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Review

# Immunopharmacological perspective on zinc in SARS-CoV-2 infection

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ABSTRACT

The novel SARS-CoV-2 which was first reported in China is the cause of infection known as COVID-19. In comparison with other coronaviruses such as SARS-CoV and MERS, the mortality rate of SARS-CoV-2 is lower but the transmissibility is higher. Immune dysregulation is the most common feature of the immunopathogenesis of COVID-19 that leads to hyperinflammation. Micronutrients such as zinc are essential for normal immune function. According to the assessment of WHO, approximately one-third of the world's society suffer from zinc deficiency. Low plasma levels of zinc are associated with abnormal immune system functions such as impaired chemotaxis of polymorphonuclear cells (PMNs) and phagocytosis, dysregulated intracellular killing, over-expression of the inflammatory cytokines, lymphopenia, decreased antibody production, and sensitivity to microbes especially viral respiratory infections. Zinc exerts numerous direct and indirect effects against a wide variety of viral species particularly RNA viruses. The use of zinc and a combination of zinc-pyrithione at low concentrations impede SARS-CoV replication in vitro. Accordingly, zinc can inhibit the elongation step of RNA transcription. Furthermore, zinc might improve antiviral immunity by up-regulation of IFNα through JAK/STAT1 signaling pathway in leukocytes. On the other hand, zinc supplementation might ameliorate tissue damage caused by mechanical ventilation in critical COVID-19 patients. Finally, zinc might be used in combination with antiviral medications for the management of COVID-19 patients. In the current review article, we review and discuss the immunobiological roles and antiviral properties as well as the therapeutic application of zinc in SARS-CoV-2 and related coronaviruses infections.

## 1. Introduction

Novel coronavirus infections have become visible periodically in different areas of the world in recent years. Coronaviruses are classified as a member of the Orthocoronavirinae subfamily, in the Coronaviridae family and the Nidovirales order [1,2]. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) was first identified in 2002 [1,3,4]. During the epidemic of SARS-CoV, there were 8422 infected cases and 916 deaths worldwide [3,4]. The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) occurred in 2012 [1] reportedly infected 1401 people and killed 543 (~39%) people around the world [3,5]. Lately, another type of coronavirus has caused a pandemic that has impacted

*Abbreviations:* ACE2, Angiotensin-converting enzyme 2; A2M, α2-macroglobulin; ARDS, Acute respiratory distress syndrome; 3CLpro, 3C-like protease; COVID-19, Coronavirus Disease 2019; CRP, C-reactive protein; DCs, dendritic cells; HAIs, healthcare-associated infections; IFN-α, interferon α; MTs, metallothionein proteins; MERS-CoV, the Middle East Respiratory Syndrome Coronavirus; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κB; PLpro, papain-like protease; PMNs, Polymorphonuclear cells; RdRp, RNA-dependent RNA polymerase; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; Th, T helper; TMPRSS2, transmembrane protease serine 2; TNF-α, tumor necrosis factor α; WHO, World Health Organization; ZnTs, zinc transporters.

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the health infrastructure, social, and economy of the world at large. The International Committee on Taxonomy of Viruses designated SARS-CoV-2 as the pathogen and the World Health Organization (WHO) named this pneumonia as Coronavirus Disease 2019 (COVID-19) [2,6–9]. The first case of COVID-19 was identified in November 2019 in Wuhan, China [2,10,11]. Its transmission had rapidly spread to other Asian countries followed by the middle east, Europe, the Americas, Oceania, and Africa [12]. This pandemic is presumed to be originated from a zoonotic source, most likely from bats [13]. The routes of transmission are established to be through respiratory droplets from coughing and sneezing from human to human as well as through aerosols [2,10]. The symptoms in infected individuals can be a mild upper respiratory tract disorder including shortness of breath, cough, chills, fever, and tiredness while late complications such as sepsis, ARDS (acute respiratory distress syndrome), septic shock, heart failure, and ultimately death may present in severe cases [10,14,15]. The rapid growth of patient numbers, particularly critical or mortal patients, imposed a great obstacle to public health [7]. According to the WHO, the ratio of crude mortality (calculated as reported deaths divided by total reported cases) is 2–5%, while these rates are variable for patient age, presence of co-morbidness, and the country of transmission [2,16,17]. The mortality rate of COVID-19 is lower in comparison with SARS (10%) and MERS (40%) [18], but the transmissibility of SARS-CoV-2 is higher than SARS and MERS [19]. However, death may still happen following the severe COVID-19-associated pneumonia [8], thereby clinicians are to carefully consider the risk factors of COVID-19, recognize critical patients at an early stage, and reduce the risk of mortality by a rational treatment plan [7].

Multiple reports have demonstrated that vitamin supplements such as A, B6, B12, C, D, E, and folate along with trace elements including copper, iron, magnesium, selenium, and zinc are essential for supporting the immune system [20,21]. The significant role of zinc in human life was not identified until 1961 [22]. According to the most recent literature, the administration of zinc supplements demonstrates a potential role to enhance antiviral immunity. Such effect is observed in both innate and humoral responses [23], especially in immunocompromised and elderly patients improving immune function [24]. Zinc is associated with a variety of basic cellular functions like proliferation, differentiation, RNA and DNA synthesis, and survival [25–29]. Moreover, zinc is essential for the development of both the innate and adaptive immune cells [1,21]. Zinc deficiency, however, is extensively prevalent [29,30], and it can cause life-threatening diarrhea and respiratory distress particularly in children [21]. Based on the WHO statistics, nearly two billion people in the developing world may have nutritional zinc deficiency [31]. Zinc deficiency in humans may be severe, moderate, or marginal [31]. Severe zinc deficiency occurs in acrodermatitis enteropathica (AE), after penicillamine therapy, and in acute alcoholism [31]. Average deficiency is observed in malabsorption, sickle cell disease, and chronic renal disease particularly in females [31]. A soybean protein-based diet is also associated with a rare zinc deficiency in healthy people [31]. From nearly 56 years ago, zinc deficiency has been recognized as a disease playing critical roles in growth retardation, hypogonadism, and cognitive impairment [32]. Also, according to the past and current evidence, there is a strong association between natural low plasma levels of zinc with abnormal immune system functions such as delayed wound healing, increased oxidative stress, inflammation-independent low-grade production of inflammatory cytokines, and sensitivity to infections [25–27,33–35]. Zinc serves as a cofactor for proteins and controls the activity of more than 300 enzymes and transcription factors, exerting auxiliary effects on the immune system [25,26,32,36–39]. Zinc-deficient patients were reported to exhibit severe immune dysfunctions [40], inclusive of thymic atrophy and lymphopenia, particularly decreased number of $CD4^+$ T helper (Th) cells, which subsequently lead to a decreased $CD4^+/CD8^+$ ratio [27,41,42]. Additionally, the activity of natural killer (NK) cells is reduced and cytotoxicity of monocytes is augmented in zinc-deficient cases [27,43].

Effective treatment outcomes for recent viral infections of the respiratory tract, particularly those caused by influenza viruses, remains to be determined [44]. Due to the altering nature of antigenic structures of respiratory viruses, especially RNA viruses like SARS-CoV-2, the production of an effective vaccine is extremely challenging to achieve [44]. Based on the available literature, it seems reasonable the use of natural remedies can play an alternative role in enhancing immune function especially the protective role until safe and effective vaccines will be available [44]. Scientific evidence suggests that several complementary therapies like taking vitamin C supplements, oral zinc, and probiotics help fight viral infections by reducing the severity of the common cold; however, robust randomized clinical trials will certainly shed more light on the clinical efficacy of such supplements especially in the era of COVID-19 [44]. Approximately 16% of all deep respiratory infections are associated with zinc deficiency [45]. Zinc acts as an anti-inflammatory agent. In zinc deficiency, the proinflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) are rapidly increased during infection which then results in acute respiratory distress syndrome (ARDS), vascular hyperpermeability, diffuse coagulopathy, multi-organ failure, and ultimately death [32]. Zinc-deficient populations exhibit an improved risk for viral infections [29], hence zinc level is a key mediator influencing antiviral immunity [29]. Currently, details on the influence of zinc ions for Nidovirales like SARS, MERS, and other human coronaviruses are almost unknown [46]. According to previous studies, it is believed that spike protein, angiotensin-converting enzyme 2 (ACE2) [47], transmembrane protease serine 2 (TMPRSS2), 3C-like protease (3CLpro), RNA-dependent RNA polymerase (RdRp), and papain-like protease (PLpro) can be the main targets for antiviral drugs against coronavirus infections [46] mainly against SARS-CoV-2 [48,49]. For example, increased intracellular zinc ion concentrations damage the replication of several RNA viruses such as coronaviruses including SARS-COV, MERS-COV, and also SARS-COV-2 [46].

This review aimed to focus on the most recent findings of the potential effect of zinc as an essential micronutrient and its antiviral properties in the prevention, treatment, and management of COVID-19.

