









The Implications of Zinc Therapy in Combating the COVID-19 Global Pandemic

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Nandeeta Samad ¹
Temitayo Eniola Sodunke ²
Abdullahi Rabi Abubakar ³
Iffat Jahan ⁴
Paras Sharma ⁵
Salequl Islam ⁶
Siddhartha Dutta ⁷
Mainul Haque ⁸

¹Department of Public Health, North South University, Dhaka, 1229, Bangladesh; ²Department of Anatomy, University of Ilorin, Ilorin, Kwara State, Nigeria; ³Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Bayero University, Kano, 700233, Nigeria; ⁴Department of Physiology, Eastern Medical College, Cumilla, Bangladesh; ⁵Department of Pharmacognosy, BVM College of Pharmacy, Gwalior, India; ⁶Department of Microbiology, Jahangirnagar University, Dhaka, 1342, Bangladesh; ⁷Department of Pharmacology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India; ⁸The Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kuala Lumpur, Malaysia

Abstract: The global pandemic from COVID-19 infection has generated significant public health concerns, both health-wise and economically. There is no specific pharmacological antiviral therapeutic option to date available for COVID-19 management. Also, there is an urgent need to discover effective medicines, prevention, and control methods because of the harsh death toll from this novel coronavirus infection. Acute respiratory tract infections, significantly lower respiratory tract infections, and pneumonia are the primary cause of millions of deaths worldwide. The role of micronutrients, including trace elements, boosted the human immune system and was well established. Several vitamins such as vitamin A, B6, B12, C, D, E, and folate; microelement including zinc, iron, selenium, magnesium, and copper; omega-3 fatty acids as eicosapentaenoic acid and docosahexaenoic acid plays essential physiological roles in promoting the immune system. Furthermore, zinc is an indispensable microelement essential for a thorough enzymatic physiological process. It also helps regulate gene-transcription such as DNA replication, RNA transcription, cell division, and cell activation in the human biological system. Subsequently, zinc, together with natural scavenger cells and neutrophils, are also involved in developing cells responsible for regulating nonspecific immunity. The modern food habit often promotes zinc deficiency; as such, quite a few COVID-19 patients presented to hospitals were frequently diagnosed as zinc deficient. Earlier studies documented that zinc deficiency predisposes patients to a viral infection such as herpes simplex, common cold, hepatitis C, severe acute respiratory syndrome coronavirus (SARS-CoV-1), the human immunodeficiency virus (HIV) because of reducing antiviral immunity. This manuscript aimed to discuss the various roles played by zinc in the management of COVID-19 infection.

Keywords: zinc therapy, microelement, immune-boosting, efficacy, COVID-19, viral infections, pneumonia, pandemic

Introduction

The Global COVID-19 Pandemic

Several mysterious and puzzling cases of severe acute respiratory disorders were reported in Wuhan's city, the capital city of Hubei Province, of the People's Republic of China in December 2019.¹ In the early days, the disease was named Wuhan-pneumonia by the media after the area of the initial outbreak and based on pneumonia-like signs and symptoms.² The World Health Organization (WHO), on 30th January 2020, declared a public health emergency with global outrage because of this novel pneumonia-related health threat.³ Recent Whole-genome sequencing to identify the causative agent reported that the causative microbes are novel coronavirus. Besides, this virus is one of the seventh fellows of the coronavirus

Correspondence: Mainul Haque
Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kem Perdana Sungai Besi, Kuala Lumpur, 57000, Malaysia
Tel +60 10 926 5543
Email runurono@gmail.com

family known to infect humans.⁴ The WHO, on 20th January 2020, named the new viral infection of 2019 as novel coronavirus (2019-nCoV). Furthermore, the WHO on 12th February 2020 publicly declared this infectious coronavirus disease 2019 (COVID-19) as a global pandemic.^{2,5-7} The *Coronaviridae* Study Group of the International Committee on Taxonomy of Viruses opted for the viral nomenclature as “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)”, selected according to the phylogeny and taxonomy.^{8,9} According to WHO, as of 10:38 pm CET, 18 January 2021, there were 93,805,612 confirmed cases of COVID-19, with a total of 2,026,093 deaths globally.¹⁰ The summary of month-wise cumulative COVID-19 cases and associated deaths in the year 2020 is depicted in Figure 1.¹⁰

The Briefs on Global Pandemics

The COVID-19 came after the previous pandemic such as 1918 Spanish flu (H1N1), 1957 Asian flu (H2N2), 1968 Hong Kong flu (H3N2), and 2009 Pandemic flu (H1N1), which caused an estimated global death toll of 50 million, 1.5 million, 1 million, and 0.3 million, respectively.¹¹⁻²¹ The Spanish H1N1 flu pandemic of 1918 to 1919 remains the fatal global health disaster ever recorded in human history, with an estimated 40–100 million human lives lost.^{11,22-25} The Spanish H1N1 flu was extremely

contagious, and around 25–30% (500 million) of the global population was affected.²⁶⁻²⁹ Additionally, the average lifespan of the US national dropped by ten years. Furthermore, later pandemics caused by flu were less devastating, with the average fatality rates below 0.1%.^{30,31} During the Spanish flu, the severity of pneumonia among 15–34 years’ age group patients was twenty times higher than among children.^{24,32,33} It has been further reported that Spanish flu killed many young adults who rarely suffer fatal outcomes due to influenza virus infection.³⁴⁻³⁶ The majority of patients who passed away due to Spanish flu resulted from secondary bacterial pneumonia because antimicrobial agents were not available until 1918–1919.³⁷⁻⁴⁰ Precisely, sudden death within five days among a large percentage of patients occurs due to acute hemorrhage, hemorrhagic pneumonia, hemorrhagic bronchitis, intra-alveolar edema, and pulmonary edema.^{37,38,41-45}

The human influenza virus was first isolated in 1933, following a flu-like infection.^{46,47} During that period, paleomicrobiology science was introduced in microbiology, anthropology, history, paleontology, and archaeology. The development was to study microbial diseases associated with prehistoric material. Paleomicrobiology profoundly depends on ancient DNA (aDNA) of microbes to recognize ancient microbial diseases, virulence, evolution,

