Potential health benefits of zinc supplementation for the management of COVID-19 pandemic

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiological agent for the Coronavirus Disease 2019 (COVID-19). The COVID-19 pandemic has created unimaginable and unprecedented global health crisis. Since the outbreak of COVID-19, millions of dollars have been spent, hospitalization overstretched with increasing morbidity and mortality. All these have resulted in unprecedented global economic catastrophe. Several drugs and vaccines are currently being evaluated, tested, and administered in the frantic efforts to stem the dire consequences of COVID-19 with varying degrees of successes. Zinc possesses potential health benefits against COVID-19 pandemic by improving immune response, minimizing infection and inflammation, preventing lung injury, inhibiting viral replication through the interference of the viral genome transcription, protein translation, attachment, and host infectivity. However, this review focuses on the various mechanisms of action of zinc and its supplementation as adjuvant for vaccines an effective therapeutic regimen in the management of the ravaging COVID-19 pandemic.

Practical applications

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent for the Coronavirus Disease 2019 (COVID-19), has brought unprecedented untold hardship to both developing and developed countries. The global race for vaccine development against COVID-19 continues with success in sight with attendant increasing hospitalization, morbidity, and mortality. Available drugs with anti-inflammatory actions have become alternative to stem the tide of COVID-19 with attendant global financial crises. However, Zinc is known to modulate several physiological functions including intracellular signaling, enzyme function, gustation, and olfaction, as well as reproductive, skeletal, neuronal, and cardiovascular systems. Hence, achieving a significant therapeutic approach against COVID-19 could imply the use of zinc as a supplement together with available drugs and vaccines waiting for emergency authorization to win the battle of COVID-19. Together, it becomes innovative and creative to supplement zinc with currently available drugs and vaccines.

KEYWORDS: antioxidant, antiviral, immunomodulatory, SARS-CoV-2, zinc supplementation

1 INTRODUCTION

The infection of humans with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, the capital of Hubei Province in the People's Republic of China in December 2019 led to the staggeringly devastating Coronavirus disease 2019 (COVID-19). The COVID-19 pandemic has reached unprecedented global magnitude in which almost every country affected in the first two quarters of 2020 (Zhu et al., 2020). The etiological agent of COVID-19 is SARS-CoV-2. It is transmitted rapidly from one individual to the other in close proximity via contact with virus-laden aerosols discharged in coughs and sneezes of symptomatic patients (Dhama et al., 2020). COVID-19 is a systemic disease that can move beyond the lungs by blood-based dissemination affecting multiple organs, tissues, and blood vessels (see Figure 1). Although, most affected patients die as a result of acute respiratory distress syndrome. Also,

several organs including the liver, hearts, kidney, muscles, spleen, and nervous system are severely affected worsening prognostic outcomes initiated by epithelial infection and alveolar macrophage activation in the lungs (Nishiga et al., 2020). Although, several drugs have been evaluated, tested, and administered in the frantic efforts to stem the dire consequences of the COVID-19. A definitive therapeutic regimen is yet to be established for disease prevention and or management in symptomatic patients. However, drugs such as remdesivir, lopinavir/ritonavir, favipiravir, are some of the antiviral agents that have been used with varying degrees of successes in the management of COVID-19 (Wang et al., 2020). The intravenous administration of remdesivir has been reported to ameliorate the disease symptoms in COVID-19 patients in the United States of America (Holshue et al., 2020). Similarly, favipiravir has been reported to show promising desirable therapeutic effects, without apparent side effects, in COVID-19 (Chen et al., 2020). Furthermore, tocilizumab (a recombinant humanized monoclonal antibody of the IgG1 class) have been recommended for the treatment of severe rheumatoid arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, and life-threatening cytokine release syndrome (see Figure 2). Similarly, dexamethasone, has been used as supportive therapy for COVID-19 (Lester et al., 2020). Recently, Ebselen, a new therapeutic candidate against SARS-CoV-2 have been reported to significantly alter the disease outcomes in hospitalized COVID-19 patients, albeit with some controversy, (Guaraldi et al., 2020; Haritha et al., 2020).