## 2. The biological roles of zinc in human

It is well established that micronutrients and nutrition are vital in health [43]. After iron, zinc is the second most abundant trace metal in the human body with a total amount of 2–4 g [22,27,29,50–52]. The concentration of zinc in the plasma is 12–16 μmol/L [43,52]. To maintain one's health, sufficient zinc intake is necessary, because the human body has no specific storage system for zinc [43]. The biochemical features of zinc were revealed in 1939 when it was found that the carbonic anhydrase enzyme in erythrocytes contained stoichiometric amounts of zinc, which was essential for the enzymatic function [53]. Fifteen years later, bovine pancreatic carboxypeptidase was identified as another zinc-associated enzyme [53]. The biochemical and clinical aspects of zinc are important because zinc deficiency was discovered as a human health problem [22,54,55]. Compared to plasma zinc levels, the analysis of cellular zinc was suggested as a more sensitive approach to detecting zinc deficiency since the amount of zinc in granulocytes, lymphocytes, and platelets decrease within 8–12 weeks while plasma zinc levels decline after 4–5 months [56].

As a harmless supplement for humans [51], zinc is important in homeostasis, oxidative stress, immune function, and apoptosis throughout growth [55,57]. Cellular zinc is very important in homeostatic control [51]. Human cells have at least 10 zinc transporters (ZnTs) that carry zinc out of the cytosol as well as 15 zip transporters (Zrt/Irt-like proteins) to import zinc into the cytosolic environment from other intracellular compartments or extracellular space [43,51,54,58]. The amount of free zinc ions is controlled at the single-cell level, and zinc-binding motifs are present in several human proteins [55]. The three general functions of zinc include catalytic, structural, and regulatory functions [22,54–56,59]. Investigations regarding the number of zinc proteins in the human zinc proteome revealed that zinc is ubiquitous in

subcellular metabolism [50,53]. The International Union of Biochemistry discovered six categories of enzymes including hydrolases, isomerases, ligases, lyases, oxidoreductases, and transferases in which zinc is a basic component of the catalytic site/sites of at least one enzyme in each group [50,59,60]. The structural roles of zinc are important in cellular and subcellular metabolism. The zinc finger motif is a remarkable example that is a commonly recurring motif in transcription proteins [50]. Important examples of regulatory functions mediated by zinc include regulation of gene expression, apoptosis, cell growth, and differentiation [50]. Zinc also functions as an antioxidant and can stabilize membranes [61]. The absorption of water and electrolytes may be damaged in zinc deficiency, so gastrointestinal diseases can happen [62]. Zinc deficiency makes organisms sensitive to bacterial toxins and viral infections that result in diarrhea and decreased absorption of nutrients [62,63]. Zinc deficiency affects cells of both innate and adaptive immunity [40]. The production of pro-inflammatory cytokines increases during chronic zinc deficiency [64]. This in turn influences the clinical outcome of inflammatory conditions [65].

## 3. Zinc and immune function

The role of zinc in the immune system functions have been recently explored, and it is now widely accepted that zinc is one of the main micronutrients in human health and nutrition [40,66]. Zinc regulates basic cellular functions such as DNA replication, RNA transcription, cell division, and cell activation [40,61]. Zinc homeostasis is essential for the immune system to do its adequate function and both cell-mediated and humoral immunity need zinc [1,2,23,52]. Almost every immunological process is affected by zinc in some way [43]. The immune response involves two mechanisms; innate (fast, non-antigen specific) and adaptive immunity (slower, antigen-specific), and zinc strongly affects numerous aspects of both of them [40,58,61,67,68]. Polymorphonuclear cells (PMNs), NK cells, and macrophages are some of the first responder cells that encounter invasive pathogens and destroy them as innate immunity mechanisms [43] and zinc is important for normal development (proliferation, differentiation, and maturation) and also all the functions of them [2,23,61,67,69] because zinc deficiency influences on the number and function of these immunologic mediators [61,70]. PMN chemotaxis and phagocytosis are reduced during zinc deficiency [43]. The macrophage, an essential cell in many immunologic functions, is adversely affected by zinc deficiency, which can deregulate intracellular killing, cytokine production, and phagocytosis [61,71]. Following phagocytosis, pathogens are eradicated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzymes, which were reported to be repressed by both zinc surplus and the deficiency [43,72]. It was shown that the generation of proinflammatory cytokines including IL-1β, IL-6, and TNF-α is increased in zinc deficiency [2,23,32,40,43,63,73,74]. In the adaptive immune system, zinc deficiency leads to T cell lymphopenia, thymic atrophy, decreased number of premature and immature B cells, and declined antibody generation [2,42,43,67]. Between diverse alterations in immunity that relate to zinc deficiency, T lymphocytes are more sensitive [23]. Reduced percentage of peripheral and thymic T cells, compromised proliferation, and function of Th and cytotoxic T cells are some of the results of zinc deficiency [23]. Previous investigations reported that even mild zinc deficiency in humans can lead to an unregulated resistance to infection by creating an imbalance between Th1 and Th2 cell reactivity [40,75]. Zinc also inhibits caspases 3, −6, and −9, and increases the ratio of Bcl-2/Bax, thus improving cellular persistence to apoptosis and as a result, increasing the number of Th cells [2].

## 4. Impact of zinc supplementation on infectious diseases

The cause of morbidity and mortality worldwide depends on healthcare-associated infections (HAIs) by pathogenic microorganisms such as bacteria, viruses, fungal pathogens, and other microorganisms [76]. Several studies have shown the value of zinc supplementation on infectious diseases in human populations [68,73,77–79]. Outbreak and period of chronic diarrhea can reduce up to 25–30% by using daily zinc supplementation. Furthermore, the use of a daily zinc supplement can lower the acute respiratory infection rate by up to 45% in addition to the reduction of the common cold duration [68]. Both host and pathogens need trace minerals especially zinc so that competition could take place between the invading pathogens and the infected host [43]. Pathogens rely on zinc for propagation, survival, and disease formation [43]. During an infection, the levels of plasma zinc are greatly reduced. The human body has developed certain mechanisms that do not let the pathogen reduce the amount of zinc, however, some pathogens employ strategies to conquer these mechanisms [43].

Certain population groups such as infants, preterm ones in particular, and the elderly present with a greater risk for zinc deficiency and its complications [62,80]. According to past studies, one of the leading causes of pneumonia in the elderly is low zinc status as almost 15% of people with community-acquired pneumonia, Serum zinc levels are low and respiratory failure, ventilator-induced injury, and sepsis are its complications [69]. Zinc is one of the key mediators regulating the function and development of immune cells. According to a study by Acevedo-Murillo et al., pneumonia patients who received zinc supplements recovered significantly and the cytokine response in the Th1 pattern (IL-2 and INF-γ) was increased [81]. Based on a review, zinc supplementation limited the occurrence of pneumonia in children by 13–41% [82].

## 5. The role of zinc in antiviral immunity

Micronutrient deficiency is often associated with viral infections because of its impaired effect on the immune system, mostly cell-mediated immunity, phagocyte activity, cytokine generation, antibody affinity and secretion, and the complement system [8]. Therefore, a healthy food habitation that contains a high amount of minerals, vitamins, and antioxidants improves immune functions to a great extent [8,66,71,83]. According to a study by Calder et al., the optimal nutritional status is important to protect against viral infections [21,79]. Vitamin C, E, zinc, and beta-carotene are antioxidants that increase the number of T cells, IL-2 production, NK cell activity, improve the response of lymphocytes to mitogen, and immune response to influenza virus vaccine [8]. Accumulating evidence reveals an association between zinc deficiency and a variety of infectious diseases inclusive of acute cutaneous leishmaniasis, shigellosis, malaria, tuberculosis, human immunodeficiency virus (HIV), pneumonia, and measles [27]. Zinc exerts numerous direct and indirect effects against a wide variety of viral species [2,14,69,78], particularly RNA viruses such as rhinovirus, respiratory syncytial virus, and SARS-CoV [84]. These effects are achieved through different mechanisms including regulation of viral entry, fusion, propagation, and viral protein production [2,29,85]. Moreover, zinc most probably preserves the cellular membrane by blocking virus entry into the cells [2,86]. As decreased integrity of the mucosal layer and damage of tight junction structure can deteriorate viral inflammation, zinc contributes to antiviral immunity by regulating the proteins of tight junction, rendering in the preservation of mucosal membrane integrity [29,67]. Zinc also demonstrates the antiviral effect by disrupting the viral replication pathway [68,86,87] through changing the proteolytic processing of RNA-dependent RNA polymerase (RdRp) and replicase polyproteins in HCV, influenza virus, and rhinovirus, thus it is hypothesized that zinc may modify the RNA synthesis of nidovirales such as SARS-CoV-2 [2,63,88]. Several clinical trials have proven that zinc supplementation reduced inflammatory cytokines and oxidative stress biomarkers in the elderly [68,89]. Additionally, zinc supplementation could lead to the upregulation of zinc-containing transcriptional factor (A20) and blockade of the nuclear factor-κB (NF-κB) signaling mode (a classical pro-inflammatory signaling pathway during cell responses) [69,90,91], thereby the generation of inflammatory cytokines were

significantly decreased [68]. A study by Te Velthuis et al. showed that the antiviral activity of zinc was raised by increasing the production of interferon α (IFN-α) by leukocytes [67,69]. The shortage of zinc during lung inflammation can cause the alteration of the extracellular matrix to fibrotic tissue [92].

