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Review Article

Importance of Zn Supplementation in Food to Fight Unimaginable Global Pandemic COVID-19

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ABSTRACT

As the twenty-first century has arrived an epidemic caused by the Middle East Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and its associated disease, COVID-19, are currently underway. The illness first seen in (Wuhan) China, in December 2019, there have been no cures. The prior research shown that the scientists predict the developing a corona virus vaccine will require a minimum one year. Before the vaccine is given out, a number of precautions must be taken to guarantee both safety and affordability, particularly in developing countries. In this situation, taking specific safety precautions and boosting one's immune system are the only ways to prevent getting the disease. It has been found that Zn, an important trace component involved in many physiological and enzymatic activities, is crucial for triggering and effectively controlling the host's defence mechanisms against viral infections. In addition to being available as a dietary supplement, Zn can also be found naturally in some foods and is fortified in others. Men and women should consume 12 mg and 10 mg of Zn daily, respectively, according to the most recent RDA. Zn is the 2nd most prevalent trace mineral in the cell after iron. It is a constituent of all six classes of enzymes, which together make up roughly 2000 enzymes, and is distributed throughout the body's systems and tissues. Numerous physiological activities, including growth, DNA synthesis and RNA transcription, depend on Zn. Zn deficiency may give the results of compromised immune system and a number of metabolic problems. In this review, the importance of Zn in boosting and regulating host defence *vs.* virus reproduction is examined, in the prevalence of COVID-19.

Keywords: Prophylaxis; SARAS-CoV-2; Zn; COVID-19; Viral infection

INTRODUCTION

World health organization suggested the family of viruses known as coronaviruses is large. Human respiratory infections caused by coronaviruses started from the common cold to more serious illness conditions like Middle-East Respiratory Syndrome (MARS). COVID-19 is the abbreviation for the most recent coronavirus to cause sickness. The disease-causing virus has been identified as SARS-CoV-2 by the Partner Research Group (PRG) of the International Committee Taxonomy of Viruses (ICTV), which also determined that the virus is a conceptual model of a living person as well as catcher SARS coronavirus of a species caused severe acute respiratory type symptoms [1]. We rely on our immune systems to defend against a variety of hazards when pathogenic organisms like viruses attack the human body, which is a big and intricate concept in and of itself. Although the creation and distribution of vaccinations seem to take a while, it is preferable to fortify our immune system since when it is in good shape, the other systems may concentrate on their individual tasks. It has been observed that immune system dysfunction also affects metabolic processes. The epithelium layer of intestine starts to carry out some of the missing immunological functions, such IgA (Immunoglobin A) secretion, somewhere at the expense of its metabolic activities. Both the innate and adaptive immunological responses in immune cells require Zn (Zn) to function effectively.

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Immunological function is compromised by Zn homeostasis, weakening the host's defences. The focus of this review will be on Zn's potential function in boosting immunity and battling the COVID-19 pandemic [2].

LITERATURE REVIEW

Importance of Zn in human body and innate immunity

In 1869, (Raulin) became the first person to recognize significance of Zn in biological processes. Raulin was a Louis Pasteur's student investigated the aspergillus niger fungus, which is responsible for the black mould that affects a number of agricultural products. He said Zn was necessary for the fungus to develop. However, the role of Zn remained controversial up until 1961, when a study revealed how nutritional (Zn) deficits may have caused stunted growth or congenital hypothyroidism in Iranian boys. The therapeutic benefit of Zn supplements in children with severe viral hepatitis, shigellosis, leprosy, TB, bronchitis, lung inflammatory sickness, cold symptoms and leishmaniasis have been carried out.

The best supply of Zn is a diet rich in eggs and shellfish, particularly oysters. Zn is really the second most common trace mineral in cells, right after iron. It is present in every body tissue and secretion (Approx 2 g of Zn content available in total body weight). Zn can be found in a variety of tissues, including the brain, kidneys, pancreas, and heart, and makes up about 60% of muscle tissue, 30% of bone, 5% of liver and skin. Plasma only contains about 0.1 percent of the metal ions, yet this fraction is crucial for maintaining the homeostasis of the body. Urinary excretion makes up a very small percentage of the overall amount of excess Zn that is eliminated, with the majority occurring through gastrointestinal outflow and endogenous outflow (Figure 1) [3].