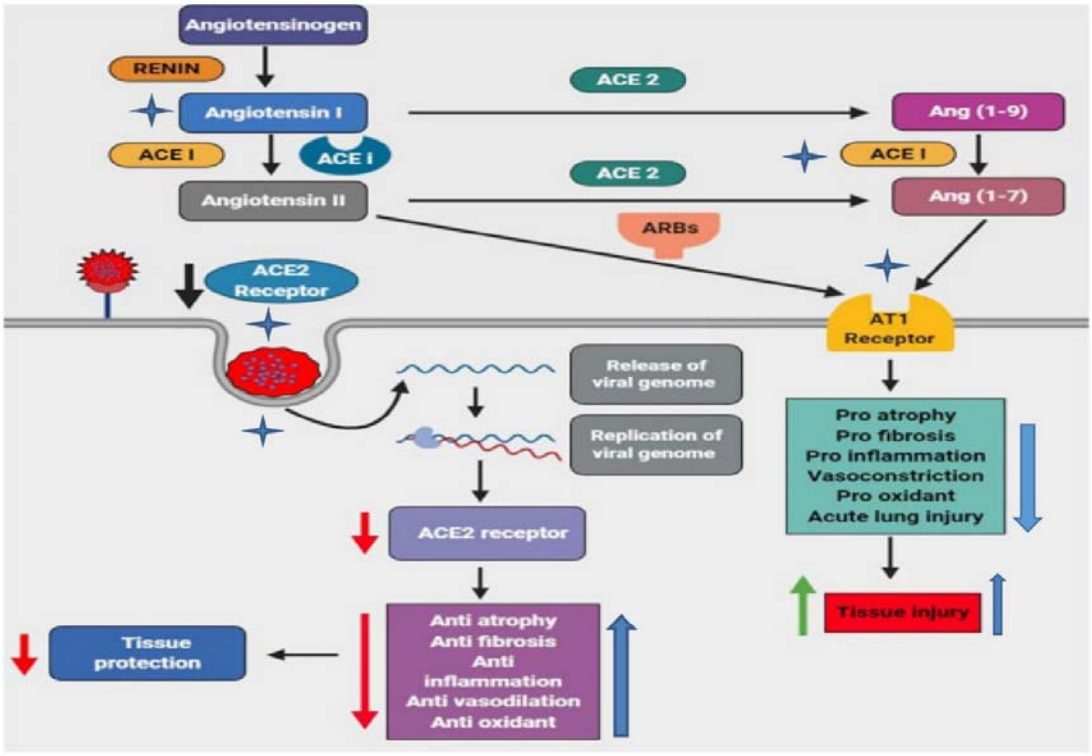

FIGURE 1. This shows the renin angiotensin aldosterone system (RAAS) and the involvement of novel angiotensin converting enzyme (ACE2) in the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2. Angiotensinogen (AGT) is cleaved by renal renin to produce angiotensin I, while angiotensin converting enzyme (ACE) produces angiotensin II (a vaso-constrictive agent) from angiotensin 1. However, a novel angiotensin converting enzyme 2 (ACE2) cleaves angiotensin II to produce two molecules namely Ang (1–7) Ang (1–9), respectively. The same ACE2 is the receptor for SARS-CoV-2. Binding of SARS-CoV-2 its receptor ACE2 facilitates the entry of the virus in the host cell with ultimate initiation of COVID-19 pathogenesis

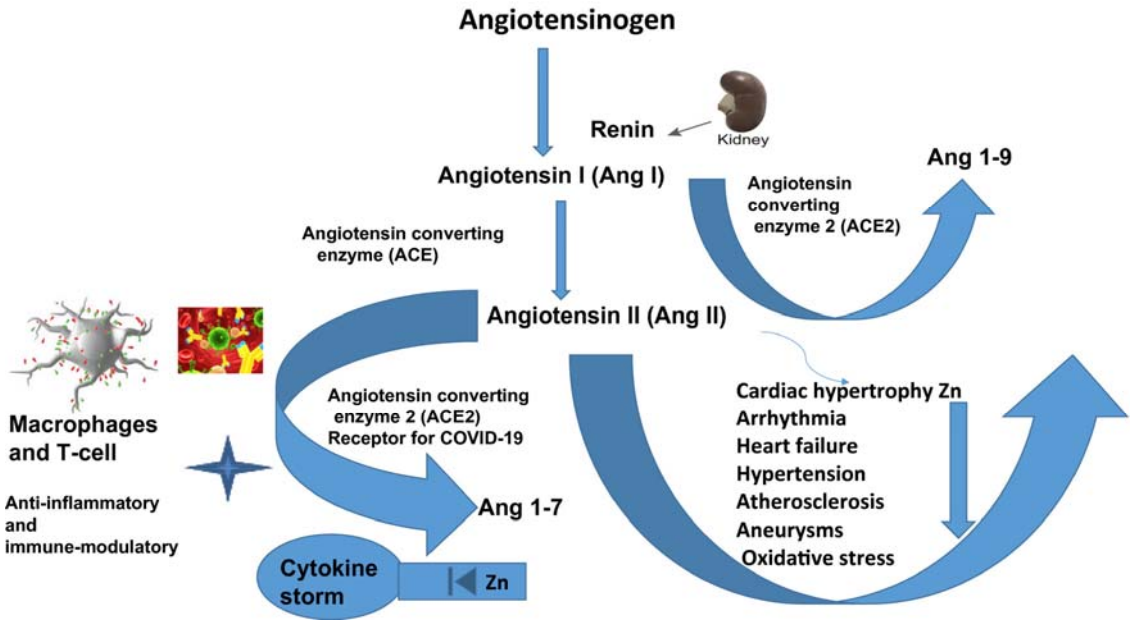

FIGURE 2. This shows the roles of cytokine storm, novel angiotensin converting enzyme (ACE2) and cardiovascular dysfunctions in the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 and the potential benefits of zinc supplementation. Zinc inhibits macrophage infiltration and T-cell activation, thereby attenuating production of pro-inflammatory cytokine, lung inflammation and ultimately, cytokine storm, oxidative stress and organ damage. In pathological condition as in COVID-19, ACE2 activity is reduced, therefore, production of beneficial molecules such as Ang (1–7) Ang (1–9) s significantly impeded. Zinc supplementation could therefore offer protection against cytokine storm-induced organ damage