## 6. Role of zinc against coronavirus infection

In viral infections, the immune system tries to remove the virus from the body. As mentioned before, minerals, antioxidants, and vitamins are essential to improve immune functions. According to Wu et al., nutritional factors are important to prevent damage and protect the lungs against coronaviruses [78] and zinc is an essential factor for the regulation of the immune system. Zinc has an important effect on NK cell function, phagocytosis, generation of oxidative burst, $CD4^+$ and $CD8^+$ T cells, and chemotactic activity of granulocytes [93]. Zinc supplementation enhances the number of T cells and NK cells and promotes the production of IL-2 and soluble IL-2 receptor [93]. However, the mechanism of action of zinc in airway inflammation is still unclear [94]. Zinc plays a pivotal role in the differentiation of T cells in the thymus [32]. The real function of macrophages is under the influence of zinc homeostasis [95] and macrophages have an essential role in iron homeostasis [96]. Fe regulates the function of macrophages through reduction of NF-κB p65 translocation into the nucleus and zinc can indirectly inhibit the expression of proinflammatory cytokines [97]. The use of zinc and a combination of zinc-pyrithione at low concentrations impede SARS-CoV replication [1,8,46]. The single spike (S) protein of coronavirus should be cleaved by host proteases so that the virus can enter the host cells [98]. At least four groups of proteases including cathepsins B and L, transmembrane protease especially TMPRSS2, elastases, and furin were shown to be involved in the cleavage of a single spike (S) protein [98]. Cathepsins B and L are acid-dependent cysteine proteases of the endosomal compartment, and cathepsin-inhibitors block the cell entry of coronaviruses particularly SARS-CoV and MERS-CoV [98,99]. Transmembrane proteases are acid-independent serine proteases located on the cell surface with a less defined biological role [98,100]. Elastases are extracellular serine proteases of the lung tissue that have been distinguished within a single spike (S) protein [98]. The structure of furin possesses a motif for cleavage substrate at the N terminal of the MERS-CoV fusion peptide [98]. Several protease inhibitors have been suggested as antiviral agents [98]. Zinc metalloproteases strongly decreased both the entry of these viruses and also cell-cell fusion [98]. According to one study, metalloprotease ADAM17/TACE plays a role in SARS-CoV entry by cleaving ACE2 [101], though another study has rejected it [100]. As mentioned before, RdRps are key targets for antiviral research, and increased intracellular zinc concentrations damage the replication of several RNA viruses inclusive of SARS-CoV and MERS-CoV [46,102].

## 7. Antiviral activity of the zinc ionophores against coronaviruses

Zn ions and Zn ionophores have the potential to inhibit various RNA viruses [46]. Hinokitiol and pyrithione are two zinc ionophores involved in the import of extracellular zinc into the cytosol, increasing intracellular zinc concentrations. Therefore, disturbance of the proteolytic processing of viral polyproteins will efficiently impair the replication of RNA viruses [103]. According to Hoang et al., hinokitiol can be utilized in the prevention and treatment of COVID-19 and other respiratory viral infections [86]. Another zinc ionophore is hydroxychloroquine (HCQ) which is used both for prevention and therapy combined with azithromycin in COVID-19. Despite the immunosuppressive, anti-inflammatory, anti-autophagy, and antimalarial functions of HCQ [104], its exact mechanism in COVID-19 remains unclear. Chloroquine and HCQ tend to accumulate in acidic environments such as lysosomes and inflamed tissues [104,105]. They increase the pH of lysosomes and reduce the viral load through glycosylation of the cellular receptor of SARS-CoV-2 [106,107]. Given that patients with severe SARS-CoV-2 infection are at high risk of thrombosis [108], HCQ and chloroquine can reduce the procoagulatory state by inhibition of antiphospholipid antibody binding [108] or inhibition of platelet aggregation [109] both in vitro and in vivo [104]. According to recent studies, CQ and HCQ represent two candidate drugs that reduce the morbidity and mortality of COVID-19 patients by indirectly impeding virus replication and RdRp activity. Thus, CQ/HCQ therapy in combination with zinc may be more efficient in COVID-19 treatment [9,15,58] by enhancing drug cytotoxicity and inducing apoptosis in infected cells [58]. Unfortunately, HCQ inhibits the proliferation of T cells which is not good for severe COVID-19 cases who suffer from acute respiratory problems [106]. Flavonoids such as quercetin and epigallocatechin 3-gallate (EGCG) demonstrate antioxidant activity [110]. According to a hypothesis, flavonoids can ameliorate SARS-CoV-2 infection by reducing both the transmembrane peptidase serine 2 (TMPRSS2) and Furin [111]. Husam Dabbagh-Bazarbachi et. al. further verify this by showing that polyphenols such as the flavonoids quercetin (QC) and epigallocatechin-gallate have ionophore activity and they can chelate zinc cations and transport them through the plasma membrane. Therefore, they can be used to control zinc homeostasis and modulate zinc-dependent biological pathways [109]. EGCG is known for its antiviral activity against a wide range of DNA and RNA viruses and the ability to control the tissue damage caused by SARS-CoV-2 infection [112]. Quercetin demonstrates an antiviral effect on a wide range of the coronaviridae family by interfering the viral entry and replication [75,113–116]. Furthermore, Quercetin regulates the angiotensin-converting enzyme 2 (ACE2) expression, thereby blocking the entry of SARS-CoV into the host cells [117]. Quercetin also affects the life cycle of virus [118]. Quercetin was shown to prevent the production of TNFα in macrophages in vitro [119] and promote the antiviral activity of zinc through facilitating the zinc transport across lipid membranes [113]. As reported in a study by Anil Pawar et al., the combination of quercetin and zinc can be a preventative and curative choice for COVID-19 patients [120].

## 8. Role of zinc in SARS-CoV-2-mediated inflammatory pathways

Immune responses in COVID-19 patients are either normal or manifested as lower count of white blood cells, thrombocytopenia, lymphopenia, enhanced levels of C-reactive protein (CRP), delayed secretion of cytokines and chemokines [80] by innate immune cells such as monocytes, macrophages, and dendritic cells (DCs) at early stages of the disease [58,121,122]. Furthermore, increased secretion of IFNs and proinflammatory cytokines like IL-1β, IL-6, IL-7, IL-8, IL-17 and TNF -α occurs in the late stages of the disease [32]. Dysregulation of the immune system leads to the hyperinflammatory stage of COVID-19 termed as the “cytokine storm” [11,32] that eventually results in ARDS [120]. Inflammatory pathways activated in SARS-CoV-2 infection comprise the IL-6/Janus kinase/STAT (IL-6/JAK/STAT) [78,123], IFN cell signaling pathway [124,125], TNFα/NF-κB [126], toll-like receptor (TLR) pathway [127], T cell receptor (TCR) pathway [78], and JAK-STAT pathway [128,129].

Food habitation and stressful conditions are very important in predisposing one to infection by SARS-CoV-2 [8]. Regularly, low serum zinc levels were observed in patients with pre-existing noncommunicable [15]. Since 16% of deep respiratory infections are associated with zinc deficiency [45], it is presumed that zinc supplementation is beneficial to COVID-19 prevention and treatment [69]. Therefore, the daily use of zinc up to 50 mg may protect the body by modifying the host’s immune resistance to viral infection [10,87]. Zinc is one of the primary elements that control the activity and proliferation of neutrophils, macrophages, NK cells, T and B lymphocytes, and cytokine production by immune cells [56,58,69,80,130] so regulates inflammatory response. It may regulate T-cell functions as a result of inflammatory responses [69,131]. In COVID-19 patients, secretion of type I and type II IFNs are decreased.

Zinc raises the production of IFN-α by human leukocytes and enhances its antiviral influence through JAK/STAT1 signaling pathway [15,69]. Zn deficiency caused upregulation of IL-1β, TNFα, and ICAM-1 and increase proinflammatory cytokines including IL-6, IL-8, and TNF by enhancement NF-κB p65 mRNA expression [94]. Zinc plays critical roles in the production of IL-2 and IFN-γ and also the secretion of IL-12 from macrophages as a stimulant of NK and cytotoxic T cells [32]. Zinc deficiency affects the production of the anti-inflammatory IL-10 cytokine which is important for Th1 response and the function of macrophages [32].