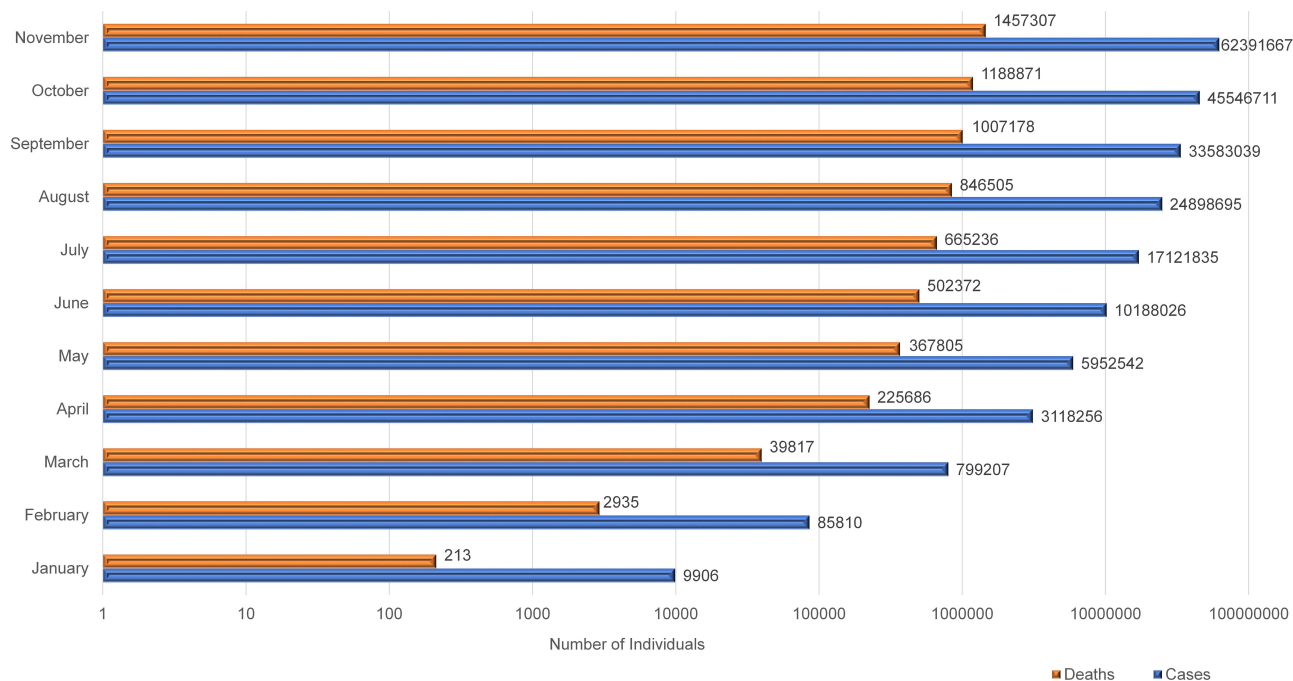


Figure 1 Cumulative cases and deaths associated with COVID-19 in the year 2020.

and pathogenesis.⁴⁸ The paleomicrobiology identified the pathogenic microbes of historic epidemics such as *Yersinia pestis*, *Mycobacterium leprae*, *Treponema pallidum*,^{49–52} and more importantly, the 1918 influenza pandemic.^{53–55} The reverse transcription-polymerase chain reaction (RT-PCR) and the amplification of viral RNA sequencing techniques made it possible to detect and sequencing the 1918 causative agent. The microbe was identified as H1N1 virus from a formalin-fixed, paraffin-embedded, frozen autopsy lung tissue samples.^{35,53,56–58}

Objectives of the Study

This review aims and scope to highlight: i. the role of Zinc Boosting, ii. the immunity mechanism of Zinc's antiviral activity, iii. Zinc's efficacy and safety in combating COVID-19 and iv. to conclude and give prescribers and policymakers direction.

Materials and Methods

Although the literature exploration is a mandatory segment for systematic review and meta-analysis,^{59–61} nevertheless, multiple critical studies regarding narrative review advocated incorporating a section about search strategies.^{62–64} Thereby, this manuscript incorporates the section of materials and methods. The literature search was not systematic but was based on the Baethge et al⁶² strategies and performed using four core bibliographic databases (Google Scholar, PubMed, Scopus, and China National Knowledge Infrastructure). We were aware of the strength of the web of science but could not include because of financial constraint as the current manuscript did not obtain any financial support. The authors relied principally on open access journals and access to journals granted by the Universiti Pertahanan Nasional Malaysia (UPNM), the National Defence University of Malaysia (UPNM), Kuala Lumpur, Malaysia, and North South University, Dhaka-1219, Bangladesh. Articles those not available in full-text or not written in English were excluded. The only non-English papers utilized refer to the history of zinc therapy. The study was conducted between early June 2020 and late November 2020. The search terms used include “Zinc Therapy, Microelement, Therapeutic Potential, Immune-Boosting, Efficacy, COVID-19, Viral infections, Pneumonia, Pandemic”. This is followed by the snowballing of references cited by critical articles. We had included all types of peer-reviewed articles published in English. Subsequently, after the first-round search, additional references were identified through labor-intensive

search using the selected references. The present article's narrative nature, both recent and older publications with historical significance, were incorporated.

Zinc Role in Human Health

Zinc is essential in maintaining human physiology and was first identified in an Iranian patient in 1961.⁶⁵ The patient was suffering from growth impedance, hypogonadism, dwarfism, hepato-splenomegaly, rough and dry skin, geophagia, and severe iron deficiency anemia.⁶⁶ He was a 21-year-old agriculturalist whose food was limited to less nutritious hand-made bread, potatoes, and milk.^{65,66} The essentiality of zinc among microbial systems,⁶⁷ experimental animals,⁶⁸ higher plants,⁶⁹ and animals including chickens^{70,71} and pigs⁷² were identified much earlier in 1869, 1934, 1926, and 1950–1960, respectively. Subsequently, among humans, zinc deficiency was associated with hypogonadism/dwarfism,^{66,73} an autosomal recessive defect known as acrodermatitis enteropathica (AE),^{74,75} and limiting-growth among healthy children.^{73–76}

Zinc is a trace element; however, it remains a vital micronutrient for maintaining cellular physiology such as vision, taste perception, cognition, cell reproduction, growth, and immunity.^{74–82} Zinc deficits dampen equally innate and adaptive immune responses.⁸³ Zinc deficiencies are evident by oxidant stress, increased inflammatory process, and life-threatening situations, as well as premature cell death at the cellular and sub-cellular levels.^{84,85} It has been reported that over 300 regulatory enzymes require zinc for their inhibition-activation processes.^{65,86,87} Furthermore, the sepsis process's signal transduction pathways are positively correlated to zinc deficiency.^{84,88} Nuclear Factor Kappa B (NF- κ B), a transcription factor known as the principal controller of the proinflammatory process, especially in infectious diseases, is also affected by zinc deficiency.^{83,89} Additionally, NF- κ B controls several characteristics of innate and adaptive immune purposes.⁹⁰ Moreover, common pathogenic microbes, including viruses, activate NF- κ B, are remain raised among infected individuals.^{91,92} High NF- κ B is related to marked pro-inflammatory effects, and high death rates among infected patients, especially aggressive infections, were instigating sepsis and septic shock, which could minimize with dietary zinc.^{93,94} NF- κ B inhibits the formation of superoxide dismutases (SODs). Low-level SODs promote the synthesis of reactive oxygen species (ROS) due to the inflammatory process.⁹⁵ Multiple studies reported that a low level of zinc weakens SOD activity

and favors the formation of a high amount of ROS, leading to irreversible damaging effects within the cell.^{96–98} Although zinc is an inactive redox metal; nonetheless, zinc possesses indirect antioxidant properties by its ability to interact with sulfur.^{99,100} Zinc-Sulphur bonding is reversible and controls enzyme catalysis mechanisms within the cell; thereby, intercellularly zinc binds strongly with redox-active and converts to the redox-inert zinc ion. In that way allows zinc to promote in shielding oxidant environment.^{99,101} Overall, zinc subsidizes to preserve the cell redox equilibrium through five different strategies. These include i. the synchronization of oxidant synthesis and metal-induced oxidative impairment; ii. the potential relation of zinc with sulfur in protein cysteine clusters; iii) zinc role in rummaging oxidants; iv. its role in glutathione metabolism and the comprehensive protein thiol redox status; and v. its direct or indirect role in controlling redox signaling.⁹⁹ Therefore, low-level intracellular zinc decreases the capability to endure exceedingly oxidant settings commonly occurring in severe infectious diseases.^{102–104}