Zinc (Zn) is the second most abundant trace metal in the human body after iron. Zinc is a transition element in the periodic table with atomic number 30 and atomic weight 65.37. Zinc exists as a divalent, non-redox active cation that is neither a reducing nor an oxidizing agent in mammalian physiological systems (Solomons, 2001). The physiological and biochemical effects of this essential element is manifested in all organs and cell types, with zinc representing an integral component of approximately 10% of the human proteome, and encompassing hundreds of key enzymes and transcription factors. Consequently, zinc is an essential modulator of the mammalian epigenome with well characterized structural, catalytic, and regulatory roles. In humans, Zn is found in all tissues and approximately 1.4–2.3 g of zinc is found in the body of an adult. The distribution of zinc in mammalian tissues and organs vary greatly, with 85% of total amount found in muscles and bones, up to 11% occurring in the skin, and only 0.1% of total body zinc of 1µg/ml is found in plasma. In extracellular fluids, zinc is predominantly bound to proteins including albumin, alpha-2-macroglobulin (A2M), transferrin, and others (Livingstone, 2015).

The intracellular zinc level is tightly regulated via the modulation of the zinc-sequestering proteins such as metallothioneins, which are low molecular mass metal-binding protein of approximately 6,500 Da that induces cytokine secretion from macrophages. The zinc transporter proteins are divided into two general subtypes, that is, the 14-membered SLC39s/ZIPs subtype and the 10-membered SLC30s/ZnTs subtype, both of which are responsible for the transportation of zinc intracellularly (Hojyo & Fukada, 2016). The ZnT1 located in the cell membrane transports zinc from the basolateral membrane of erythrocytes

into the systemic circulation, while ZnT2 promotes the accumulation of zinc in lysosomes and endosomes thereby ameliorating toxic cellular effects of zinc. The ZnT3 is found in the synaptic vesicles and is concerned with zinc transportation to synaptic vesicles. Furthermore, ZnT4 modulates zinc absorption at the apical membrane of enterocytes and prominently involved in mammary gland zinc metabolism. However, ZnT5 is highly expressed in pancreatic tissues but is found in other mammalian tissue where it plays several modulatory roles, for instance, the loading of zinc to alkaline phosphatase in secretory vesicles and maturation of osteoblasts in bone. ZnT6 modulates the translocation of zinc to intracellular organelles including the secretory vesicles and Golgi apparatus, but ZnT7 is essential for the incorporation of zinc into the metalloenzymes that modulates various physiological processes in mammalian tissues. The ZnT8 also contributes to the translocation of cytoplasmic zinc to secretory vessels and is the key transporter for the provision of zinc to the storage process in the insulin-secreting pancreatic beta cells. The ZnT9 is present in many cells and tissues, and is probably a contributor to periparturient and increased lactogenesis, while ZnT10 transports zinc to secretory vesicle and is reported to be highly expressed in various tissues including the brain and the liver (Baltaci et al., 2017). This review strengthens the need for a global cooperative effort to urgently identify and develop effective therapeutic strategies in the absence of vaccine.

1.1 Epidemiology

The unprecedented COVID-19 pandemic is caused by a novel RNA coronavirus called SARS-CoV-2 that produces a severe acute respiratory distress syndrome (ARDS) (Gao et al., 2020). The SARS-CoV-2 was first detected in Wuhan province of China in December 2019 (14), and by March 11 2020, COVID-19 was declared as a global pandemic by World Health Organization (2020). This virus is highly infectious with a high prevalence rate. As of December 5, 2020, 66,000,000 people have tested positive to the COVID-19 with mortality rate of more than 1,520,000, and 42, 400, 000 recovered globally. Presently in Nigeria, there are more than 68,627 confirmed cases with over 1,179 deaths due to COVID-19. The inflammation of the lungs has been implicated as one of the initiating factors in the pathogenesis of COVID-19 infection, while underlying medical conditions such as hypertension, asthma, and diabetes are co-morbidities associated with COVID-19. For now, some vaccines are in the last stage clinical trial, and while drugs currently in-use have achieved limited success. Interestingly, vaccines from Pfizer and BioNTech (USA/Germany) have received emergency authorization for use. Similarly, vaccines from Moderna (USA), Sinovac (China), and Sputnik V (Russia) have also been approved accordingly for use. There is, therefore, an urgent need to identify, develop, and deploy trace element such as zinc as adjuvant for vaccines/drugs treatment and management of COVID-19.

1.2 Structure and genome of the SARS-CoV-2

The family Coronaviridae is a large group of viruses that infect both animals and humans. The SARS-CoV-2 is an enveloped virus with roughly spherical or moderately pleomorphic virions of approximately 60–140 nm in diameter (Yan et al., 2020). The membrane of the virus contains the spike (S) glycoprotein that forms the peplomers on the virion surface, giving the virus its “corona”—or crown-like morphology as elucidated by electron microscopy. The membrane (M) glycoprotein and the envelope (E) protein are known to provide the ring

structure. Within the interior of the entire virus particle is the helical nucleocapsid comprised of the nucleocapsid (N) protein complexed with a single positive-strand RNA genome of about 30 kb in length (Gralinski & Menachery, 2020). The first genomic sequence of SARS-CoV-2 named Wuhan-Hu-1 was isolated and sequenced in China in January 2020 as documented by Gralinski and Menachery (2020) and Yan et al. (2020). It is worth to note that the SARS-CoV-2 genome has approximately 96% similarity to the bat coronavirus Bat CoV RaTH13 with an estimated 80% similarity with SARS-CoV-2 (Gralinski & Menachery, 2020), and similarly an estimated 50% identity with MERS-CoV (Wu, Peng, et al., 2020; Wu, Liu, et al., 2020).