## 9. Role of zinc in SARS-CoV-2-mediated viral entry and replication

As indicated earlier, zinc has a variety of direct and indirect antiviral confidants against SARS-COV-2 through different mechanisms including modulation of viral entry, fusion, and replication [2,16,80]. Modulation of ACE2 receptor and transmembrane proteases, especially TMPRSS2, was discussed as the potential therapeutic strategy in COVID-19 treatment [47] since the entry of SARS-CoV-2 into target cells requires ACE2 and the TMPRSS2 protease [15,132,133]. According to a very recent report, SARS-CoV-2 enters the host cells via molecular communications occurring between the peptidase domain of ACE2, which is a zinc-metalloenzyme, and the receptor-binding domain of the spike glycoprotein (S protein) of SARS-CoV-2 [71,134]. Sirt-1 regulates ACE-2 expression [15] and zinc is decreased the activity of Sirt-1 so inhibitors of Sirt-1 can decrease the activity of ACE2 [15,16,135] which is a possible therapeutic factor against COVID-19 that prevent SARS-CoV-2 to infect cells [15,16]. Owing to its antioxidant and anti-inflammatory activity [32,136], zinc is essential for respiratory epithelium function and reduction of zinc levels can increase the permeance of respiratory epithelium [69] and increase its barrier functions by regulating ZO-1 and claudin-1, the proteins of tight junction structure [15,137]. Furthermore, mechanical ventilation may damage the lungs that high zinc levels can improve that [15]. Te Velthuis et al. proved a hypothesis of the direct effect of zinc ions on template binding [46]. In this way increased zinc levels can inhibit coronavirus replication by inhibiting the activity of SARS-CoV RdRp primarily in SARS-CoV-2 during the elongation step of RNA transcription [2,9,15,46,58,138]. Such findings indicate that zinc can be considered as a particular antiviral factor in the therapy of SARS-CoV-2 infection. According to a separate set of studies, zinc ions probably are localized into the mitochondria and the corresponding inhibition mechanism remains uncertain [103]. However, the mechanisms underlying zinc antiviral activity in COVID-19 require further researches [69] (Fig. 1).

## 10. Interventional clinical trials of zinc in COVID-19

The elderly and people who have preexisting chronic metabolic diseases like coronary heart disease, hypertension, diabetes, lung diseases, bronchial asthma, autoimmune diseases, kidney diseases, and cancer are more at risk of severe disease and have higher associated mortality rate [2,8–10,15,67,69,139,140]. Therefore, developing targeted and cost-effective therapies against COVID-19 is global urgent. Almost 14% of COVID-19 patients show a severe form of the disease, increasing the need for hospitalization and oxygen support, and 5% of them require intensive care unit [139]. Worldwide the main purpose of the scientific community is finding medicines that can target SARS-Cov 2 and help control the pandemic of COVID-19. Up to now, 46 studies were found about Zn and COVID-19 at the clinical trial website https://clinicaltrials.gov/ct2/home that the abstract of them is shown in Table 1. Ten studies are completed thus far, two of which have published their results. Reaz Mahmud et al. [141] conducted an experimental clinical trial using a combination of ivermectin and doxycycline for the treatment of COVID-19 along with other standard approaches. These two drugs have different mechanisms. Ivermectin can control viral replication within 24–48 h [142] and doxycycline shows antiviral and anti-inflammatory effects by suppressing the cytokine storm. Coronaviruses are strongly dependent on MMPs for survival, cell infiltration, and replication, and doxycycline is a highly lipophilic antibiotic that can chelate the zinc component of MMPs. In the second study, Naseem et al. evaluated the efficacy of HCQ in reducing COVID-19 progression in patients with mild disease [143]. They showed that the addition of HCQ, as a zinc ionophore, to the standard of care (SOC) neither stopped the disease progression nor helped in early and sustained viral clearance [143]. In an independent study by Elgazzar et al., the efficacy of ivermectin and HCQ in addition to the standard care including zinc was compared in treatment of mild to severe COVID-19 cases. They reported that using ivermectin plus standard care was very effective in controlling COVID-19 by ameliorating the cytokine storm, reducing mortality and

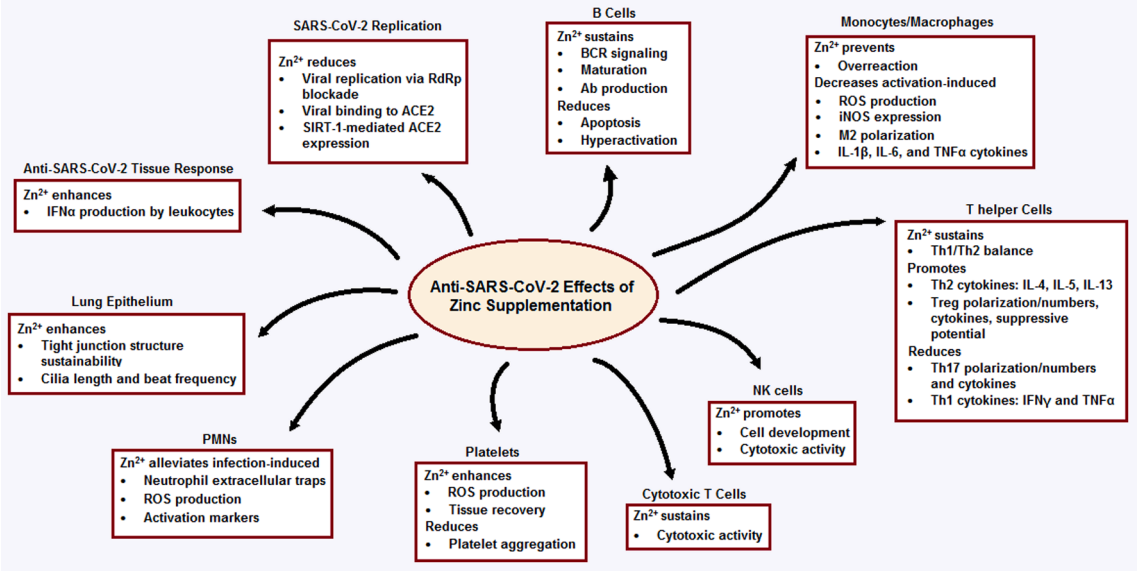


**Fig. 1.** Effects of zinc supplementation on SARS-CoV-2 infection. Information regarding each point can be tracked in the text. ACE2: angiotensin-converting enzyme 2; IFN: interferon; IL: interleukin; iNOS: inducible nitric oxide synthase; ROS: reactive oxygen species; RdRP: RNA-dependent RNA polymerase; SIRT-1: Sirtuin 1; Th: helper T cell; TNF: tumor necrosis factor.