Zinc and Viral Infection

Zinc is an essential trace element that significantly impacts health, especially in maintaining immune physiology, growth, and development. Zinc is also considered an agent of antiviral immunity and an enhancer of both inherent and acquired immunity.^{105,106} Earlier studies reported that high dose zinc consumption has effectively boosted patients' immune systems with several viral diseases, including torquetenovirus (TTV), common cold (rhinovirus).^{107–109} Apart from its effect on cellular division, differentiation, and rapid growth in humans, its role in preventing common cold and viral infections is underscored to date.¹¹⁰ Increased susceptibility of viral infections has significantly been associated with zinc deficiency in the human body. Zinc-deficient individuals are more prone to severe viral infections like HIV and devastating outcomes in viral and bacterial co-infections. These include influenza-MRSA bacterial superinfection, *S. aureus* infections, and many more.^{111,112} In light of the sudden onset of the COVID-19 global pandemic, there has been an increasing interest in searching for potential protective and therapeutic measures necessary to curb the uncontrollable spread of this virus.^{113,114} Respiratory system pathology and oxygen saturation have improved with zinc supplements in clinical trials.^{111,115} Notably, the elderly population that usually develops acute respiratory

syndrome has lower serum Zinc levels.^{116–118} Similarly, 80% incidence of pediatric pneumonia is associated with low serum zinc levels.¹¹⁷ However, in the case of COVID-19, natural immunity and resistance capacity, in-built in children, are likely to categorize them into less vulnerable groups.^{119,120} Since no approved effective treatment is yet available to minimize the current global pandemic's intensity, micronutrients like zinc, for its immune-boosting effect, and the antiviral mechanism is presumed to combat COVID-19 to some extent.^{105,106,121,122} Although studies to date have rarely focused on clinical data and the number of randomized control trials to test the immunity-boosting effects of zinc supplement, and certain speculations have supported the fact that the modulation of a person's zinc status will most likely create a positive influence in the therapy of COVID-19.^{105,117}

Anti-Viral Effects of Zinc as a Therapy for COVID-19

Even though available data on the direct effect of zinc and COVID-19 is still rare, its antiviral effect has been proven against other viral diseases. This pattern was evident on viral infections through several modulation pathways such as fusion, replication, viral protein translation, viral particle entry, especially those involving respiratory system pathology.^{105,118,121,123,124} A possible clarification for the relevance of zinc in the treatment of COVID-19 conditions has been attributed to its immunomodulatory effect, antiviral property, as well as its ability to regulate the inflammatory response.^{112,125,126}

The possible mechanisms by which zinc might be effective in the therapy of COVID-19 are based on the previous evidence with other common viral infections and limited experience with COVID-19 [Figure 2]. Zinc has been found to refine and improve cilia's morphology and increase its length and beating frequency.¹²⁷ It is also considered as a membrane stabilizer and helps to maintain cytoskeletal integrity.¹²⁸ The membrane tight junction proteins like ZO-1 and claudin-1 expression are enhanced to strengthen the respiratory epithelium's barrier function.¹²⁹ Enhanced antioxidants' functioning of respiratory epithelium and the suppression of caspase activation and apoptosis further protect the respiratory epithelial lining.¹²⁸ Zinc is proposed to prevent viral entry and block its replication by inhibiting the RNA dependent RNA polymerase (RdRp) of the virus.^{121,130} Zinc also minimizes the Sirtuin 1 (SIRT-1) induced angiotensin-converting enzyme

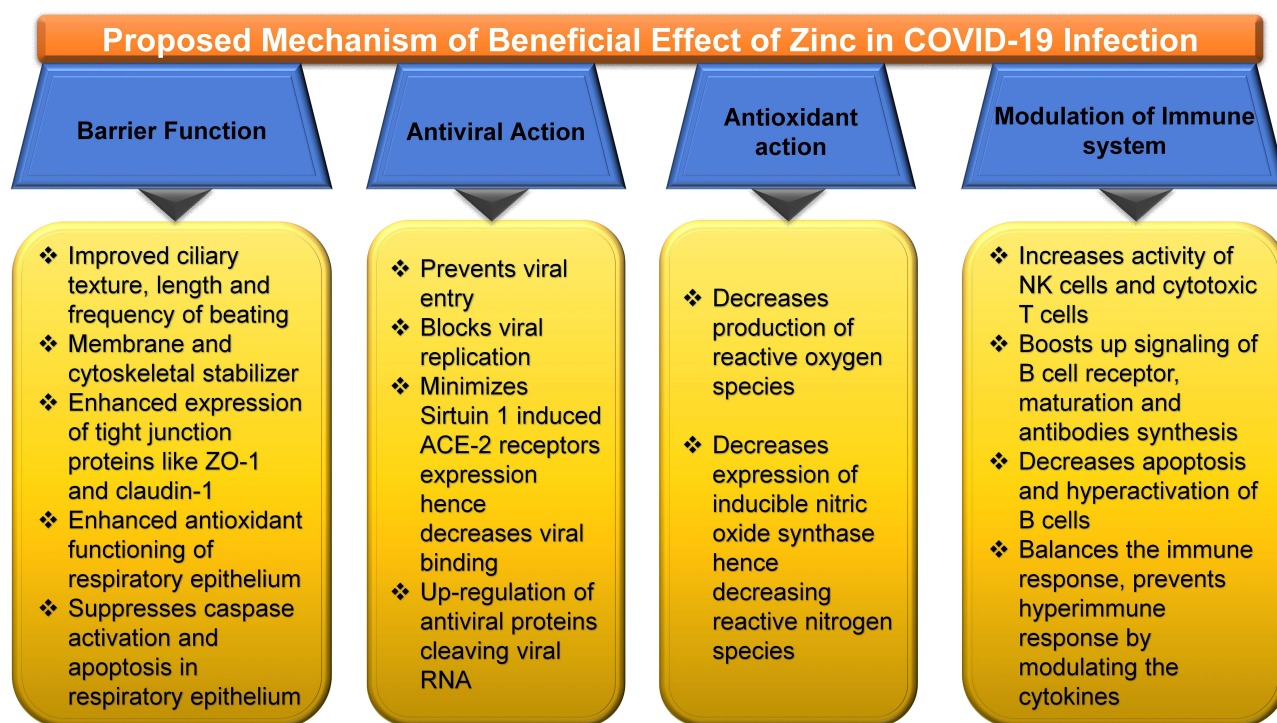


Figure 2 Zinc and its plausible effectiveness in COVID-19.

Notes: Barrier function,^{127–129} antiviral,^{105,118,121,123,124,130,131,133} antioxidant,¹³⁴ immunomodulatory.^{131–139}

Abbreviations: ACE-2, angiotensin-converting enzyme 2; NK cells, natural killer cells; ZO-1, zonula occludens-1.