Zn transporter activity and intracellular mammalian cell function

In mammalian cells, Zn can be found in both intracellular and extracellular forms.

- Proteins and amino acid receptors are only weakly bound, whereas metalloenzymes, metalloproteins, and nucleoproteins are firmly bound.
- Very low amounts of unbound Zn ions are present in cell to given the singling message to control the cell proliferation and they are involved in cell control and cell-to-cell communication.

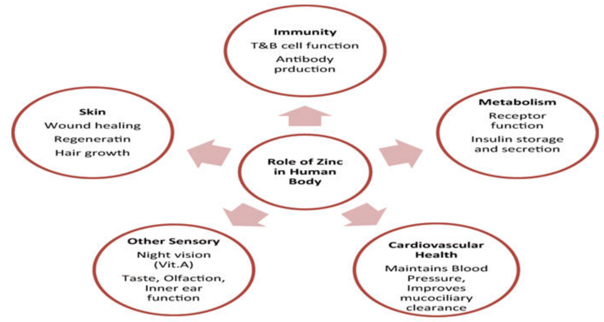
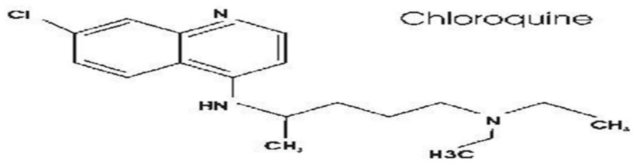
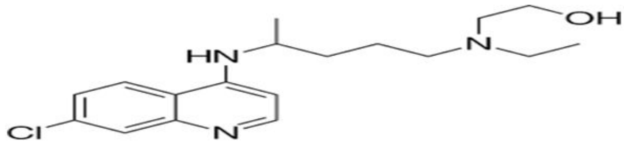


Figure 1: Role of Zn in human body.

As a result, precise monitoring of both the intracellular Zn quantity is required to maintain physiological conditions. The active targeting classes ZnT and ZIP are in charge of maintaining intracellular and fractional Zn homeostasis. Zn intracellular or cytoplasmic concentration is regulated by Zn transporter proteins, also known as Zn exchangers, which are integral membrane proteins of the solute carrier family. They are separated into two groups: The Zn Transporter (ZnT) or which regulate Zn efflux from the cytoplasm into vesicles and out of the cell. Both the Zn importers, Zrt and Irt-like Protein (ZIP), and Solute Carrier 39A (SLC39A) family and the Zn supplier, Zrt or Irt-like protein (ZIP), community, which regulates the inflow of Zn into cytoplasm from outside the cell from vesicles, have ten subtypes (ZnT1-10) each. The family (ZIP1-14) contains 14 subtypes. Cells' intracellular Zn levels are maintained by these crucial transporters. These transporters are either tissue-specific or widely expressed in tissues, based on the transporter subtype. The dysregulation or malfunction of these trans porters contributes to a number of illnesses. Zn is a catalytic component of all six types of enzymes (hydrolase, transferase, oxide-reductase, ligase, lyase, and isomerase) as well as a structural component of over 750 Zn-finger transcription factors that facilitate gene transcription. 17% to 20% of the world's population is expected to suffer from Zn insufficiency, with the majority of cases occurring in the most underdeveloped nations in Africa and Asia. Elderly people, vegetarians, and residents of high-income countries are more susceptible to Zn deficiency. Zn insufficiency is a problem for the older age, vegetarians and whose people suffer with chronic diseases like hepatic cirrhosis and irritable bowel syndrome. Zn deficiency may cause cancer like myeloid leukaemia, low number of lymphocytes (Leukopenia) or defective lymphocyte responses in animal studies, all of which point to a weakened immune system. Moderate Zn deficiency symptoms include growth retardation, male genetic hypothyroidism in adolescence, reddish skin, unexplained weight loss, mental drowsiness, slow wound healing, cell-mediated immunological disorde or atypical neurosensory modifications [4].