**Table 1**
Zinc clinical trials in COVID-19 (https://clinicaltrials.gov/).

| ROW | Study Title | Intervention | Phase | The number of participants | Outcome Measures |
|---|---|---|---|---|---|
| 1 | Vitamin D and **Zinc** Supplementation for Improving Treatment Outcomes Among **COVID-19** Patients in India | Dietary Supplement: Vitamin D3 (cholecalciferol): 180,000 international units (IU) of vitamin D3 at enrollment, followed by 2000 IU once per day from enrollment to 8 weeks<br>Dietary Supplement: Zinc gluconate: 40 mg of zinc gluconate taken once per day from enrollment to 8 weeks<br>Dietary Supplement: Zinc (zinc gluconate) & Vitamin D (cholecalciferol): 180,000 IU of vitamin D3 at enrollment, followed by 2000 IU of vitamin D3 and 40 mg of zinc gluconate once per day from enrollment to 8 weeks<br>Placebo: Placebo vitamin D bolus at enrollment followed by placebo daily vitamin D maintenance doses and placebo daily zinc supplements. | Phase 3 | 700 | Time to recovery<br>All-cause mortality<br>Necessity for assisted ventilation<br>Individual symptoms duration<br>Vitamin D<br>Zinc<br>Interleukin 6 (IL-6)<br>Angiopoietin-2<br>sTREM-1<br>Immunoglobulin M (IgM)<br>Immunoglobulin (IgG) |
| 2 | Hydroxychloroquine and Zinc With Either Azithromycin or Doxycycline for Treatment of COVID-19 in Outpatient Setting | Drug: Hydroxychloroquine: 400 mg twice a day (BID) on day 1, followed by 200 mg BID for days 2–5<br>Drug: Azithromycin: 500 mg on day 1, followed by 250 mg once daily for days 2–5<br>Drug: Zinc Sulfate: 220 mg once daily for 5 days<br>Drug: Doxycycline: 200 mg once daily for 5 days | Phase 4 | 18 | Time to Resolution of Symptoms relative to baseline<br>Number of participants hospitalized and/or requiring repeat ER visits<br>ICU Length of Stay<br>Ventilator<br>Severity of symptoms<br>Number of participants with adverse events due to drug regimen<br>Number of participants with QTc prolongation >500ms |
| 3 | RCT,Double Blind, Placebo to Evaluate the Effect of Zinc and Ascorbic Acid Supplementation in COVID-19 Positive Hospitalized Patients in BSMMU | Dietary Supplement: zinc gluconate and ascorbic acid: 220 mg zinc and 1 gm ascorbic acid for 10 days in addition to their standard treatment | Not Applicable | 50 | symptoms reduction time frame<br>Symptom Resolution: Fever<br>Symptom Resolution: Cough<br>Symptom Resolution: Fatigue<br>Symptom Resolution: Muscle/body aches<br>Symptom Resolution: Headache<br>Symptom Resolution: New loss of taste<br>Symptom Resolution: New loss of smell<br>Symptom Resolution: Congestion/ runny nose<br>Symptom Resolution: Nausea<br>Symptom Resolution: Vomiting<br>Symptom Resolution: Diarrhea<br>Day 5 Symptoms<br>Severity of Symptoms<br>Adjunctive Medications<br>Supplementation Side Effects |
| 4 | The Study of Quadruple Therapy Zinc, Quercetin, Bromelain and Vitamin C on the Clinical Outcomes of Patients Infected With COVID-19 | Drug: Quercetin: a daily dose of quercetin (500 mg)<br>• Dietary Supplement: bromelain: a daily dose of bromelain (500 mg)<br>• Drug: Zinc: 50 mg orally daily dose<br>• Drug: Vitamin C: 1000 mg orally daily | Phase 4 | 60 | days of stay at hospital after treatment and discharge<br>serum zinc before and after treatment<br>questionnaire including parameters like BMI,smoking, underling diseases, immunological treatment<br>day of negative conversion for nasopharyngeal swab for rt-PCR FOR covid-19 |
| 5 | Can SARS-CoV-2 Viral Load and COVID-19 Disease Severity be Reduced by Resveratrol-assisted Zinc Therapy | • Dietary Supplement: Zinc Picolinate: 50 mg PO TID × 5 days<br>• Dietary Supplement: Resveratrol: 2 grams po BID × 5 days<br>• Dietary Supplement: Zinc Picolinate Placebo: PO TID × 5 days<br>Dietary Supplement: Resveratrol Placebo: PO BID × 5 days | Phase 2 | 60 | Reduction in SARS-CoV-2 Viral load<br>Reduction in Severity of COVID-19 Disease |
| 6 | A Study of Hydroxychloroquine and Zinc in the Prevention of COVID-19 Infection in Military Healthcare Workers | • Drug: Hydroxychloroquine: 400 mg at day 1 and day 2, then 400 mg weekly up to 2 months<br>• Drug: Hydroxychloroquine (placebo): 1 pill at day 1 and day 2, then 1 pill weekly up to 2 months<br>• Drug: Zinc: 15 mg per day up to 2 months<br>• Drug: Zinc (Placebo): 1 pill per day up to 2 months | Phase 3 | 660 | SARS CoV2 infection<br>COVID-19 symptoms description<br>Adverse Events |

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**Table 1** (*continued*)

| ROW | Study Title | Intervention | Phase | The number of participants | Outcome Measures |
|---|---|---|---|---|---|
| 7 | Zinc With Chloroquine/ Hydroxychloroquine in Treatment of COVID-19 | • Drug: Chloroquine<br>• Drug: zinc | Phase 3 | 200 | Number of patients with improvement or mortality |
| 8 | Impact of Zinc and Vitamin D3 Supplementation on the Survival of Aged Patients Infected With COVID-19 | • Dietary Supplement: Zinc gluconate: 15 mg x 2 per day during 2 months<br>• Dietary Supplement: 25-OH cholecalciferol: drinkable solution 10 drops (2000 IU) per day during 2 months | Not Applicable | 3140 | Survival rate in asymptomatic subjects at inclusion<br>Survival rate in symptomatic subjects at inclusion<br>Survival rate in overall subjects<br>Cumulative incidence of Covid-19 infection in asymptomatic subjects at inclusion |
| 9 | Evaluation of the Relationship Between Zinc, Vitamin D and B12 Levels in the Covid-19 Positive Pregnant Women | tomography and treatment | | 44 | Serum zinc, vitamin d vitamin b12 deficiency levels |
| 10 | Efficacy of Subcutaneous Ivermectin With or Without Zinc and Nigella Sativa in COVID-19 Patients | Drug: Nigella Sativa / Black Cumin: 80 mg/ Kg/Day divided in 2–3 doses<br>Drug: Ivermectin Injectable Solution: 200 µg/kg body weight 48 hourly<br>Other: Placebo: 0.9% normal saline with empty capsule<br>Drug: Zinc: Zinc Sulphate 20 mg 3 times a day | Phase 1<br>Phase 2 | 40 | • qRT-PCR<br>• Severity of symptoms |
| 11 | International ALLIANCE Study of Therapies to Prevent Progression of COVID-19 | Dietary Supplement: Vitamin C: 50 mg/kg every 6 hrs on day 1, followed by 100 mg/kg every 6 hrs for 7 days<br>Drug: Hydroxychloroquine: 400 mg (2 × 200 mg) PO for 1 day, followed by 200 mg PO per day for 6 days<br>Drug: Azithromycin: 500 mg PO on day 1, followed by 250 mg PO once daily for 4 days<br>Dietary Supplement: Zinc Citrate: 30 mg elemental zinc PO daily<br>Dietary Supplement: Vitamin D3: 5,000iu PO daily for 14 days<br>Dietary Supplement: Vitamin B12: 500 mcg PO daily for 14 days | Phase 2 | 200 | Symptoms<br>Length of hospital stay<br>invasive mechanical ventilation or mortality<br>Mortality<br>mechanical ventilation<br>oxygen<br>ICU<br>days in hospital<br>days in ICU<br>renal replacement therapy<br>Extracorporeal support |
| 12 | Coronavirus 2019 (COVID-19)- Using Ascorbic Acid and Zinc Supplementation | Dietary Supplement: Ascorbic Acid: 8000 mg of ascorbic acid divided into 2-3 doses/day with food<br>Dietary Supplement: Zinc Gluconate: 50 mg of zinc gluconate to be taken daily at bedtime<br>Dietary Supplement: Ascorbic Acid and Zinc Gluconate: 8000 mg of ascorbic acid divided into 2-3 doses/day with food and 50 mg of zinc gluconate to be taken daily at bedtime<br>Other: Standard of Care medications only as prescribed by patient's physician | Not Applicable | 520 | Symptom Reduction<br>Symptom Resolution: Fever<br>Symptom Resolution: Cough<br>Symptom Resolution: Shortness of Breath<br>Symptom Resolution: Fatigue<br>Symptom Resolution: Muscle/body aches<br>Symptom Resolution: Headache<br>Symptom Resolution: New loss of taste<br>Symptom Resolution: New loss of smell<br>Symptom Resolution: Congestion/ runny nose<br>Symptom Resolution: Nausea<br>ymptom Resolution: Vomiting<br>Symptom Resolution: Diarrhea<br>Day 5 Symptoms<br>Hospitalizations<br>Severity of Symptoms<br>Adjunctive Medications<br>Supplementation Side Effects |
| 13 | A Preventive Treatment for Migrant Workers at High-risk of COVID-19 | Drug: Hydroxychloroquine Sulfate Tablets: 400 mg loading dose, followed by 200 mg daily for 42 days<br>Drug: Ivermectin 3 mg Tab: 12 mg single dose<br>Drug: Zinc: 80 mg daily for 42 days<br>Drug:vitamin C: 500 mg daily for 42 days<br>Drug: Povidone-Iodine: 3 times daily for 42 days | Phase 3 | 4257 | • Laboratory-confirmed COVID-19 in treatment arms (hydroxychloroquine, ivermectin, zinc and povidone iodine)<br>• Acute respiratory illness in treatment arms (hydroxychloroquine, ivermectin, zinc and povidone iodine)<br>• Febrile respiratory illness in treatment arms (hydroxychloroquine, ivermectin, zinc and povidone iodine)<br>• ate of oxygen supplementation and mechanical ventilation in treatment arms (hydroxychloroquine, ivermectin, zinc and povidone iodine)<br>• Duration of oxygen supplementation and mechanical ventilation in treatment arms (hydroxychloroquine, ivermectin, zinc and povidone iodine) |