2 (ACE-2) receptors expression, decreasing the probability of Viral binding ACE2 receptors.^{121,131} Zinc also modulates the immune system and increases the production of IFN α production by leucocytes.¹³² Zinc, by increasing the levels of IFN α production, indirectly increases the synthesis of antiviral proteins like latent ribonuclease and protein kinase RNA-activated, which can degrade viral RNA.^{131,133} Zinc has a well-known antioxidant action with reduced reactive oxygen species production and reactive nitrogen species.¹³⁴ It also exhibits anti-inflammatory action by inhibiting NF- κ B signaling leading to decreased production of proinflammatory cytokine.^{135–137} Zinc has been found to increase Natural Killer cells' activity, Cytotoxic T cells activity, and B Cell Receptor Signaling, along with increased production of antibodies. It also modulates regulatory T-cell functions preventing hyperactivation of the immune system's hyperimmune response by modulating and balancing the cytokines.^{138,139}

Multiple comprehensive reviews on this subject matter through in-vitro experiments have demonstrated that Zn²⁺ ions, combined with Zn ionophore pyrithione, are instrumental in inhibiting SARS-coronavirus RNA polymerase activity, mainly by reducing its replication, hence prevent common colds.^{130,140} These findings have not only pointed

its probable value in the treatment of COVID-19 but has specifically been linked to chloroquine (CQ) efficiency. This is due to its antiviral ability as zinc ionophore, which increased the influx of Zn²⁺ ions into the cell.^{130,141,142} Nevertheless, the observations show that even though this ideology has positive prospects, there is a need to investigate further the mechanism of zinc's antiviral activity.¹⁴² Additionally, a comprehensive study by Guastalegname and Vallone¹⁴³ showed that the use of zinc supplements without CQ could produce positive outcomes with the exclusion of the side-effects that a CQ treatment could cause.

Generally, the role of Zinc as a stimulant of antiviral immunity coupled with its negative repercussions if deficient in the elderly persons or individuals with certain metabolic diseases like diabetes, obesity, or cardiovascular diseases has buttressed several hypotheses that claimed the use of zinc compounds might serve as an adjunct therapy in COVID-19 treatment.^{105,125,144–146} However, some critics have challenged its consumption rate notwithstanding the positive effects of using Zinc. It was suggested that 25–50 mg zinc per day is affordable and would not cause adverse effects than a higher intake of 200 to 400mg per day, triggering epigastric pain, lethargy, vomiting, and

nausea, and fatigue.^{147,148} Interestingly, zinc supplementation has been influential in reducing the replication of influenza virus, reduction of hepatitis in HCV infected patients, enhancement of response to antiviral treatment, improvement of both cutaneous and genital warts which are induced by human papillomavirus (HPV), and most notable is the significant reduction of prevalence in pneumonia, especially in developing countries.^{149–152} Overall, these observations strengthen the fact that adequate zinc balance is essential to protect an individual from microorganisms, including viral infections. An uptake of up to 40mg per day of zinc as recommended will likely reduce the potential threat of the COVID-19 pandemic, resulting from the rise in the host resistance to viral infections. The efficacy, tolerability, and safety of combining zinc with CQ remain a viable option in conquering COVID-19.¹¹¹

Zinc, Its Immune-Boosting Effects, and Association with Pneumonia

Previous studies have acknowledged the importance of zinc as a dietary trace mineral capable of influencing the immune system regarding zinc relevance to immunity.^{112,153,154} Dietary trace minerals are vital in regulating, multiplication, growth, and differentiation of lymphocytes and leukocytes, functioning as the body's immune system.¹³² Moreover, it is often noted that zinc plays a significant role in the activation and inactivation of numerous enzymes and co-enzymes crucial in cellular functions such as DNA synthesis, RNA transcription, and energy metabolism.^{153,154} These findings broadly support the work of earlier studies that have ascertained that any disruption in an individual's zinc contents will undoubtedly affect their immune system responses.^{84,155–157} This alteration gives rise to an increased predisposition to infectious and inflammatory conditions that include acquired immune deficiency syndrome, pneumonia, measles, malaria, tuberculosis, and others.⁸⁴ Evidence has shown that an adequate level of zinc in individuals stimulates an increase in immune reactivity. An insufficient zinc supply level may be a potential risk to these individuals' upper and lower respiratory tracts in the same way.¹¹² Furthermore, earlier studies have shown that the prevalence of respiratory tract infections in children and adults has been linked to their Zinc uptake levels.^{112,158,159} From the estimated decline in zinc incidence globally (up to 17%), its impact on public health is considered an issue of grave concern.¹⁶⁰

According to the research, a decline in zinc levels could affect B-cells' development, reduce immunoglobulin

production, increase infection rate, and most notably increase death rates.^{161–163} Despite this understanding, a specific category of people, such as infants (pre-term) and elders, are considered more vulnerable to having a reduced level of zinc and its adverse effects.¹⁶⁴ The risk factors associated with COVID-19 include aging, immune deficiency, diabetes, obesity, and atherosclerosis, closely associated with zinc deficiency.^{165–168} It is imperative to note that these findings, alongside various evidence on zinc's role in immune function, have instigated interest in zinc's possible potential benefit for preventing and treating the common cold and COVID-19 infection. According to a review published by Singh and Das,¹⁶⁹ zinc supplementations produced a significant reduction in the duration of the common cold and the incidence rate of common cold development. This distinction is further exemplified in studies that have revealed the connection between zinc status and respiratory syncytial virus (RSV) infection. This could be explicitly found in cases of significantly low blood zinc levels amongst children with RSV pneumonia.^{112,170–172} Several surveys conducted have claimed that zinc consumption is likely to reduce the intensity of COVID-19 infection due to its antiviral properties; it also helps to alleviate respiratory tract infections.^{105,173,174} It is noteworthy, researchers have found that the level of ionic zinc present in oral and nasal mucosa positively correlates with the duration of the common cold in that person. This implies that a higher dose of zinc uptake demonstrates a reduction in common cold duration, and a lower amount produces otherwise.^{173–176} It is also important to note the similarity between the route by which COVID-19 enters the body, such as lungs, and that of the common cold. However, there is a need for further investigations (clinical validation), which can ascertain if the availability of a particular concentration of zinc at the site of infection will cause a decline of COVID-19 disease or not.¹²³

Evidence of Zinc's Effectivity on COVID-19, Toxicity, and Prospects of Oral Zinc Therapy

There are quite a few published studies that illustrate the efficacy of zinc therapy in managing COVID-19 patients.^{177–179} Many individuals globally consume zinc tablets, vitamin C, and B because of immune booster effects and combating COVID-19 and its antiviral.^{180,181} However, a recent pre-print United States-based retrospective analysis utilizing electronic medical records

found that patients treated with hydroxychloroquine and azithromycin with the addition of zinc sulfate had a higher recovery rate.¹⁸² Interestingly, additional input of zinc sulfate was claimed to be associated with lower mortality rate, need for hospice care, and less invasive ventilation requirements. However, this association remained null when observed among Intensive Care Unit (ICU) patients.¹⁸² These associations should further be studied in different clinical trials and laboratory tests to provide more robust shreds of evidence. Preventive measures by zinc supplement should be accompanied by a standard of care among COVID-19 patients. Henceforth more double-blind controlled clinical trials should be conducted to confirm the effectiveness. Generally, zinc should be prescribed as an optimal zinc supplement. This is because the recommended intake depends on particular conditions or specific illnesses. Acute zinc toxicity could lead to nausea, vomiting, abdominal cramps, persistent diarrhea, and other gastrointestinal abnormalities like hematemesis, haematuria, and renal syndromes. At the same time, chronic overdose manifests as sideroblastic anemia, neurological disorders, granulocytopenia, myelodysplastic syndrome, and copper deficiency.^{183–185} Furthermore, there have been no reports of deaths or significant life-threatening adverse drug reactions related to zinc supplementation.¹⁸⁶ Therefore, both preventive and therapeutic doses should be determined for COVID-19 patients considering age, gender, and comorbidity to avoid further consequences. As there is some zinc-related toxicity; thereby, an individual should seek health professional advice before zinc supplementation. However, these supplementary medicines are sold as over-the-counter products without prescription. Oral zinc supplements are likely to be recommended in arresting the burden of COVID-19. This is due to its oral bioavailability and because zinc participates in protecting the body from viral and bacterial infections and improving immunity.¹²⁶ Therefore, vigorous clinical studies should commence urgently to validate the therapeutic efficacy of oral administered dose and investigate its limitations. It is noteworthy, although SARS-CoV-2, influenza, and rhinoviruses employ distinct cellular receptors, angiotensin-converting enzyme-2 (ACE2) present in the oral cavity and upper airway's epithelium further suggests reasons to initiate oral zinc therapy.¹⁸⁷ Unless a comprehensive study is conducted with scientific approval of oral zinc therapy for COVID-19 patients, nobody should take it as self-prescribed. This is to avoid overdose