Zn is given special significance today due to the COVID-19 pandemic's global effects. Direct antiviral immunomodulatory effects are both present. Low Zn levels have been linked with diabetes, adiposity, and cardiovascular disease as well as with aging. A decade earlier, Zn was also found to offer protection against HIN1 influenza (swine flu) (Table 1) [5].

Table 1: Role of Zn-Ionophores in antiviral innate immunity.

Name of the chemical	Structure
Chloroquine	
Hydroxychloroquine	
Zn Pyrithione	

The definition of "Ionophores" is "ion carriers." Ionophores are substances that combine with specific ions to permit easier passage across cell membranes. In an ionosphere, a hydrophobic patch (or hole) creates a temporary binding site that is tailored for a specific ion. The hydrophobic external surface area of an ionophore allows the mixed ion inside to pass through the hydrophobic membrane. The figure displays the structures of the main Zn-ionophores.

A Zn-Ionophores called Pyrithione (PT) has been demonstrated to suppress the reproduction of RNA viruses like picornaviruses. By reducing replication in Figure 2, PT reduces SARS coronavirus polymerase (RNA-dependent RNA polymerase, RdRp) activity. This shows that one or more viral propagation phases are influenced by intracellular Zn^{2+} levels. Zn^{2+} 0-19 and Zn-ionophore work together to effectively stop norovirus replication in cell culture. For immune system cells, Zn is a secondary abundant messenger that alters intracellular status in response to external stimulation. This intracellular Zn then participates in signalling events. Numerous enzymatic activity and transcription factors have been demonstrated to require Zn ions for proper folding and operation in cell. Zn shortage affects the generation of cytokines, phagocytosis and intracellular killing (Figure 3) [6].

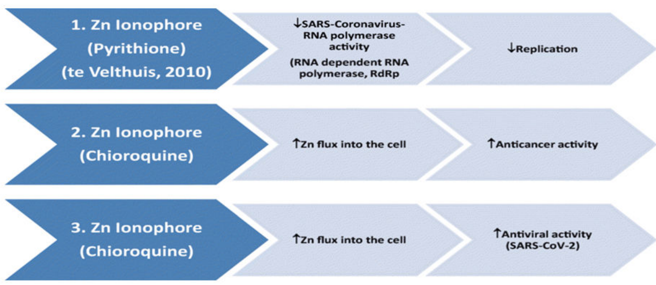


Figure 3: Zn influxes in the cell is shown to have a beneficial effect.

Zn-ionophore CQ was developed as a result of these findings. Chloroquine (CQ), 4 aminoquinoline antimalarial medication is another Zn-Ionophores (Table 1). CQ enhanced Zn^{2+} flow into the cell, which is thought to be responsible for the compound's anticancer effect. Based on these findings, it is hypothesized that chloroquine's antiviral activity targeting SARS CoV-2. In these trials the concentration of chloroquine's antiviral activity has been done and confirmed to be efficacious on mediated by increasing intracellular Zn^{2+} concentration. CQ can transport substantial amounts of ion ligands from the cell membrane into the cell. CQ as well as its precursor Hydroxychloroquine (HCQ) are competitive inhibitors that can target important cell signalling organelles like lysosomes or Golgi apparats. CQ concentration increased the endosomal and lysosomal pH in these organelles' catalyses' considerable disruption of downstream signalling cascades. In the A2780 cancer cell line, Zn has been shown to promote chloroquine-induced apoptosis. Zn and CQ equal concentration both suppressed autophagy in infected cell and organelles [7].