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**Table 1** (*continued*)

| ROW | Study Title | Intervention | Phase | The number of participants | Outcome Measures |
|---|---|---|---|---|---|
| | | | | | • Length of hospital stay in treatment arms (hydroxychloroquine, ivermectin, zinc and povidone iodine)<br>• Rate of laboratory-confirmed COVID-19 in treatment arms (hydroxychloroquine, ivermectin, zinc and povidone iodine)<br>• Adverse events and serious adverse events in control arm (Vitamin C)<br>• Drug discontinuation due to adverse events in control arm (Vitamin C) |
| 14 | A Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection | Drug: Hydroxychloroquine: 1 day<br>Dietary Supplement: Vitamin C: : last 12 weeks<br>Dietary Supplement: Vitamin D: last 12 weeks<br>Dietary Supplement: Zinc: last 12 weeks | Phase 2 | 600 | Prevention of COVID-19 symptoms as recorded in a daily diary<br>Safety as determined by presence or absence of Adverse Events and Serious Adverse Events |
| 15 | Changing of Trace Element, Homocysteine, Oxidative Stress Parameters and Physical Activity Levels in Covid-19 | Routine COVID-19 treatment | | 20 | • Change of the levels of Trace Element at baseline and discharge<br>• Change of Physical Activity Level at baseline and discharge<br>• Change of the levels of Homocystein at baseline and discharge<br>• Change of the levels of Oxidative Stress Parameters at baseline and discharge<br>• Change of the levels of Routine Blood Samples (vitamin D, Troponin T, D-Dimer, iron and ferritin) at baseline and discharge<br>• Change of the levels of Routine Blood Samples (C-reactive protein (CRP) and procalcitonin) at baseline and discharge<br>• Change of the levels of Routine Blood Samples (uric acid, chlorine, blood urea nitrogen (BUN) creatine, albumin and bilirubin) at baseline and discharge |
| 16 | Zinc Versus Multivitamin Micronutrient Supplementation in the Setting of COVID-19 | Dietary Supplement: PreserVision AREDS formulation gels or tablets: Two tabs taken daily for three months<br>Dietary Supplement: Multivitamin with 11 mg of zinc: One tab taken daily for three months | Not Applicable | 4500 | COVID-19 illness requiring hospitalization<br>Illness without hospitalization<br>Supplemental oxygen therapy during hospitalization<br>Invasive ventilation during hospitalization<br>Mortality |
| 17 | New Antiviral Drugs for Treatment of COVID-19 | Drug: Treatment group: will receive a combination of Nitazoxanide, Ribavirin and Ivermectin for a duration of seven days | Phase 3 | 100 | PCR for COVID-19 will be done on serial visits till turn to negative, first after 5 day then serial every 48 hours till become negative for two consecutive samples |
| 18 | OD-doxy-PNV-COVID-19 Old Drug " DOXY " for Prevention of New Virus " COVID-19 " | • Drug: Doxycyclin: daily (100 mg)<br>• Zinc: 15 mg/day | Phase 3 | 1100 | • decreasing the number of cases infected with covid 19<br>• Measurement of the emergence of clincal symptoms of COVID 19<br>• the seroprevalence of SARS- CoV 2 IgM/IgG positive samples at study entry and study conclusion in all participants receiving DOXY compared to those receiving placebo |
| 19 | Proflaxis Using Hydroxychloroquine Plus Vitamins-Zinc During COVID-19 Pandemia | Drug: Plaquenil 200 Mg Tablet | | 80 | Protection against COVID-19 |
| 20 | Managing Endothelial Dysfunction in COVID-19 : A Randomized Controlled Trial at LAUMC | Drug: Atorvastatin + L-arginine + Folic acid + Nicorandil + Nebivolol: (until 14 days)<br>(1) Atorvastatin: 40 mg tablet once daily<br>(2) Nicorandil: 10 mg PO BID<br>(3) Nebivolol: 5 mg PO daily<br>(4) Folic Acid: 5 mg PO daily<br>(5) L-Arginine: 1 g PO 3 times daily<br>Drug: Placebo Atrovastatin | Phase 3 | 80 | Clinical Improvement<br>Need for invasive mechanical ventilation<br>Length of ICU stay<br>Length of hospital Stay<br>Length of need of mechanical ventilation<br>All cause mortality<br>Occurrence of side effects |
| 21 | Evaluation of the Efficacy and Safety of Treatments for Patients Hospitalized for COVID-19 Infection Without Signs of Acute Respiratory Failure, in Tunisia | Drug: HCQ: 600 mg on the 1st day as a starting dose then 200 mg * 2 /D for 9 days<br>Drug: Azithromycin: 500 mg (1st day) then 250 mg / D for 4 days<br>Drug: Doxycycline: 200 mg per day for 10 days | Phase 3 | 0 | Evaluate the rate of patients cured at the end of the study.<br>Evaluate the rate of patients are pauci-symptomatic at the end of the study.<br>Evaluate the rate of patients with worsening clinical signs |

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**Table 1** (*continued*)

| ROW | Study Title | Intervention | Phase | The number of participants | Outcome Measures |
|---|---|---|---|---|---|
| | | • Dietary Supplement: Zinc: 220 mg per day for 10 days | | | |
| 22 | A Study of Quintuple Therapy to Treat COVID-19 Infection | Drug: Hydroxychloroquine<br>Drug: Azithromycin<br>Dietary Supplement: Vitamin C<br>Dietary Supplement: Vitamin D<br>Dietary Supplement: Zinc | Phase 2 | 600 | The rate of recovery of mild or moderate COVID-19 in patients using Quintuple Therapy<br>Reduction or Progression of Symptomatic Days<br>Assess the safety of Quintuple Therapy<br>Assess the safety of Quintuple Therapy via pulse<br>Assess the safety of Quintuple Therapy via oxygen saturation<br>Assess the safety of Quintuple Therapy via EKG<br>Assess Tolerability of Quintuple Therapy |
| 23 | Trial of Combination Therapy to Treat COVID-19 Infection | Drug: Ivermectin: Treatment day 1 and day 4<br>Drug: Doxycycline Hcl: 10 day treatment<br>Dietary Supplement: Zinc: 10 Day treatment<br>Dietary Supplement: Vitamin D3: 10 Day treatment<br>Dietary Supplement: Vitamin C: 10 Day treatment<br>(patients will be followed for 6 months) | Phase 2 | 30 | Time to Non-Infectivity by RT-PCR<br>Time to Symptom progression in days as measured by NEWS scoring system (National Early Warning Score)<br>Time to Symptom improvement as measured by NEWS scoring system (National Early Warning Score)<br>Efficacy of Treatment as measured by Titer<br>Efficacy of Treatment as measured by RT-PCR<br>Safety of Treatment as Measured by D-Dimer<br>Safety of Treatment as Measured by Pro-Calcitonin<br>Safety of Treatment as Measured by C-Reactive Protein<br>Safety of Treatment as Measured by Ferritin<br>Safety of Treatment as Measured by Liver Enzymes<br>Safety of Treatment as Measured by Complete Blood Count<br>Safety of Treatment as Measured by Electrolyte Levels<br>Safety of Treatment as Measured by Treatment Related Adverse Events |
| 24 | Comparative Study of Hydroxychloroquine and Ivermectin in COVID-19 Prophylaxis | Drug: Hydroxychloroquine: Oral hydroxychloroquine 400 mg twice a day on day 1, one 400 mg tablet on day 2, 3, 4, and 5, followed by one 400 mg tablets every 05 days until day 50th associated with 66 mg of zinc sulfate.<br>• Drug: Ivermectin: Oral ivermectin dosage guidelines based on participant body weight, once on day for 2 consecutive days. This dose schedule should be repeated every 14 days for 45 days associated with 20 milligrams twice on day of active zinc. | Not Applicable | 400 | Proportion of participants in whom there was a positivity for SARS-CoV-2.<br>Participants who developed mild, moderate, or severe forms of COVID-19.<br>Measurement of the QT interval.<br>Widening of the corrected QT interval or with changes in heart rate on the ECG.<br>Comparison of hematological and biochemical parameters.<br>Occurrence of adverse events.<br>Assessment of COVID-19 symptom severity.<br>Proportion of participants who discontinue study intervention.<br>Proportion of participants who required hospital care.<br>Proportion of participants who required mechanical ventilation. |
| 25 | COVID-19 Disease Duration and GIT Manifestations. A New Disease Severity Classification. An Egyptian Experience | • Drug: Hydroxychloroquine Pill<br>• hydroxychloroquine 400 mg twice daily first day and maintained on 200 mg twice daily for 6 days in mild cases and 10 days in moderate cases. Also they received anticoagulants, vitamin c and zinc. In case of secondary bacterial infection, empiric antibiotics are started | | 199 | COVID-19 disease spectrum and duration<br>GIT manifestations among COVID-19 patients<br>Non-communicable disease and COVID-19<br>Seasonal change and COVID-19<br>Possible region specific classification for COVID-19 disease |
| 26 | Safety and Efficacy of Hydroxychloroquine for the Treatment & Prevention of Coronavirus Disease 2019 (COVID-19) Caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) | Drug: Hydroxychloroquine: 0-400 mg<br>Dietary Supplement: Vitamins and Minerals<br>• Drug: Azithromycin: 0-500 mg | Phase 1 | 5000 | • Percentage of individuals who develop COVID-19 symptoms |
| 27 | DISulfiram for COvid-19 (DISCO) Trial | Drug: Disulfiram<br>Participants in Cohort 1 receiving disulfiram will take 2 capsules of disulfiram (each capsule contains 500 mg DSF plus 27.75 mg | Phase 2 | 60 | • Immunologic impact of 5 days of disulfiram, as measured by the fold-change in plasma levels of pro- |