1.3 Possible mechanisms of Zinc in COVID-19-related pathogenesis

Previous study suggested that ACE-2 expression is regulated by Sirtuin 1 (SIRT1); and that zinc decreases SIRT1 activity, hence, regulation of SIRT1 by zinc could decrease ACE-2 expression and ultimately viral entry into the cell (Cao et al., 2019; Patel et al., 2016; Rosenkranz et al., 2016). Serum zinc concentration has been positively correlated to healthy pulmonary function, as high zinc levels have been shown to improve lung tolerance against damage by mechanical ventilation (Boudreault et al., 2017). In an ex vivo model of the chronic obstructive pulmonary disease (COPD), decreasing zinc levels was reported to exacerbate the leakage of the epithelium of the respiratory tract (Roscioli et al., 2017). Moreover, zinc supplementation has been reported to improve lung integrity in an in vivo murine model of acute lung injury (Wessels et al., 2020). Therefore, infections with coronaviruses has been reported to precipitate damage of the ciliated epithelium and ciliary dyskinesia with ultimate impairment of the mucociliar clearance (Chilvers et al., 2001). It is particularly important to note that physiological concentrations of zinc increase ciliary beat frequency, thereby preventing the infection of the lung by COVID-19 (Woodworth et al., 2010). More importantly, persistent low serum zinc has been documented in critically ill patients, and this is associated with recurrent sepsis and inversely correlated with mortality from sepsis, emphasizing the importance of zinc supplementation in COVID-19 therapy (Hoeger et al., 2017).

1.4 Interaction of SARS-CoV with zinc

Recently, Prasad (2013) reported that supportive therapy of zinc supplementation along with vitamin C, and D could be used to mitigate COVID-19 infection as zinc inhibits pH-dependent steps of coronavirus replication by increasing pH in intracellular vesicles and also interfere with the virus entry into cells. Again, the effectiveness of zinc can be enhanced using chloroquine as an ionophore while zinc inside the infected cell can stop SARS-CoV-2 replication (Rahman & Idid, 2020). In addition to SARS-CoV, a number of other viruses, including HIV, HSV, and vaccinia virus, are known to be inhibited by zinc salts (Rahman & Idid, 2020). Abd-Elsalam et al. (2020) and Skalny et al. (2020) reported that chloroquine can act as ionophore for zinc. Chloroquine enhances uptake of zinc by the lysosomes, and the combination of zinc and chloroquine enhances chloroquine cytotoxicity and induces apoptosis in malignant cells. It has also been reported that Zn2 + found to specifically inhibit the SARS-CoV RdRp elongation and template binding (Celik et al., 2020;). Earlier, it was also shown that Zn2+ inhibited the proteolytic processing of replicase polyproteins (Celik et al., 2020; Mossink, 2020).

2 DIETARY SOURCES OF ZINC

Zinc is found in large quantities in many types of food sources including meat, milk, shell fish, chocolate, legumes, seeds, nuts, eggs, whole grains, and some vegetables. Although, zinc occurs naturally in a wide variety of food sources, the bioavailability, that is the quantity available for systemic use, also varies overwhelmingly. Interestingly, red meat, leguminous crops, and whole grains are some of the food types with highest bioavailability of zinc following ingestion. Generally, plant-based diets are poorer zinc sources than animal-based diets, with consequent higher prevalence of zinc deficiency in vegetarians than people on meat-based diets (Allès et al., 2017). Inadequacy of dietary intake of zinc has been characterized as zinc deficiency a common medical phenomenon particularly in the aged and patients consuming meat-free diets (Haase et al., 2006). Although, diet-related zinc deficiency is more prevalent in third world countries it has also been reported in developed nations such as the United States of America and Japan, where less acute deficiency states have been suggested to occur with high prevalence (Mayneris-Perxachs et al., 2016).

Clinically, absence of zinc in the diet may manifest as altered reproductive functioning, severe immune dysfunctions leading to increased susceptibility to infections, hyperammonemia, neurosensory disorders, decreased lean body mass, diarrhea, skin lesions, stunted growth, and increased susceptibility to chronic noncommunicable diseases (Prasad, 2008). Moreover, patients consuming zinc-deficient diet have also been reported to suffer from thymic and splenic atrophy. *In utero*, adverse effects of chronic consumption of zinc-deficient diets have been reported to include high rates of fetal resorption, reduced litter size, congenital malformations, reduced splenocyte responsiveness to mitogen, and reduced serum levels of IgG2a and IgA (Raqib et al., 2007). Also, inadequacy of zinc in diets has been associated with attenuated activity of the osteoblast, and reduced synthesis of collagen and proteoglycans in the presence of reduced phosphatase activity (Tapiero & Tew, 2003). In addition to inadequate dietary zinc intake, deficiency of zinc may result from impaired absorption or resorption or increased excretion of zinc, and several pathologic statuses including chronic diarrhea, extensive burns, or traumatic and surgical wounds (Aliev et al., 2019).