leading to substance abuse and worsen the patient's condition.¹⁸⁷ It should also be investigated and see if the elevated level of oral zinc helps combat SARS-CoV-2 and mitigate the intensity, complications, and duration of COVID-19. All efforts should continue until the globally approved vaccination process is concluded. The nutritional therapy, particularly zinc considering its antiviral and immunity-boosting potency, should be further investigated in order to recognize its possible role in prophylactic as well as an adjuvant during treatment against SARS-CoV-2.

A Brief Overview Regarding Various Zinc Ionophores and Cytokine Strom

Several drug molecules such as hydroxychloroquine, CQ, pyriithione, hinokitiol (β -thujaplicin), and dietary supplements [quercetin and epigallocatechin-gallate (ECGC)], act as Zn ionophore. Thereby, it facilitates Zn's entry across a cell's lipid membrane and considerably increases Zn's intracellular levels, particularly in the endosomal-lysosomal section.^{142,188–191} Raised concentration intracellular Zn²⁺ demonstrates antiviral activity, including COVID-19 involving three distinct antiviral mechanisms of action [Figure 3].^{142,190,192}

The exact mode of action of hydroxychloroquine remains elusive to date.¹⁹³ Several ongoing studies are utilizing various updated scientific approaches to accomplish a better understanding of antiviral pharmacodynamics.¹⁹⁴ Those hi-tech scientific tools comprise computational biology,¹⁹⁴ Immunology,^{195,196} Structural biology,^{197,198} Modern molecular medicine,^{199,200} Synthetic biology,^{201,202} and big data-dependent public health research.^{203,204} Viral access into the human host cells is perhaps the most imperative factor regarding viral infection. Acidification endosomes and lysosomes remain the critical issue for membrane fusion and entry of enveloped viruses into the cell. Moreover, several enzymes disrupt the viral unit to release infectious nucleic acid.^{193,205,206} Then again, CQ, Hydroxychloroquine (HCQ), being a weak base, accrues within these acidic vesicles, increases the pH, and stops the pH-dependent endosome-mediated viral entry. Additionally, HCQ or its other active zinc-derivatives bind to the host cell surface gangliosides via sialic acids and restrict attaching the viral S protein and, in that way, impedes the infection of the virus.^{193,205} This mechanism of action of HCQ ultimately disrupts the viral attachment and supports as a repositioned drug to treat

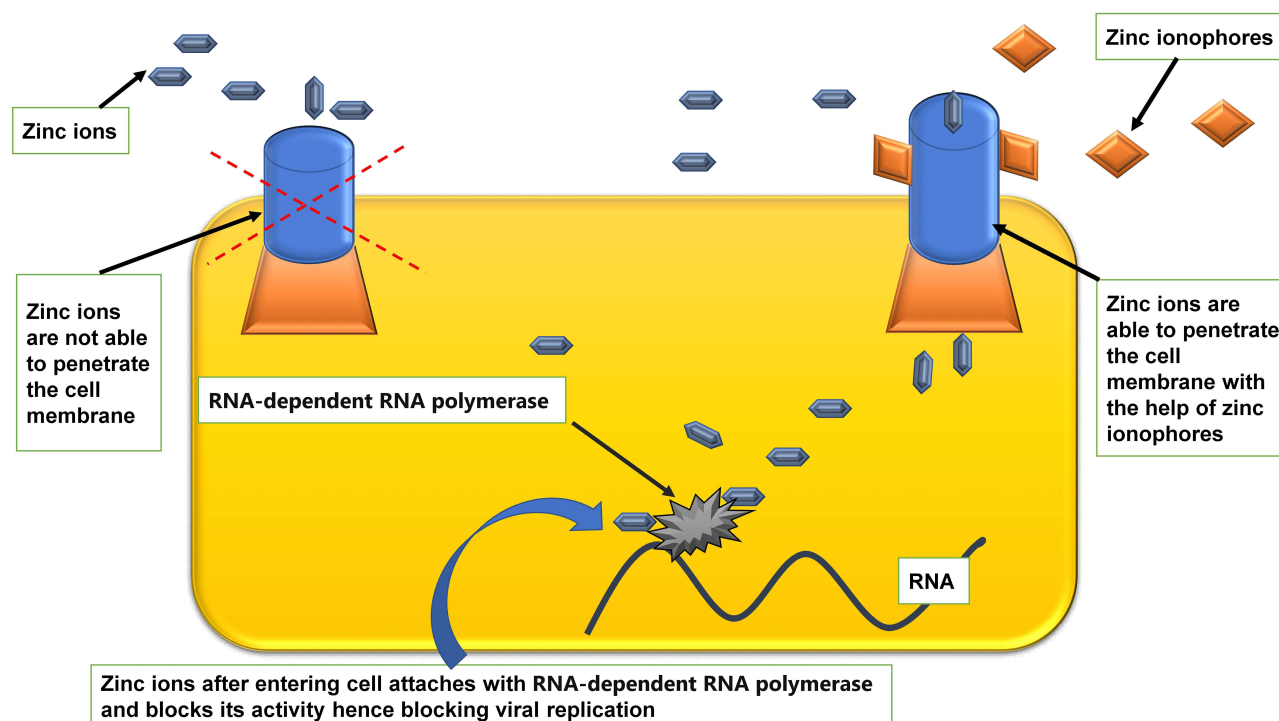


Figure 3 Facilitatory mechanism of zinc ionophores in entry of zinc into cell. ^{130,140–142,188–191}

patients infected with SARS-CoV-2. Among severe cases of COVID-19, especially in ICU, minimizing pro-inflammatory cytokines is an urgent need.^{207–209} Multiple studies reported that both HCQ and CQ possess potential in curtailing pro-inflammatory cytokines (IL-1 β , IL-6, GM-CSF, NF- κ B, etc.) effects.^{210–215} These proinflammatory cytokines are a potentially troubling issue in the management of COVID-19.^{216–218}

Zinc's Role in the Renin-Angiotensin System Mediated Bradykinin Storm in COVID-19

The severe cases of COVID-19 often necessitate ICU admission. It has been documented that among these patients, the concentrations of granulocyte-colony stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), and tumor necrosis factor-alpha (TNF α) are higher as compared to patients who do not require ICU.^{219,220} Additionally, specific chemokines like interleukin-2 (IL-2) receptor, interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), and TNF α were found raised in severe cases with COVID-19 than patients who had improved.^{220–222} These immunologic manifestations due to unrestrained cytokine release among COVID-19 patients,

leading to grave clinicopathological expression is coined as Cytokine Storm.²²³ Abandoned cytokine response among COVID-19 cases frequently go together with more immune cell activation, including T helper 17 cells (Th17) differentiation from CD4+ lymphocytes.^{224,225} In reality, augmented Th17 responses were stated in MERS-CoV, SARS-CoV, and SARS-CoV-2.^{224,226–228}