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**Table 1** (*continued*)

| ROW | Study Title | Intervention | Phase | The number of participants | Outcome Measures |
|---|---|---|---|---|---|
| | | microcrystalline cellulose powder) per day for a total of 5 consecutive days. Participants in Cohort 2 receiving placebo will take 4 capsules of disulfiram (each capsule contains 500 mg DSF plus 27.75 mg microcrystalline cellulose powder) per day for a total of 5 consecutive days.<br>Drug: Placebo<br>Participants in Cohort 1 receiving placebo will take 2 capsules of placebo (each capsule contains only microcrystalline cellulose powder) per day for a total of 5 consecutive days. Participants in Cohort 2 receiving placebo will take 4 capsules of placebo (each capsule contains only microcrystalline cellulose powder) per day for a total of 5 consecutive days | | | inflammatory cytokines (e.g, interleukin 6, interleukin 1-beta, etc.).<br>• Virologic impact of 5 days of disulfiram, as measured by the fold-change in copies of SARS-CoV-2 virus per million cells between Baseline and Day 31.<br>• Number of participants with treatment-related adverse events as assessed by CTCAE v4.0<br>• Change in COVID-19 symptom severity score as assessed by a 5-point adapted somatic symptom severity score (SSS-8) |
| 28 | Effect of a Nss to Reduce Complications in Patients With Covid-19 and Comorbidities in Stage III | Dietary Supplement: Nutritional support system (NSS):<br>Diet based on the Basal Energy Expenditure plus the stress factor using the Harris Benedict equation. The distribution of macronutrients will be 50% for carbohydrates, 30% for lipids and 20% for proteins. Food will be established according to the provisions of the ISSEMYM Toluca Arturo Montiel Rojas Medical Center, in addition: Neurobion 10 mg solution for injection, 1 every 24 hours for 5 days IM; one sachet of NSS-1 in the morning and one sachet in the afternoon mixed with 400 ml of water each, contain: Spirulina Maxima 2.5 g, folic acid 5 mg, Glutamine 5 g, Cyanomax Ultra (10 grams of powder), ascorbic acid 1 g, zinc 20 mg, selenium 100 mcg, cholecalciferol 2000 IU, resveratrol 200 mg, concentrated omega 3 fatty acids (10 grams of powder), L-Arginine 1.5 g, and magnesium 400 mg. During the entire intervention, 500 mg of Saccharomyces Bourllardii will be administered 1 250 mg capsule every 12 hours during the first 6 days<br>• Other: Control | Not Applicable | 240 | • Oxygen saturation<br>• Body temperature<br>• Blood pressure<br>Heart rate<br>Breathing frequency<br>Death<br>Hospital stay<br>AB0 system<br>(and 165 more) |
| 29 | An Outpatient Study Investigating Non-prescription Treatments for COVID-19 | Other: chlorine dioxide<br>Dietary Supplement: zinc acetate<br>Drug: Famotidine<br>Dietary Supplement: lactoferrin, green tea extract | Phase 2 | 120 | • Reduction in Participant Symptoms of COVID-19<br>• Incidence of Treatment-Emergent Adverse Events<br>• Rate of Hospitalization<br>Change in Oxygen Saturation<br>Change in Body Temperature |
| 30 | Clinical Trial of Ivermectin Plus Doxycycline for the Treatment of Confirmed Covid-19 Infection | Drug: Ivermectin and Doxycycline: Ivermectin 6 mg, 2 tab stat and Doxycycline 100 mg twice daily for 5 days<br>Drug: Standard of care: Paracetamol, Vitamin D, Oxygen if indicated, Low molecular weight heparin, dexamethasone if indicated | Phase 3 | 400 | Number of Patients With Early Clinical Improvement<br>Number of Participants With Late Clinical Recovery<br>Number of Patients Having Clinical Deterioration.<br>Number of Patients Remain Persistently Positive for RT-PCR of Covid-19 |
| 31 | DYNAMIC Study (DoxycYcliNe AMbulatoIre COVID-19) | Drug: Doxycycline: Doxycycline is given at 200 mg once a day and administered per os during 2 weeks<br>Drug: Placebo: lactose, 380 mg/capsule: Doxycycline placebo is given once a day and administered per os during 2 weeks | Phase 3 | 330 | • Percentage of Patients with Clinical Respiratory Aggravation<br>• Percentage of patients hospitalized<br>• Percentage of patients requiring ventilatory assistance<br>Positive SARS-CoV-2 PCR Test<br>Duration of symptoms<br>Duration of hospitalization<br>Hospitalization intensive care or reanimation<br>Duration of mechanical ventilatory assistance<br>Percentage of deaths related to SARS-CoV-2 |
| 32 | Anti-inflammatory/Antioxidant Oral Nutrition Supplementation in COVID-19 | Dietary Supplement: Oral supplement enriched in antioxidants | Phase 2<br>Phase 3 | 40 | |

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**Table 1** (*continued*)

| ROW | Study Title | Intervention | Phase | The number of participants | Outcome Measures |
|---|---|---|---|---|---|
| | | the intervention group will receive a commercially available antioxidant supplement, which will be given to patients with COVID-19 in the morning after breakfast.<br>Dietary Supplement: cellulose-containing placebo capsules<br>The placebo group will receive an oral supplement at the same time in the same shape/size/color. | | | • Change from baseline score of Nutrition risk screening-2002 (NRS-2002) at end of the trial<br>• Change from baseline Serum ferritin level, serum Interleukin-6 concentration, serum C-reactive protein concentration, serum Tumor necrosis factor-α concentration, monocyte chemoattractant protein 1 (MCP-1)at end of the trial<br>• Change from baseline Weight at end of the trial<br>• Height<br>• Change from baseline BMI at end of the trial<br>• Change from baseline mid arm circumference at end of the trial<br>• Change from baseline triceps skin-fold thickness at end of the trial<br>• Change from baseline percentage of peripheral O2 saturation at end of the trial<br>• Change from baseline degree of body temperature at end of the trial<br>• Change from baseline count the total leukocyte at end of the trial<br>• Change from baseline differential lymphocytic count at end of the trial<br>• Change from baseline Neutrophil count at end of the trial<br>• Change from baseline neutrophil to lymphocyte ratio at end of the trial |
| 33 | Evaluationof the Load of SARS-CoV-2 Virus in Oral Cavity, Oropharinge and Saliva of Patients With Covid-19 After Disinfection With Oral Antimicrobial Solutions: a Pilot Study | Colgate periogard mouthwash<br>Colgate Peroxyl mouthwash<br>Colgate Total mouthwash<br>Placebo mouthwash (water) | Not Applicable | 70 | • Viral load of SARS-CoV-2 in the oral mucosa, oropharynx and saliva of hospitalized patients already considered positive for the virus |
| 34 | Clearing the Fog: Is Hydroxychloroquine Effective in Reducing COVID-19 Progression | Drug: HCQ:<br>Tab HCQ 400 mg 12 hourly day 0 followed by tab HCQ 200 mg 12 hrly for next 5 days | Phase 3 | 540 | Number of Participants With Progression<br>Viral Clearance |
| 35 | Effectiveness of Ivermectin and Doxycycline on COVID-19 Patients | • Drug: Ivermectin and Doxycyline:<br>• Ivermectin 200 μg/kg PO per day for two days, and in some patients who needed more time to recover, a third dose 200 μg/kg PO per day was given 7 days after the first dose. Doxycycline 100 mg capsule PO every 12 h per day was given for 5-10 days, based on the clinical improvement of patients<br>Drug: Standard of care:<br>• Acetaminophen 500 mg on need<br>• Vitamin C 1000 mg twice/ day<br>• Zinc 75-125 mg/day<br>• Vitamin D3 5000 IU/day<br>• Azithromycin 250 mg/day for 5 days<br>• Oxygen therapy/ C-Pap if needed<br>• dexamethasone 6 mg/day or methylprednisolone 40 mg twice per day, if needed<br>• Mechanical ventilation, if needed | Phase 1<br>Phase 2 | 140 | • Mortality rate<br>• Rate of progression disease<br>• Time to recovery |
| 36 | Covid-19 and Diabetes in West of Algeria | • Drug: MANAGEMENT OF COVID-19 | | 100 | Prevalence of diabetes among all hospitalized COVID-19<br>Diabetes-related factors risk |
| 37 | Therapeutic Plasma Exchange for Coronavirus Disease-2019 Triggered Cytokine Release Storm; | • Procedure: Therapeutic Plasma Exchange | Not Applicable | 280 | Survival<br>Duration of Hospitalization<br>Timing of PCR negativity<br>Time to CRS resolution<br>Complications |
| 38 | Dipeptidyl Peptidase-4 Inhibitor (DPP4i) for the Control of Hyperglycemia in Patients With COVID-19 | Drug: Linagliptin tablet: Linagliptin 5 mg once daily plus a basal-bolus insulin scheme<br>• Drug: Insulin: Basal-bolus insulin scheme | Phase 3 | 28 | Glucose levels<br>Number of patients who achieve metabolic control<br>Number of patients who die or need mechanical ventilation<br>C reactive protein levels |
| 39 | COVID-19 Treatment in South Africa | | Phase 2 | 250 | • Incidence of SARS-CoV-2 clearance |