Replenishing body zinc through adequate dietary intake is required for optimal physiological functioning of mammalian organs or tissues due to the non-availability of dedicated storage compartment for zinc and almost absolute reliance on tightly regulated homeostatic concentrations (Gibson et al., 2016). Zinc is hydrophilic and cannot diffuse passively through the cell membrane. As a result, zinc is absorbed actively from the gastrointestinal tract with the aid of the transmembrane protein transporter. Zinc transporter (ZIP4) also known as solute carrier family member A4 in humans is encoded by the SLC39A4 gene and is located at the apical surface of the intestinal enterocytes, whereas, the uptake of zinc from blood is believed to be the function of ZIP5 which is largely expressed in intestine, pancreas, kidney, and embryonic yolk sac (Jeong & Eide, 2013). The zinc transporters function as zinc/hydrogen exchangers and play several important modulatory effects in diverse physiologic and pathologic mechanisms in the mammalian systems (Lu et al., 2008). Genetic abnormalities with polymorphisms of the SLC39A4 gene encoding the ZIP4 transporter manifest clinically as acrodermatitis enteropathica, a form of zinc deficiency.

Zinc modulates several physiological functioning, an ability that has been attributed to the essentiality of zinc to the formation of several endogenous enzymatic antioxidants and the stabilization of protein domains that interact intracellularly with deoxyribonucleic acid (Skrajnowska & Bobrowska-Korczak, 2019). Established physiological roles for zinc are seen in immunomodulation, with effects on innate and adaptive immunity. Hojyo et al. (2014) reported decreased immune system response with consequent altered resistance to pathogenic organism in zinc-deficient individuals. Moreover, zinc plays important roles in protein and deoxyribonucleic acid synthesis, growth and development *in utero*, intracellular signaling, enzyme function, gustation, and olfaction, as well as reproductive, skeletal, neuronal, cardiovascular systems, and wound healing (King et al., 2016; Yu et al., 2018).

3 ROLES OF ZINC AS AN IMMUNE BOOSTER

Zinc is an important regulator of the immune system activities, with adequate level of zinc in the systemic circulation required for T cells maturation and thymulin activity. The administration of zinc reportedly elevated CD4+ and CD8+ cells in zinc-deficient patients, and adequate zinc level is required for the activation of natural killer cells (Baltaci et al., 2018). Furthermore, the number and functional ability of granulocytes to phagocytose invading pathogenic organisms are significantly reduced in zinc-deficient patients (Rosenkranz et al., 2011). Zinc is important for the maturation of T and B lymphocytes, but the development of the T lymphocytes under physiological conditions are more severely affected in zinc-deficient individuals (Chung et al., 2009). Zinc deficiency has been reported to directly or indirectly induce a dysregulation of physiological zinc homeostasis via mechanisms that interferes with specific immunomodulatory activities such as the recruitment, chemotactic, and phagocytic activities of granulocytes, as well as alteration of monocyte adhesion to epithelial cells and cytotoxicity of natural killer cells (Nishikawa et al., 2020). Moreover, zinc modulates the recognition of major histocompatibility complex (MHC) by natural killer cells, and the CD3+ differentiation and cytotoxic activity has been reported to significantly increase zinc availability (Jarosz et al., 2017).

4 ANTI-INFLAMMATORY ROLE OF ZINC

Several cytokines such as interleukins 1, 2, 6, 10, and 12, tumor necrosis factor alpha (TNFα), transforming growth factor (TGF), and interferon gamma (IFγ) enhance local and systemic inflammatory effects, fever, hormone release, and increased migration of leukocytes have been reported to be modulated by varying physiological levels of zinc in mammalian systems (see Figure 3). Moreover, zinc has been reported to inhibit the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in the DNA nuclear-binding domain by increasing the expression of peroxisome proliferator-activated receptor α (PPAR-α), which is a mediator for lipoprotein metabolism, inflammation, and glucose homeostasis. Increase in PPAR-α leads to the downregulation of inflammatory cytokines and adhesion molecule (see Figure 3). Consequently, the suppression of the immune system manifesting as increased susceptibility of the patients to opportunistic pathogenic agents is, therefore, observed. Zinc has been reported to inhibit phosphodiesterase with consequent elevation of cyclic guanosine monophosphate (cGMP), activation of protein kinase A, and NF-κB inhibition. The mechanisms that can lead to NF-κB inhibition include blockage of the incoming stimulating signal at an early stage, interference with a cytoplasmic step in the NF-κB activation pathway

by blockage of a specific component of the cascade, and inhibition of NF-κB binding to DNA, thereby altering the modulatory roles in inflammation (Gilmore & Herscovitch, 2006).