Multiple studies have reported that COVID-19 severe cases recurrently develop arrhythmia and unforeseen cardiac failure correlated with hypokalemia because of high serum bradykinin levels.^{208,229–238} Moreover, several COVID-19 symptoms such as myalgia, fatigue, nausea, vomiting, diarrhea, anorexia, headaches, and decreased cognitive function are strangely similar hyper-bradykinin settings develop due to vascular hyper-permeabilization leading to angioedema.^{238–240} Thereafter, Garvin et al concluded that the “pathology of COVID-19 is likely because of Bradykinin Storms rather than cytokine storms”.²³⁸ Bradykinin is a proinflammatory peptide synthesized from an inactive pre-protein kininogen through stimulation by the serine protease kallikrein (KLK).^{241,242} KLK is characterized by a group of serine proteases (KLK1–KLK15) found in several tissues; KLKB1 is usually found in the pancreas and is responsible for plasma kallikrein.^{243,244} Furthermore, bradykinin serum level is

dependent on the Renin-Angiotensin System (RAS).^{245,246} Zn²⁺ is divalent cations and inhibits serine proteases (KLK4, KLK5, KLK7, KLK2) by binding with the active sites.^{247–252}

Role of Micronutrients, Vitamins, and Other Trace Elements in the Management of COVID-19

To reduce the global COVID-19 burden, enhancing immunity by maintaining functional nutritional status is desirable, and more importantly, such enhancement is achievable by consuming a balanced diet. ... with an active lifestyle can boost the immune responses to combat the SARS-CoV-2 infection better.²⁵³

Adequate nutritional level promotes better immune status regarding microbial diseases, including viral infection.²⁵⁴ Several micronutrients, particularly vitamins A, C, D, E, B2, B6, and B12, folic acid, iron, selenium, zinc, arginine, glutamine, omega-3 fatty acids, and polyphenols, are of critical necessity for the development of good immune status.^{255,256} Selenium is a crucial component of the enzyme system of our body and to a great extent, deficiency of selenium leads to improper functioning of the cellular immunity and increases the probability of oxidative stress which can further amplify the risk of viral genome mutation, enhanced pathogenicity and difficulty in treating the infection hence growing mortality.^{254,257,258} Although evidence is limited yet early experience in COVID-19 patients shows that adequate selenium levels were associated with a better recovery rate than COVID-19 patients from the cities or high selenium levels had a high cure rate and low mortality as compared to low selenium levels areas.²⁵⁹ The effectiveness of selenium in viral infections is supported by previous poliovirus infection, HIV, and epidemic hemorrhagic fever.^{260–262} Copper is a crucial element for an intact and robust immune system, and its deficiency has been seen to be associated with an increased rate of infections.²⁶³ Copper has been found to modulate neutrophil, macrophage, and functioning of natural killer cell activity. Evidence shows that copper enhances T lymphocyte functioning and proliferation and helps synthesize IL-2, hence improving immunity.²⁶⁴ Previous evidence reveals that copper or ceruloplasmin deficiency leads to improper copper metabolism in the body and can increase the probability of developing various bacterial infections, diarrhea, recurrent respiratory tract infections, and even pneumonia.^{265–267} Iron as an element is a well-

established modulator for the immune system's proper functioning.²⁶⁸ On the contrary, it has been seen that the activity of SARS-CoV2 and its viral replication needs iron, and now iron chelators are being considered as a therapy in COVID-19 [Figure 4].^{269,270}

Apart from these elements, contemporary lifestyles often encourage families to consume fast food (junk food) because of their easy availability. These foods frequently do not possess essential nutrients.²⁷¹ Multiple studies have been reported that infectious diseases often affect individuals with deficiencies in essential micronutrients and trace elements.^{272–274} Moreover, research studies reported that the immune physiology could be restored to the normal level by consuming a balanced diet and, if necessary, supplementing micronutrients and trace elements.^{274,275} In this manner increases resistance to infection and supports quicker recovery from infectious diseases by reducing both inflammation and oxidative stress triggered by several reasons.^{255,272,274,275} By this means, micronutrient insufficiencies have been identified as an international public health concern.^{258,276,277} A recent study by Darnton-Hill reported that selenium, iron, potassium, sodium, calcium, magnesium, folic acid, copper, and zinc play an important role in improving the immune physiology and patient recovers earlier and decrease hospital stay among COVID-19 patients.²⁵⁸ In support of that, several studies across the world advocated the importance of a balanced diet with relevant nutrients and trace elements as an extenuation approach to build robust immune physiology to fight back the COVID-19 pandemic.^{254,268,278–280}

Conclusion

COVID-19 is a formidable challenge to the entire current world as there is no specified antiviral treatment possibility to date, thereby, preventive and control measures, or potent medicine available to fight the disease back. The host immune system plays pivotal roles against COVID-19 disease progression, similar to many other viral infections. The micronutrient zinc was found to strengthen both the innate and adaptive immune cells. The antiviral effects of zinc have been reported in several viral diseases by boosting the immune systems. Furthermore, zinc augments the normal physiological process by facilitating epidermal, gastrointestinal, central nervous, skeletal, and reproductive systems in the human body. Altogether, zinc inhibits the virus's entry in the human cell, the viral

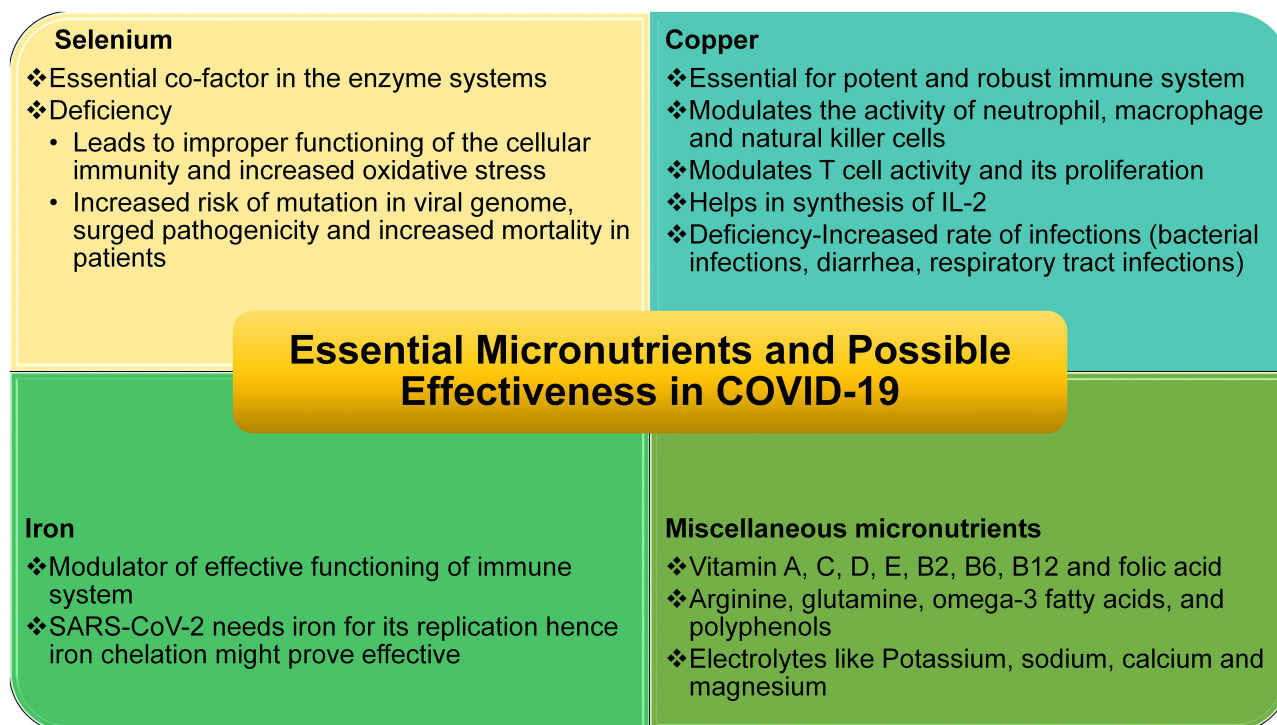


Figure 4 Potential micronutrients effective in COVID-19. Selenium,^{254,257–259} copper,^{263–267} iron,^{268–270} misc.^{258,272–274}