Zn has been administered to treat COVID-19 patients, who has been infected with COVID-19. Other viruses like (RNA viruses, including such hepatitis C virus, coronavirus, HIV or influenza virus) have had their interactions with Zn examined previously. When coronaviruses cause the common cold, typical Zn supplementation have been utilized to treat the condition. Zn supplementation has been associated with less severe illness, shorter symptom duration, and, most critically, lower morbidity and mortality in children [8].

Zn has antiviral effects because it suppresses gene transcription, viral replication, Taq polymerase, transcriptase or viral proteases. However, there is a lot of inaccurate material in the literature about Zn and SARS-CoV-2. It's interesting noted that hydroxy-chloroquine, a drug first used to treat COVID-19. Ionophore that transfers Zn through hydrophobic cell surfaces. Furthermore, studies show that the antiviral drugs containing Zn ionophores, when taken with Zn supplements, specifically target and bind SARS-CoV-2, suppressing proliferation within damaged cells. Zn interacts with intracellular viral enzyme like RNA-dependent (RNA polymerase), preventing distention and reducing viral mRNA template binding. Zn is an immunomodulator and therefore is essential for the development of the immune system at various stages. Lack of Zn has been associated with compromised innate immunity due to impaired lymphoid tissue growth and diminished Natural Killer (NK) cell activity. Zn deficit is associated with reduce microglial mobilization cytokine generation and immunological response T cell or B-cell activity are both impacted by Zn deficiency. Thymulin, a thymus hormone that depends on Zn, binds to the T-cell receptor to promote T-cell activation and cytotoxicity. Additionally, interferon gamma downregulation caused by Zn deficiency results in a severe impairment of cell-mediated immunity. Additionally, it enhances the synthesis of interleukin, specifically IL-2, by stimulating Nuclear Factor B. (NF-KB). According to *in vitro* study, a Zn shortage is associated with impaired immune function and a higher risk of infection. It is obvious that more clinical research into the importance of Zn in immunologic SARS-CoV-2 infection is required [9].

More clinical research on the involvement of Zn in the immunotherapy of SARS-CoV-2 illness is clearly needed

The pro-inflammatory cytokine Tumour Necrosis Factor Alpha (TNF-α) is activated, in membrane-bound (m) IL-6 is transformed into soluble (s) IL-6 by the ADAM enzymes, a protein that is found on Zn-dependent cell surfaces. The cofactor site inhibits the enzyme by inhibiting these two pathways, which suppresses the inflammatory response. This *in vitro* result indicates that Zn has a very broad range of functions and may be important in COVID-19 (Figure 2). The lack of micronutrients in COVID-19 patients may therefore be more than a coincidence. The connection between Zn and COVID-19 requires further investigation [10].

According to the study's findings, COVID-19 patients who lack Zn have a higher complication rate (71.4% *vs.* 31.0%, p=0.008) and 5.44. Additionally, patients were substantially more likely to get ARDS (17.5% *vs.* 0%, p=0.05), spend longer in the hospital (assume 7.8 *vs.* 5.8 days, p=0.058), be given corticosteroids (45.4% *vs.* 12%, p=0.03), and die earlier (6 (19.5%) *vs.* 0 (0%), p=0.05. Zn has a variety of direct and indirect antiviral actions and is involved in many cellular processes. Zn deficiency has been associated with decreased antibody formation, innate immune system activity (remarkably low phagocytic cell activity), diminished cytokine operation by monocytes, the chemo taxis of oxidative outburst of neutrophil phagocytes. Increases in infection frequency and duration are caused by thymic shrinkage, diminished thymic hormone production, lymphopenia, and defective cellular and antibody-mediated processes. Zn deficiency affects T helper or cytotoxic T cell production, proliferation in response to phytohemagglutinin, and number of peripheral and thymic T cells. Additionally, a Zn deficiency reduces the generation of energetic serum thymulin, a Zn-dependent nonapeptide hormone that controls the maturation of immature T cells in the thymus, which in turn influences the activity of mature peripheral T cells. Zn, on the other hand, can interfere with the leukocytes' ability to adhere to ICAM-1 by blocking the synthesis of pro-inflammatory cytokines and other components of the monocyte signalling pathways, which limits the inflammatory response. Numerous biological enzymes and transcription factors depend on Zn^{2+} for proper folding and function, and it may also be an essential co-factor for a number of viral proteins. Zn^{2+} misfolding can prevent viral polyproteins from being broken down by proteases [11].