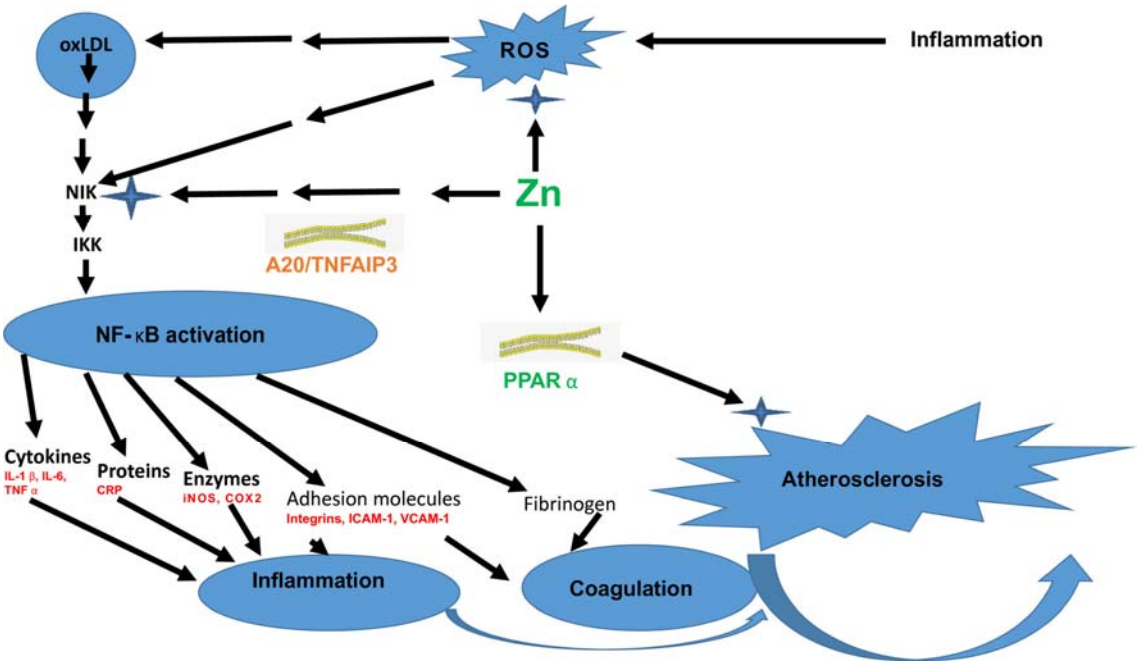

FIGURE 3. This shows biological and pharmacological roles of Zinc in the management and prevention of COVID-19 pandemic. Anti-inflammatory property of zinc is demonstrated through the inhibition of translocation of NF-κB from cytoplasm to nucleus where it binds to pro-inflammatory genes leading to exaggerated production of pro-inflammatory cytokines and inflammatory mediators such as Interleukin 1 beta (IL-1β), Interleukin 6 (IL-6), tumor necrosis factor alpha (TNFα), Integrins, Intercellular Adhesion Molecule 1 (ICAM-1), Vascular cell adhesion protein 1 (VCAM-1), Inducible nitric oxide synthase (iNOS) and yclooxygenase-2 (COX2) with attendant intravascular disseminated coagulation and atherosclerosis

Supplementation of zinc in diets has been reported to downregulate the production of inflammatory cytokines from T helper cells and macrophages probably by decreasing gene expression of IL-1β and TNF-α through upregulation of mRNA and DNA-specific binding for A20, subsequently inhibiting NF-κB activation (Prasad et al., 2004). In in vitro studies, decreased levels of NF-κB, TNF-α, and IL-1β are associated with altered zinc levels (see Figure 3). Similarly, zinc can bind to a zinc finger-like motif found on protein kinase C (PKC) and inhibit PMA-mediated PKC translocation to the membrane. When this occurs in mast cells, NF-κB activity is indirectly inhibited (Brieger et al., 2013). Furthermore, zinc has been shown to influence cellular signal transduction by inhibition of several dephosphorylating enzymes like protein tyrosine phosphatase (PTPs), cyclic nucleotide phosphodiesterases, and dual specificity phosphatases.

5 ZINC IN MANAGING COVID-19-ASSOCIATED CYTOKINE STORM

Severe infection of the respiratory epithelium can precipitate an ARDS, characterized by excessive, exaggerated, and fulminating inflammation, termed a cytokine storm (Calder, 2020). Cytokine storm occurs when an immune system is overactivated by infection,

drug, and/or some other stimuli, leading to exaggerated response of cytokines (IFN, IL, chemokines, CSF, TNF, etc.) being released into circulation with a widespread and detrimental impact on multiple organs (Tisoncik et al., 2012). It has been hypothesized that transient zinc deficiency that occurs during COVID-19 infection could result in a hyperinflammatory state, and recently, symptoms such as loss of taste and smell have been positively correlated COVID-19 (Pisano & Hilas, 2016; Stratton et al., 2020; Vaira et al., 2020). Pro-inflammatory cytokines such as IL-1 and IL-6 have been reported to play an important role in severe lung inflammation, leading to ARDS, and ultimately death of COVID-19 patients (Conti et al., 2020; Wang et al., 2020). Furthermore, high serum levels of pro-inflammatory cytokines [IL-1, IL-6, IL-12, interferon g (IFN-g), and transforming growth factor-β] and chemokines (CCL2, CXCL9, CXCL10, and IL-8) were found in patients with SARS compared with individuals with uncomplicated SARS (Martinez-Urbistondo et al., 2020; Wong et al., 2004). In mild diseases, C-reactive protein (CRP) levels of 15 mg/L, and a 10% decrease in zinc was observed (Galloway et al., 2000). In severe infectious diseases, CRP levels can reach 100–200 mg/L, with a much greater decrease in zinc levels (40%–60%) (Galloway et al., 2000).