replication process, protein transformation, polyprotein handing out, viral interaction with human cell, and viral uncoating. Consequently, this study suggests that zinc supplementation as an adjunct to other medications could provide dual advantages in preventing and managing COVID-19. However, well-designed double-blind controlled clinical trials must assess its long-term safety and effectiveness as affordable medicines.

Recommendations

Further studies are strongly recommended to assess Zinc's effectiveness as an enhancer in using CQ for COVID-19 treatment. SARS-CoV binds angiotensin-converting enzyme 2 (ACE2) on pneumocytes using its spike (S) proteins.^{281,282} Virus enters the susceptible host cell through endocytosis and mediates both replication and transcription. Different metallic ions are known to stimulate viral replicating enzymes as co-factors. The roles of Zinc should be checked as co-factors for SARS-CoV-2. Roles of Zinc for facilitating T cells in the Immune System need to be evaluated in light of COVID-19. Zn was found to provoke the immune system, especially the Natural Killer (NK) cells,^{83,283} that usually play antiviral roles by releasing perforin.²⁸⁴

Further detailed research to elucidate the functions of Zinc in these areas is recommended. Overall, Zinc roles should also be investigated for all other innate adaptive human antimicrobial peptides and proteins,^{285,286} potentially for COVID-19 treatment.

Professionals Annotation

According to the WHO, the urgent need to address the global outbreak caused by the coronavirus necessitated a worldwide state of a public health emergency.^{2,5–7} With no regard for status or class, the COVID-19 pandemic remains a substantial threat that disrupts both high-income-countries and low-middle-income countries globally. Despite its negative threat and there is no well-defined pharmacological antiviral therapeutic choice so far, thereafter, the preventive measure has been the mainstay to fight back the current COVID-19 infection. On this account, this review explores the role of zinc and its properties as a strategy for defeating the COVID-19 pandemic. Even though zinc is a trace element, its significance as a micronutrient essential for maintaining the body's functionality such as vision, taste perception, cognition, cell reproduction, and growth cannot be undermined.^{80–82} Similarly, it is also considered a propeller of antiviral immunity, which increases both inherent and acquired immunity.^{105,106} This

finding also accords to earlier observations that hold the view that increased uptake of zinc reflects positively on patients with several viral diseases such as torquetenovirus (TTV), common cold (rhinovirus).^{107–109} Conversely, it is interesting to note that individuals' increased susceptibility to viral infections has been significantly associated with low zinc levels. Certain facts corroborate that decreased zinc content levels are closely associated with risk factors like aging, immune deficiency, diabetes, obesity, and atherosclerosis that are relatively interconnected with COVID-19 cases.^{165–168} Consequently, zinc-deficient individuals are more inclined to severe viral infections like HIV and devastating outcomes in viral and bacterial co-infections.^{111,112} In the absence of any recognized the effective pharmacological therapeutic course of action, whereby, the uptake of Zinc as an antiviral agent and its immune-boosting feature is presumed to be a blueprint in surmounting the COVID-19 pandemic.^{105,106,121,122}

Admittedly, only a few clinical studies and randomized control trials have been able to verify the immunity-boosting effects of zinc supplements; however, certain speculations have supported the fact that the modulation of a person's zinc status will most likely create a positive influence in the therapy of COVID-19.^{105,117} Evidence of this advantageous nature has been displayed through several modulation pathways such as fusion, replication, viral protein translation, and viral particle entry, especially respiratory system pathology.^{105,118,121,123,124} Additionally, its value proposition has not only been deemed fit in the treatment of COVID-19 but has specifically been linked to CQ efficiency.^{130,141,142} Thus, these reports show that even though this ideology has positive prospects, there is a need for further research into the adoption of zinc as a treatment measure.¹⁴² Considering the pros and cons of the consumption of zinc supplements, particularly in elderly persons or those with certain metabolic diseases: diabetes, obesity, or cardiovascular diseases, these views have supported the possibility of using zinc compounds as an adjunct therapy in COVID-19 treatment.^{105,125,144–146}

Even though this compound's positive effect is widely accepted, critics have challenged its consumption rate, which could result in adverse effects if not treated with caution. These side effects have triggered epigastric pain, lethargy, vomiting, nausea, and fatigue.^{147,148} Generally, these observations have buttressed the notion that adequate zinc balance is crucial to protect an individual from microorganisms, including viral infections. Studies have claimed that an adequate level of zinc in individuals stimulates an increase in immune reactivity. The efficacy, tolerability,

and safety of combining zinc with CQ remain a viable option in conquering COVID-19.¹¹¹ Another considerable role of zinc is its activation and inactivation of numerous enzymes co-enzymes are crucial in cellular functions such as DNA synthesis, RNA transcription, and energy metabolism.^{153,154} However, prior studies have identified that any alteration to an individual's zinc contents increases their predisposition to several infectious and inflammatory conditions such as acquired immune deficiency syndrome, pneumonia, measles, malaria, tuberculosis, and others.^{84,155–157} Notably, it is often reported that a low level of zinc uptake may be a potential risk to an individuals' upper and lower respiratory tracts.¹¹² Furthermore, earlier studies have shown that the prevalence of respiratory tract infections in children and adults has been linked to their Zinc uptake levels.^{112,158,159} In a review published by Singh and Das,¹⁶⁹ consumption of zinc supplements have agreeably been critical in reducing both the incidental development of common cold and its duration in an already infected person. It is a widely held view that due to the antiviral property present in the consumption of Zinc, it is highly capable of reducing the intensity of COVID-19 infection as well as alleviating respiratory tract infections.^{105,173,178}

There is a paucity of data on the efficacy of zinc therapy in the management of COVID-19 patients. However, many of the populace globally are ingesting zinc tablets, vitamin C, and B vitamins based on antiviral and immune booster effects as preventive measures to combat COVID-19. For instance, a report from the United States-based retrospective analysis utilizing electronic medical records found that patients treated with hydroxychloroquine and azithromycin with the addition of zinc sulfate had a higher recovery rate.¹⁷¹ Surprisingly, additional uptake of zinc sulfate was identified to result in lower mortality rates, the need for hospice care, and less invasive ventilation requirements. A standard of care should accompany preventive measures by zinc supplements among COVID-19 patients as acute zinc toxicity described earlier.^{182–184} Thus, attention should be given to preventive and therapeutic doses, particularly for COVID-19 patients concerning age, gender, and comorbidity, to avoid further consequences. Finally, clinical studies on zinc considering its antiviral and immunity-boosting potency must be further investigated to recognize its possible role in prophylactic and an adjuvant in treatment against SARS-CoV-2.