It is also conceivable for viruses like the encephalomyocarditis virus and the polio virus to have direct effects on the viral enzyme protease and change its three-dimensional structure. By interacting specifically with a specific histidine residue on the viral El protein at low endosomal pH, Zn can also successfully inhibit membrane fusion in the respiratory syncytial virus and HSV, Semliki forest virus and Shinobis viruses. The free Varicella-Zoster virus can be activated *in vitro* by Zn^{2+}. According to cell culture study, RNA viruses like influenza, respiratory syncytial virus, or various pi corona viruses are prevented from reproducing by higher Zn concentrations and the addition of Pyrithione to promote cellular Zn^{2+} importer. This effect in picornaviruses coronaviruses is considered to be achieved *via* interfering with viral polyprotein production. Viral RNA-dependent or RNA polymerase (RdRp) is a good target for future antiviral medications since its activities are entirely virus-specific or can be inhibited without significantly affecting important physiological processes. By blocking the HCV (RdRp), it has been demonstrated *in vitro* that Zn salts, in particular, can reduce viral replication in *E. coli* by 50% (at 100 M $ZnSO_4$). One of the main pathogens of people and cattle is SARS-CoV, along with other human coronaviruses and retroviruses such as Equine Arteritis Virus (EAV), Pig Reproductive or Respiratory Syndrome Virus (PRRSV). Zn decreases the ability of noroviruses (including SARS-CoV) to synthesize RNA *in vitro*, which would be performed *via* changing RdRp activity [12].

DISCUSSION

Impact of Zn level on age and gender

Since Zn has a lot of indirectly and directly antiviral properties that are accomplished through several mechanisms, it may be beneficial for COVID-19 medication and therapy. According to several case studies on COVID-19, elderly sick patients are more prone to this illness. This may be because to the fact that the patients tend to have more sever conditions such as high BP, diabetes, high sugar level and cerebrovascular disease. Such people also have compromised immune systems as a result of their special diets lower food consumption. In some circumstances, drug use causes older people's appetites to be subdued (Figure 4) [13].

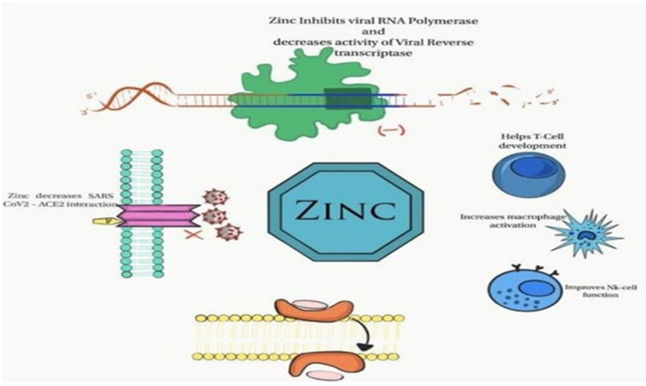


Figure 4: COVID-19 illustrates the antiviral and immunomodulatory properties of Zn.