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**Table 1** (*continued*)

| ROW | Study Title | Intervention | Phase | The number of participants | Outcome Measures |
|---|---|---|---|---|---|
| | | • Other: Standard of care (Paracetamol): SOC - 2 tablets (1000 mg) to be taken 6-hourly as needed<br>• Drug: Artesunate-amodiaquine: SOC plus artesunate-amodiaquine (ASAQ) - 2 tablets (200/540 mg artesunate/amodiaquine) daily for 3 days<br>• Drug: Pyronaridine-artesunate: SOC plus pyronaridine-artesunate (PA) Weight 45 to <65 kg: 3 tablets (540/180 mg pyronaridine/artesunate) daily for 3 days Weight ≥65 kg: 4 tablets (720/240 mg pyronaridine/artesunate) daily for 3 days<br>Drug: Favipiravir plus Nitazoxanide: SOC plus favipiravir plus nitazoxanide (FPV-NTZ) Favipiravir: 1600 mg 12-hourly for 1 day then 600 mg 12-hourly for 6 days Nitazoxanide: 2 tablets (1000 mg) 12-hourly for 7 days<br>Drug: Sofosbuvir/daclatasvir: SOC plus sofosbuvir/daclatasvir (SOF/DCV) 1 tablet (400 mg/60 mg sofosbuvir/daclatasvir) daily for 7 days<br>(The period of following up is almost 12 months) | | | • Time to clearance of nasal SARS-CoV-2<br>• Median quantity of SARS-CoV-2<br><br>Proportion of days with fever after randomization<br>Proportion of days with respiratory symptoms after randomization<br>Serious adverse events<br>Adverse events resulting in treatment discontinuation<br>Adverse events considered related to the investigational products<br>Maximum score on WHO Ordinal Scale for Clinical Improvement during study participation<br>Cumulative incidence of hospitalization<br>Days of hospitalization<br>incidence of mortality |
| 40 | Prognostic Factors and Outcomes of COVID-19 Cases in Ethiopia | • The study does not required<br>• The period of following up is 12 months | | 6390 | • Number of patients survival or death<br>• Rate of recovery time<br>• Viral shedding<br>• Viral loads<br>• Clinical symptoms and signs<br>• Blood pressure<br>• Assess the prevalence of severe forms among hospitalized patients with diabètes and COVID-19<br>• Assess the prevalence of severe forms among hospitalized patients with cancer and COVID-19<br>• Lipid Profiles<br>• Assess the prevalence of nutrient intakes<br>• Assess the prevalence of micronutrients deficiencies among hospitalized patients with COVID-19 |
| 41 | Placebo Controlled Trial to Evaluate Zinc for the Treatment of COVID-19 in the Outpatient Setting | Dietary Supplement: Zinc Sulfate 220 MG: 220 mg once daily for 5 days<br>Drug: Placebo: Once daily for 5 days | Phase 4 | 750 | • Number of participants hospitalized and/or requiring repeat emergency room visits<br>• Number of participants admitted to the Intensive care unit (ICU)<br>• Number of participants on a ventilator<br>• All-cause mortality<br>• Time to resolution of COVID-19 symptoms<br>• Severity of symptoms |
| 42 | Ivermectin vs Combined Hydroxychloroquine and Antiretroviral Drugs (ART) Among Asymptomatic COVID-19 Infection | Drug: Ivermectin Pill: 3 days of once daily oral ivermectin 600 mcg/kg/d<br>Drug: Combined ART/hydroxychloroquine:<br>(1) Day 1 hydroxychloroquine 400 mg bid, Day2-5 hydroxychloroquine 200 mg bid<br>(2) Darunavir/ritonavir (400/100 mg) q 12 hours for 5 days | Phase 4 | 80 | • Adverse event rates<br>• Efficacy for shortening duration of SAR-CoV2 detection by PCR<br>• Antibody detection rates |
| 43 | Determination of Serum Trace Element and Physical Activity Levels in COVID-19 | • No intervention | | 40 | • Levels of serum trace elements parameters<br>• Physical Activity Level<br>• Levels of Routine Blood Samples |
| 44 | Efficacy and Safety of Ivermectin for Treatment and Prophylaxis of COVID-19 Pandemic | Drug: Ivermectin: 400 mcg/kg body weight maximum 4 tablets (6 mg / tablet) once daily dose before breakfast<br>Drug: Hydroxychloroquine: 400 every 12 hours for one day followed by 200 mg every 12 hours for 5 days | Not Applicable | 600 | • number of participants with improvement of clinical condition (symptoms and signs)<br>• Reduction of recovery time, hospital stay days and mortality rate<br>• improvement of laboratory investigations and 2 consecutive negative PCR tests taken at least 48 hours apart. |
| 45 | Changes in Viral Load in COVID-19 After Probiotics | Dietary Supplement: Dietary supplementation in patients with covid disease admitted to hospital | Not Applicable | 96 | Viral load during the period of admission to the nasopharyngeal smear.<br>Clinical indicators on admission and every 48 hours thereafter<br>Analytical parameters |

(*continued on next page*)

**Table 1** (*continued*)

| ROW | Study Title | Intervention | Phase | The number of participants | Outcome Measures |
|---|---|---|---|---|---|
| 46 | Retrospective Study of ImmunoFormulation for COVID-19 | Dietary Supplement: ImmunoFormulationThe ImmunoFormulation consist of: transfer factors, 800 mg anti-inflammatory natural blend, 60 mg zinc orotate, 48 mg selenium yeast, 20,000 IU cholecalciferol, 300 mg ascorbic acid, 480 mg ferulic acid, 90 mg resveratrol, 800 mg spirulina, 560 mg N-acetylcysteine, 610 mg glucosamine sulphate potassium chloride, and 400 mg maltodextrin-stabilized orthosilicic acid | | 40 | Mobility<br>Microbiome analysis in feces<br>• Clinical symptoms duration |

recovery time compared with HCQ plus standard care [144]. Taken together, the use of various antioxidants and anti-inflammatory nutrients such as zinc in combination with antiviral drugs may be beneficial at least in reducing the symptoms and severity of COVID-19.

## 11. Zinc toxicity

Some factors such as aging, surgery and a number of disease states can cauce low serum zinc levels and zinc/copper ratios [145]. It is unknown that decreased zinc levels have an influence in poor health in elderly people or diseases so it is recommended to use 25–40 mg zinc per day in free-living populations [87]. According to a short-term pilot study, the risk of vision loss in persons with age-related macular degeneration (AMD) can reduce by use of zinc supplementation at a level of 80 mg/d of zinc sulfate [146]. As long-term use of high doses of zinc can act as a copper antagonist which can result in zinc-induced copper deficiency [32,147,148] by blocking the intestinal absorption of copper [32,149–151] so in a study by the Age-Related Eye Disease Study (AREDS) Research Group, consumption of daily, oral zinc oxide and cupric oxide supplementation was recommended in elderly people to study the effects of zinc supplementation on the improvement to late AMD [152]. When the molar ratio of zinc to copper (Zn:Cu) is high, the chance of copper deficiency is increased that it caused the low level of erythrocyte copper- zinc superoxid dismutase (ESOD) [151]. Also copper shortage induced by using zinc lozenge can cause sideroblastic anemia [153,154] because copper is an important factor for heme synthesis and iron absorption [155]. Despite being quite less harmless than other metal ions with similar chemical attributes [32], zinc toxicity is a very rare condition that can occur by consuming more than 200 to 400 mg of zinc per day with the symptoms including nausea, vomiting, epigastric pain, and fatigue [32,87]. Using supplemental zinc more than several months have been reported to be related with immunodeficiency [156]. Although zinc has antiviral effects, high levels of zinc can be harmful to the immune system by impairing lymphocyte and neutrophil function [32]. Therefore, it is necessary to monitor the levels of zinc to obtain optimum therapeutic outcomes.

## 12. Conclusion

Zinc is vital in many aspects of cellular life. Zinc supplementation has been successfully used as a therapeutic and preventive agent in many diseases. However, careful modification of zinc homeostasis is important for proper immune activity. Despite the adverse outcomes of high doses of zinc supplements, they can play an important role as adjuvants in COVID-19 therapy by decreasing lung inflammation, improving mucociliary clearance, preventing ventilation-associated lung injury, and modulating antibacterial and antiviral immune recalls particularly in the elderly. Although existing evidence implies the indirect antiviral potential of zinc against SARS-CoV-2, further experimental and clinical investigations are warranted to explain and elucidate the precise role of zinc in COVID-19 hyper inflammation including its potential role in protective effects against the virus, or in combination with other COVID-19 therapies.

## Ethics approval and consent to participate

Not applicable.

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## Authors' contributions

Conception and manuscript design: R J. and R.N Collection of data: S H A, S N, N M J, R N and R J. Manuscript writing: S H A, S N, N M J, R N, and R J. Made important revisions and confirmed final revision: R N and R J. All authors reviewed and approved the final version of the manuscript.

## Authors' information.

Not applicable.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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