Primary Health Care in the Management of the Global Pandemic: Five to Ten Year Prospect

The COVID-19 pandemic has struck a devastating blow to an already fragile global economy. Lockdowns and other restrictions needed to address the public health crisis, . . . of adverse shocks that are causing deep recessions in many advanced economies and emerging market and developing economies (EMDEs).²⁸⁷

Epidemics are characterized by the Center for Disease Control and Prevention of the USA as an upsurge, sometimes abrupt, in the number of cases of a disease above what is normally predictable in that populace within this specific geographical region. The word outbreak conveys the same description of the epidemic; nonetheless, it is frequently cast-off for a more restricted topographical zone. Pandemic mentions an epidemic that usually distresses many individuals and has blown through many republics or continents.²⁸⁸ The responsible causative microbes of pandemic and its' effective management vary extensively from country to country depending on its financial strength, health management capacities, and policies prerequisite for extenuation. Nevertheless, organizational diligence and response criteria are also identical.^{289,290} The COVID-19 pandemic resulted in 96,051,223 confirmed cases and over 2,050,543 deaths worldwide until January 19, 2021, 08:26 GMT.²⁹¹ COVID-19 has also flickered worries of an imminent pecuniary catastrophe and economic depression.²⁹² The international economy will pull back around 5.2% in 2020, according to the World Bank.²⁹³ The current expected recession (5.2%) would be the most devastating since World War II.²⁸⁷ As public authorities need to impose strict movement control, lockdown, social distancing, self-isolation, travel restrictions, border shutdowns, and many more,^{294–296} to “flatten the COVID-19 curves”.^{297,298} Although these restrictions save uncountable lives, as these measures minimize the labor force, it increases financial privation with the economic recession.^{299–301}

The coronavirus disease 2019 pandemic and its effects on health outcomes globally have further highlighted the importance of primary health care.³⁰²

It is a fact that primary health care (PHC) policy planning comprises a comprehensive approach to the overall improvement of people's health.³⁰³ Unfortunately, PHC remains deserted and poorly financed globally.^{304,305}

Internationally, the healthcare budget is predominantly consumed in secondary and tertiary hospitals, and frequently PHC obtains a negligible share,³⁰⁶ after that, the health system when principally targeted towards medical and hospital-based services. The consequences are obvious – these health systems lose the enormous prospect of developing effective, efficient, and equitable ways based on PHC strategy to mitigate the principal causes of poor health.^{307,308} Currently, it is thought PHC based healthcare systems are essential for the counter to pandemics, as such of the COVID-19 pandemic, and for preserving important health services.^{309–311} As PHC is based on “social accountability, innovation, management, and population health,”³¹² the system ensures equity, especially marginalized communities with little attention regarding essential health services.^{312–314} Strengthening the PHC program effectively people's healthcare in terms of health outcome, maintaining equity, and healthcare access. Additionally, PHC successfully addresses all-important reasons for health miseries, thereby reducing morbidity and mortality, and is a cost-effective approach for attaining universal health coverage (UHC).^{315–317}

The countries (Taiwan, Hong Kong, South Korea, and Japan) heavily invested in PHC after SARS and MERS have managed much better than others.^{310,318–327} Taiwan took lessons from SARS on fighting back against the viral epidemic.^{328,329} It has been reported that Taiwan successfully deferred and controlled community transmission of COVID-19 because the country experienced, learned, and utilized how to manage the viral epidemic of 2003. Moreover, the country positively developed awareness regarding the viral disease and its' atrocity, parallelly developed a strong public health system, supported by advanced tertiary healthcare industries, inter and intradepartmental teamwork, and innovative information technology.³³⁰ In this regard, Taiwan has established Community Healthcare Groups (CHCGs) since March 2003. These CHCGs act as the principal pillar of the PHC system in Taiwan as the front-line fighters for public health emergencies.^{319,331} As Taiwanese public authority recognized the threat of viral epidemic and timely invested heavily on the PHC program and the same paid back in combating COVID-19 pandemic.³¹⁸ Besides Taiwan, Hong Kong, and Singapore have also heavily invested in the PHC after the SARS epidemic.³³² These Asian nations equally controlled and manage COVID-19 much better than other countries of the globe.³³³ Japan established a universal health care system back in 1961. Regardless of their socioeconomic

background, it has a consistent and, in reality, affordable fee schedule and no gatekeeping.^{334,335} Moreover, the Japanese health system covers the total population living in Japan and ensures access to health care services at a reasonable cost compared to similar high-income industrialist countries because it is regulated by public authority.³³⁶ Nonetheless, globally, Japan has a maximum number of geriatric communities,³³⁷ even then, COVID-19 caused mortality rate is much lower (9.24 deaths per million) than in many other high-income countries (ie, 529.92 in the USA, 609.92 in the UK, 110.61 in Germany).³³⁸ It is believed that as the health care system ensures equity, access to healthcare is operative for the entire population remains the key factor for the country's achievement in managing the COVID-19 pandemic.^{338,339} Recently, the Japanese government renovated the PHC program with special attention to the elderly community.³⁴⁰ It is a well-known Japanese health program that achieves the highest life expectancy globally because of universal health coverage, which runs the PHC supported by advanced tertiary hospital service.³⁴¹ Thereafter, the COVID-19 pandemic once again divides our planet into countries that have robust healthcare based on PHC concept to ensure healthcare access for the entire population irrespective of socioeconomic status or like those countries have policy those who can afford healthcare only access to healthcare and rest those who cannot pay for will be enforced into life-threatening poverty.^{298,342} Moreover, the COVID-19 pandemic raises the issue of collaboration and cooperation between all sectors of communities involved in healthcare both nationally and internationally.²⁹⁸ Collaboration and cooperation are the basic notion of PHC.^{343–346} Additionally, both national and international policy must remember that “until every country is safe, no country will be safe.”²⁹⁸

This research expects that in the next five to ten years' time scientific arena and all healthcare stakeholders will have better collaboration and coordination between public and non-governmental organizations of national and international level to promote improved healthcare for all.^{347–349} Researchers expect one-decade time hopefully, all countries, especially lower-and-middle income countries, will be able to strengthen the healthcare system based on the PHC concept to ensure health-related equity.^{307–350–355} Subsequently, our planet may have universal health coverage based on the PHC concept to fight back any future viral pandemic like COVID-19 and improve access and equity healthcare.

Article Highlights

- Zinc is an essential trace element that vitalizes human growth and development and boosts antiviral immunity. The antiviral effects of zinc have been documented in several viral diseases.^{74–100}
- This review is intended to highlight Zinc's role in boosting immunity and narrate Zinc's antiviral activity, efficacy, and safety in combating COVID-19.^{105–126}
- Zinc-deficient individuals are prone to develop severe viral infections and viral-bacterial co-infections.^{111,112,117}
- Clinical trials showed zinc supplements to improve oxygen saturation in respiratory system pathology.^{111,115}
- Zinc ionophore pyrithione was reported to inhibit SARS-coronavirus RNA polymerase activity.^{130,140}
- Some preliminary research identified Zn ionophore stimulates zinc's efficiency in its antiviral ability against COVID-19.^{142,190,191}

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the essay has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they do not have any financial involvement or affiliations with any organization, association, or entity directly or indirectly with the subject matter or materials presented in this article. This also includes honoraria, expert testimony, employment, ownership of stocks or options, patents or grants received or pending, or royalties.

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