗	−
NCT04334512	−	✗	✗	+
NCT04869579	−	✗	✗	+
NCT04641195	−	+	+	+
NCT04828538	−	+	+	+
NCT04621461	−	✗	✗	+
NCT04335084	−	✗	✗	+
NCT04323228	−	+	+	−
NCT04472585	−	+	+	+
NCT04937556	−	+	+	+
NCT04621149	−	+	+	+
NCT04751669	−	+	+	+
NCT04558424	+	+	+	+
NCT04377646	−	+	+	+
NCT04551339	−	−	✗	−
NCT04584567	−	+	+	−
NCT04780061	−	+	+	+

Figure 1: Flow chart for clinical trials on zinc or selenium for COVID-19 prevention and treatment.



CRediT authorship contribution statement

TF and MV conceived the study. EB and FZ extracted and analyzed data with TF. All authors interpreted the data. EB and FZ prepared the first of the manuscript with contribution of TF and MV. All authors read and approved the final manuscript.