As was already mentioned in this article, Zn ions are essential for immune activity. Due to the frequent Zn deficiency experienced by hospitalized patients, it is fair to anticipate that Zn supplementation will balance Zn levels and as a result, restore the body's immunological response. Zn is required for metabolic processes in our bodies; hence it is necessary for homeostasis. Zn must be absorbed through into the diet on a daily basis because it is not absorbed by the body. Controlled intestinal uptake, faecal excretion and renal reabsorption can be used to maintain Zn levels in the body. Elderly patients who also have atherosclerosis, respiratory infections or cardiac arrest are more prone to have Zn deficienc. Elderly people typically steer clear of foods with high cholesterol levels, such as meat other high-Zn meals. They consume refined wheat products, which causes their bodies to become Zn-deficient over time and leave them susceptible to a number of diseases. It has been demonstrated that diabetes patients' complete blood and scalp hair contain little Zn and that the severity is greater in the older (61 years-75 years). Additionally, gastrointestinal absorption of Zn declines with age. Zn is important for manufacture, retention, secretion or structural integrity of insulin monomers. Therefore, decreased Zn levels could make it more difficult for the pancreatic islets to produce hormone like insulin. In type 2nd type of diabetes with mellitus, small amount of Zn consumption increases the risk of heart illnesses by a ratio of 2 to 4 and it may even result in mortality. Furthermore, it has been found that immunological capabilities deteriorate with aging as the Zn level declines, which could result in years morbidity, inflammation and infection. Studies show that methylation of several Zn transporters happens as people age, contributes to dysregulation of Zn transporters, age-related Zn deficiency, and inflammation. Increasing proinflammatory responses, decreased ZIP6 mRNA expression and age-specific ZIP6 deregulation have all been associated with increased ZIP6 promoter methylation [14].

The role of Zn in the COVID-19 infection

SARS-CoV-2 RNA sequences are remarkably similar. The first comprehensive description of the SARS-CoV infection process was published in 2005. Because it is believed that the two viruses share a similar mechanism, research on SARS-CoV-2 has advanced significantly [15]. Lungs are where the SARS-CoV virus most commonly infects. In the lungs, the viral receptor Angiotensin Converting Enzyme (ACE) 2 is primarily located in endothelial, vascular epithelial and alveolar cells. SARS-CoV-2 infect mammalian cells using their envelope spike proteins. The mammalian cells are affected with viruses the Spike (S) protein attached with envelope. These spike proteins have a 76.5% amino acid sequence homology and hence a virtually symmetrical 3D structure is connected to same Spike (S) protein with envelope. Its increased pathogenicity may be due to SARS-higher CoV-2's sensitivity for receptors versus SARS-CoV. The Renin-Angiotensin System's main component, ACE, is also a factor (RAS). RAS contributes to the emergence of necessary high blood pressure related problems. Hypertension may be seen additionally caused by endothelial malfunction. RAS control ACE inhibitors are therefore useful in the diagnosis of hypertension. Angiotensin 1 is converted to angiotensin 2nd by the protein ACE (vasoconstrict tor). By decomposing bradykinin, angiotensin II maintains cardiac or vascular tone (a vasodilator). Since ACE is actually a Zn metallopeptidase, Zn is necessary for the enzyme to function catalytically. One Zn g-atom is present in every mole of protein. Because of this, Zn is essential for heart health and may also help prevent viral infections [16].

CONCLUSION

There is currently no treatment or vaccine that is 100% effective against COVID-19. Many pharmaceutical companies created a vaccine and sold it to boost people's immunity, but the vaccination didn't last very long because it only temporarily shattered the immune system and eventually eliminated the transforming antibody. However, many institutions continue to researched work on booster dose of the vaccination to improve the body's immunological response. Later, it appeared that a different SARS virus strain from the group Omicron, which is much more severe than COVID-19, had been spared and was harming people globally. SARA Omicron hasn't been the subject of any significant research, but in a similar vein, Zn is significantly more effective than the same SARA-Omicron form. Zn helps in the signalling pathway, repairs the host infected cell, and stops the growth of RNA dependent RNA protease. It also diverts the chain of protease or reverse transcriptase. Approximately 8 lakh people have perished worldwide to date. In this situation, saving human life is the objective. The approach should concentrate on enhancing the immune system and reusing existing drugs to limit virus replication. One of the most crucial trace elements for reaching this intriguing objective has been called out as Zn. In mammalian cells, Zn has been found to increase antiviral activity. Such a trace element may be useful to fight versus fatal illnesses. Supplementing with Zn, like it did with SARS-CoV, may helpful in treatment and prevention of COVID-19, since Zn is a organic bio-component of several enzymes in the cell for transformation and immunological function.

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