Excessive inflammatory response elicited by SARS-CoV-2 infection has been found to result in the overproduction of pro-inflammatory cytokines and cytokine, and this is known to play a significant role in COVID-19 pathogenesis (Patterson et al., 2020). However, the anti-inflammatory activity of zinc has been demonstrated through the regulation of T-cell function, inhibition of IKK activity, and subsequent NF-κB signaling with concomitant reduction in pro-inflammatory cytokine production (Wessels et al., 2013). Previous findings demonstrated that zinc deficiency increases the susceptibility to systemic inflammation and sepsis-induced organ damage including lungs (Knoell et al., 2009). Again, Bao et al. (2010) reported that in a model of multiple infection-induced sepsis, zinc deficiency resulted in increased NF-κB p65 mRNA expression and production in lungs resulting in up-regulation of target genes such as IL-1β, TNFα, and ICAM-1, whereas neutrophil infiltration and MPO-mediated oxidative damage was attenuated by zinc supplementation (Ganatra et al., 2017). Therefore, zinc supplementation might offer unparalleled mitigation of excessive inflammation during COVID-19 infection.

6 ANTIOXIDANT PROPERTIES OF ZINC

Although zinc does not inhibit the destructive effects of reactive oxygen species (ROS) directly, zinc retards the oxidative processes on a long-term basis by inducing the expression of metallothioneins. These are metal-binding cysteine-rich proteins responsible for maintaining zinc-related cell homeostasis and act as potent electrophilic scavengers and cytoprotective agents. Furthermore, zinc increases the activation of antioxidant proteins and enzymes, such as glutathione and catalase. Zinc exerts its antioxidant effect via two acute mechanisms, one of which is the stabilization of protein sulfhydryls against oxidation, whereas, the second mechanism involves the antagonism of transition metal-catalyzed oxidative reactions. Moreover, zinc can exchange redox active metals, such as copper and iron, in certain binding sites and attenuate cellular site-specific oxidative injury. Zinc is a component of superoxide dismutase (SOD 1, SOD3) which catalyzes the dismutation of superoxide anion radicals to hydrogen peroxide (H_2O_2) and thus, preventing the generation of other toxic-free radicals and their derivatives, for example, hydroxyl or peroxynitrite radicals (Strange et al., 2003). Zinc acts as a co-factor for cytosolic and extracellular Zn/Cu

SOD enzyme, which acts as a scavenger of ROS by catalyzing the dismutation of O_2^- radical into the less harmful O_2 and H_2O_2 (Mariani, 2008).

Zinc potently inhibits the Mia40/Erv1 pathway associated with the transmembrane immunoglobulin and mucin domain family proteins that modulate T-cell proliferation and cytokine production (Morgan et al., 2009). Alteration in intracellular zinc level has been suggested to be linked with the dysregulation of physiological arrangement of mitochondrial proteins, thereby interfering with mitochondrial synthesis, and in some cases activation of stress response in the endoplasmic reticulum due to accumulation of misfolded proteins that induce a vicious cycle of endoplasmic reticulum stress and oxidative stress (Malhotra et al., 2008).Zinc has been reported to increase the levels of glutathione, catalase, glutathione S-transferase, and heme oxygenase (Goel et al., 2005; Prasad, 2014). In the same vein, low levels of zinc as seen in zinc-deficient individuals has been experimentally associated with oxidative stress-medicated tissue destruction (Zhao et al. 2011), probably by upregulating nuclear factor erythroid 2-related factor 2 (Sehsah et al., 2019).

Increased levels of ROS seen with decreased dietary intake of zinc might be associated with reduced functional activity of the zinc containing SOD (Jarosz et al., 2017). Moreover, zinc protects sulfhydryl groups in proteins against oxidative stress-mediated damage, thereby modulating the regulation of enzymatic activities and altering the total antioxidant capacity in biological systems (Krężel and Maret, 2016).

7 ANTIVIRAL PROPERTIES OF ZINC

Zinc has been reported to exert potent antiviral activities against diverse array of viruses including the herpes simplex virus 1 and 2, rhinovirus, influenza, coronaviruses, human immunodeficiency virus, and a host of other pathogenic viruses. Zinc has been reported to ameliorate the pathogenic effects of HSV-1 and HSV-2 by altering the viral polymerase function, protein production, and direct inactivation of the viruses as well as reducing HSV replication by interfering with the protein ubiquitination pathway (Qiu et al., 2013). Furthermore, in a mouse study, intra-vaginal zinc inoculation in liquid or gel form demonstrated significant reductions in HSV-2 infection, whereas topical zinc application has been reported to significantly reduce recurrence and duration of HSV-1 and HSV-2 infection (Qiu et al., 2013). The efficacy of topical application, together with in vitro results, suggest that free zinc might indeed coat HSV virions, thus preventing infection (Lim et al., 2013).

Clinical studies using zinc supplementation are primarily limited to rhinovirus infection, and are often grouped with other “common cold” viruses such as influenza and coronaviruses with several studies using zinc lozenges and formulations. The replication of rhinoviruses was potently inhibited by Zinc salts in in vitro experiments and amelioration of clinical symptoms associated with common cold has been reported to occur following increased level of zinc salts in the nasal cavity (Vakili et al., 2009). For instance, the administration of zinc bisglycinate reduced significantly the duration of illness and manifestation of symptoms under experimental conditions (Sanguansak & Lakkana, 2013). Similarly, zinc salts have been reported to inhibit respiratory syncytial virus in vitro (Suara & Crowe, 2010).

