Perspective

Importance of Zinc and Mechanism of Action in COVID-19

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Introduction

Zinc (Zn) is an essential nutrient for all forms of life because it involves in all aspects of cellular and molecular biology [1]. Global recognition of the significance of zinc for human being has increased considerably after the identification of zinc-responsive dwarfism and late sexual development in Iranian farmer in 1960 and later on in Egyptian adolescents in 1963 [2,3].

Presently, numerous available evidences in literature that recognised zinc deficiency as major health problem throughout the world which affects growth and development, immune system and cognitive functions in human beings [4,5].

Antiviral activity of Zinc and Mechanism of Action in COVID-19

Most of the existing knowledge about the effectiveness of Zn as a therapeutic agent against COVID-19 is based on studies performed with other viral diseases and limited experience with COVID-19 [6]. The significance of Zn supplementation in the treatment of COVID-19 infection has been attributed to its antiviral and antioxidant property, and its ability to modulate the inflammatory and immune response [7-10].

Infection by SARS-CoV-2 causes a reduction in mucociliary clearance with the destruction of ciliated epithelium [10,11]. Treatment with Zn has been found to improve the length and beating frequency of cilia [11]. The improvement in ciliary clearance will alter the elimination of viral particles and improve the risk of bacterial coinfections. Any disruption in the integrity of the respiratory tract epithelium promotes virus entry and leads to its entry into the bloodstream. Zn helps to maintain the integrity of the cytoskeleton by acting as a membrane stabilizer [11,12]. The expression of membrane tight junction proteins such as ZO-1 and claudin-1 are enhanced to strengthen the barrier function of the respiratory epithelium [13]. A decline in barrier function worsens the inflammatory response causing leakage of high molecular weight proteins and water in the airways, ultimately leading to edema and Acute Respiratory Distress Syndrome (ARDS) [14]. The increased activity of antioxidants and the inhibition of caspase activation and apoptosis further protect the respiratory epithelium [15].

Zn ions in combination with Zn ionophores such as pyrithione have been reported to block the replication of RNA viruses by inhibiting the RNA-dependent RNA polymerase (RdRp) of the virus [16]. Another possible Zn-related therapeutic strategy against COVID-19 targets the expression of Angiotensin-Converting Enzyme 2 (ACE-2) receptors, which are required for virus entry into the cells [17]. Zn minimizes the activity of Sirtuin-1 (SIRT-1), which regulates ACE-2 expression and thereby possibly blocks virus entry **(Figures 1 and 2)** [18].

The principal hallmark of COVID-19 infection includes an imbalance in the immune response. The entry of SARS-CoV-2 in the cells

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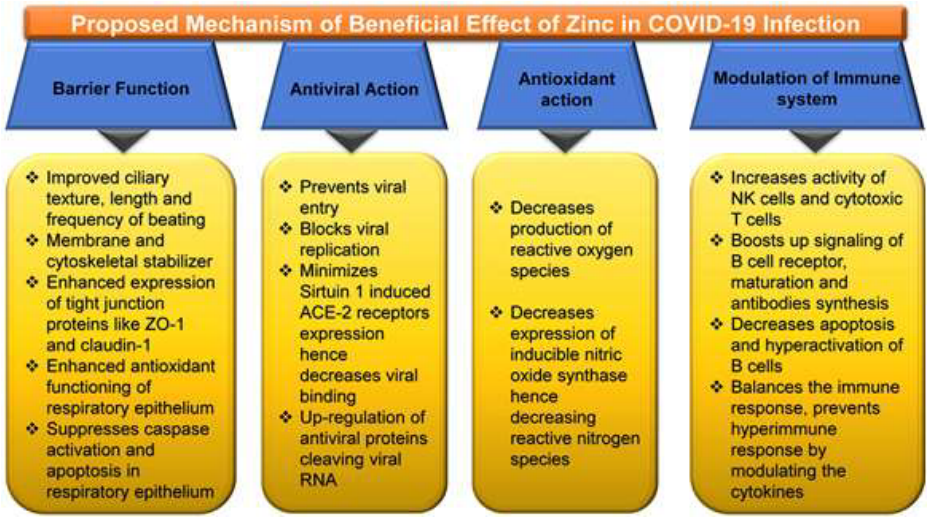

Figure 1: Zinc and its plausible effectiveness in COVID-19.

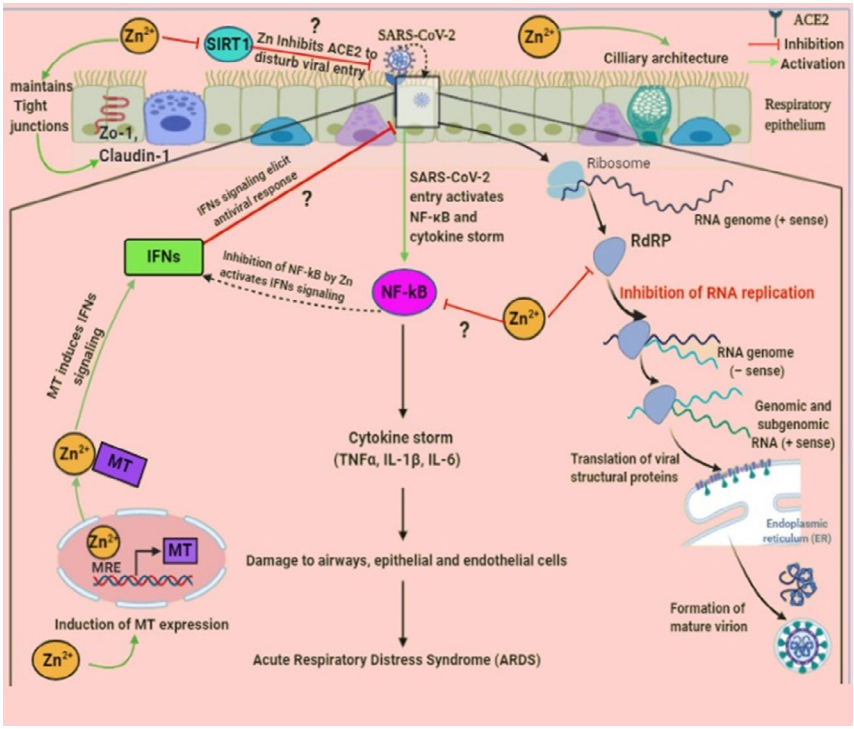

Figure 2: The underlying molecular mechanism of defense against SARS-CoV-2 infection by Zn in the respiratory epithelium.

generates a cytokine storm by activating NF-κB, which is responsible for the progression of ARDS. Zn exerts an anti-inflammatory effect by suppressing NF-κB signaling, which may lead to the downregulation of pro-inflammatory cytokines and augmentation of IFN-mediated antiviral effects [19,20]. Therefore, Zn supplementation could be very useful for attenuating a cytokine storm mediated by COVID-19 infection. Studies have reported low levels of Interferons (IFNs) in COVID-19 patients. However, Zn may stimulate the production of IFNα, eventually leading to increased synthesis of antiviral proteins like latent ribonuclease and protein kinase RNA-activated, which can degrade viral RNA [20,21].

Neutrophils are the main players involved in

lung edema and endothelial and epithelial injury, which leads to ARDS progression. Increased levels of neutrophils have been observed in COVID-19 patients [22]. Administration of Zn gluconate inhibits IκB kinase β (IKK β) and NF- κB-dependent transcription of pro-inflammatory genes thereby, reducing the infiltration of neutrophils within airways [22-24]. 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 [25-27].

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