Similar to viral RNA-dependent RNA polymerase, zinc has also been identified as an inhibitor of retrovirus reverse transcriptases with zinc cations displacing magnesium ions from HIV-1 RT, thereby potentiating the formation of an inefficient replication complex (Fenstermacher & DeStefano, 2011). In HIV-infected patients, manifestation of zinc deficiency has been reportedly linked with immunological inadequacy that sometimes contribute to the poor prognostic disease outcome. However, prophylactic application of zinc has been reported to show significant reduction in viral load of HIV patients and protected against vaginal SHIV-RT (a simian HIV virus expressing the human RT) (Mizenina et al., 2017).

8 THERAPEUTIC ROLE OF ZINC

The application of zinc as a drug to treat diseases is increasing due to advances in the understanding of modulatory roles of zinc in mammalian systems. Reported beneficial effects of zinc administration include reduction in the incidence of diarrhea and pneumonia, and the rate of mortality among young children in low-middle income countries (Tran et al., 2011). Zinc supplementation in young children has been reported to reduce child mortality by 6% in deficient populations and reduced deaths of children over 1 year of age by 18%. Moreover, supplemental administration of zinc to the diet has been reported to prevent stunted growth in children (Tran et al., 2011). Zinc has been found to be very useful in the management of acute childhood diarrhea with a recommendation of 10- to 14-day course of zinc treatment, in addition to the usual administered oral rehydration solution, by the World Health Organization and the United Nations Children's Fund (Patel et al., 2011). Zinc has been used therapeutically for the management of chronic gastrointestinal disorders, renal diseases, sickle cell anemia, and malabsorption syndrome acrodermatitis enteropathica (Rosenkranz et al., 2015).

9 CONCLUSION

The beneficial roles of zinc on physiological and pathological states have been well described in literature, and highlighted the usefulness of zinc in many clinical diseases. More importantly, the usefulness of zinc as an antiviral agent for the management of such viral diseases as influenza, rhinovirus, and coronaviruses strongly suggests potential beneficial roles and applications of zinc in the management of COVID-19, probably through the enhancement of the total antioxidant capacity and immunomodulatory effects. Therefore, the inclusion of Zinc as a component of therapeutic or prophylactic regimen in the current treatment of COVID-19 is strongly advised. Furthermore, immunomodulatory effect of zinc will be of significant benefits to patients with co-morbidity and those with severe underlying medical conditions. Interestingly, zinc supplementation might decrease angiotensin-converting enzyme 2 (ACE-2) expression, and thus, viral entry into the host cell. Therefore, the high the concentration of zinc, the lower the activity and entry of SARS-CoV-2 into the host cell. Hence, zinc supplementation could be of potential benefit for mitigating COVID-19 that has brought unprecedented global health crises and economic burden. In the current pandemic of COVID-19, zinc supplementation could play significant roles in the fight against COVID-19 as immune booster with anti-viral drugs and inhibiting SARS-CoV-2 replication in infected cells especially if combined with chloroquine and anti-inflammatory drugs such as dexamethasone by preventing the release of pro-inflammatory cytokines. Therefore, foods rich in zinc and zinc supplements could serve as adjuvants in combination with up-coming

vaccines for the treatment of COVID-19 pandemic. Together, research on inhibitory action of zinc supplementation on the pathogenesis of SARS-CoV-2 across all ages, race, and sex should be urgently conducted as alternative anti-inflammatory and immuno-modulatory regimen against the current COVID-19 pandemic. Furthermore, studies on zinc supplementation in hospitalized COVID-19 patients might give a novel insight in containing the unprecedented global health crisis and economic catastrophe created by COVID-19 pandemic.

CONFLICT OF INTEREST

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

AUTHOR CONTRIBUTIONS

Ademola Adetokunbo Oyagbemi (Conceptualization, Supervision, and Writing-review & editing), Temitayo Olabisi Ajibade (Writing-original draft and Writing-review & editing), Yapo Guillaume Aboua (Writing-review & editing), Idayat Titilayo Gbadamosi (Writing-review & editing), Aduragbenro Deborah A. Adedapo (Writing-review & editing), Abimbola Obemisola Aro (Writing-review & editing), Olumuyiwa Abiola Adejumobi (Writing-review & editing), Emma Thamahane-Katengua (Writing-review & editing), Temidayo Olutayo Omobowale (Writing-review & editing), Olufunke Olubunmi Falayi (Writing-review & editing), Taiwo Olaide Oyagbemi (Writing-review & editing), Blessing Seun Ogunpolu (Writing-review & editing), Olufunke Olubunmi Falayi (Writing-review & editing), Fasilat Oluwakemi Hassan (Writing-review & editing), Iyanuoluwa Omolola Ogunmiluyi (Writing-review & editing), Olufunke Eunice Ola-Davies (Writing-review & editing), Adebowale Benard Saba (Writing-review & editing), Adeolu Alex Adedapo (Writing-review & editing), Sanah Malomile Nkadimeng (Writing-review & editing), Lyndy Joy McGaw (Writing-review & editing), Prudence Ngalula Kayoka-Kabongo (Writing-review & editing), Oluwafemi Omoniyi Oguntibeju (Writing-review & editing), and Momoh Audu Yakubu (Writing-review & editing).

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