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Zinc Resilient Agri-Food: Possible Role as a Natural Immunity Booster in Children to Fight against COVID Infection

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Abstract: ***Prevention is a key strategy to fight, control and stop the spread of the novel Coronavirus. At present global policymakers are strongly focusing on preventive measures like economic lockdown and vaccinations to keep the pandemic in check. In support of these two preventive measures, the immune system boosting micronutrient too can play a vital role to control the spread of the pandemic.This review thus focuses on a key micronutrient, Zinc that strengthens the immune system of the human body. This micronutrient can be made available to a large percentage of the population in a short period without much logistic and infrastructure support – with measures like encouraging farmers to produce zinc resilient food like certain vegetables and fruits and by controlling its price and distribution. Since the upcoming third pandemic wave is feared to target the children, this review, therefore, discusses the Possible role of Zinc as a natural immunity booster in children to fight against the Covid infection.***

Keywords: COVID-19, SARS-CoV2, Post COVID recovery, Covid preventive measures, Zinc deficiency, Impaired immune system, Resilient Agri-food

1. Introduction

Our Health and the diet we take are closely interlinked to each other; one such example is the functionality of our immune system. Good nutrition assists the immune system to fight against various pathogens and prevent chronic inflammation following an infection. Healthy and a balanced diet is key to a strong immune system and therefore leads to a healthy body and mind. [0]

Coronavirus or covid 19 was first reported in Wuhan city, Hubei Province, China in December 2019, as a form of pneumonia of unidentified origin [[2]]. International Committee on taxonomy of virus, identified novel coronavirus SARS-CoV-2, as the causative agent of Covid 19 [[3]]. Soon, Covid 19 outbreak spreads worldwide and hence World Health Organization declared it a pandemic on 12 March 2020 [[4]]. By now it has been almost more than a year, yet the suffering continues even after the first wave, we were hit again much harder with the second Covid wavein March 2012 [[5]].

Over this period of time, we have witnessed medical calamities at their peak, with severe health complications in covid patients both during the covid positive phase as well as after becoming covid negative [[6], [7]].The latter is called Post covid symptoms, which is associated with many health issues, whose possible reason is weakened immunity. It has been observed that the most affected individuals are the ones with an immunocompromised state due to some already existing chronic disease within the patient or age-related weak immune response in the case of old aged people [[6],[7],[8],[9]].Both in the first and second covid wave, it is observed that children who tested positive with Covid infection are either asymptomatic or shows mild symptoms, while severity is rare [[10]].

During the second wave of Covid-19, the virus got mutated and displayed more virulence. In the first covid wave, children were mostly asymptomatic but the second wave showed an increase in the number of covid positive cases in children, both showing asymptomatic as well as mild effect. However, a fearof children getting severely affected by the third Covid wave emerged due to the new delta variant, which affected children in the U.K and Singapore [[11]].It is predicted by experts that third wave is going to hit India soon, majorly affecting children, while it is equally believed and argumented thatthe third wave will affect children equally as an adult but without much severity. The Indian Academy of Pediatrics (IAP), released a statement on May 22, stating just like adults, children are equally susceptible to Covid but chances of severity are negligible and that it is highly unlikely that children will exclusively or predominantly get affected by the third wave but still emphasized on increasing inpatient beds and intensive care bed for children and advised parents not to panic but to remain prepared [[12]].

The future is unseen, unknown and unpredictable as we do not know, to what extent the Coronavirus will mutate in the near future and also, to how many folds of increased virulence it will exhibit [[13]] However, it is a wise decision to remain prepared for any adverse situation, just in case.Social distancing and increasing medical infrastructure will surely be a vital step towards this preparedness but it is equally important to boost and enhance our immunity either with supplements or naturally with a healthy balanced diet. Hence it is advisable to maintain and enhance the immunity within children, naturally with an easy and effective diet plan with nutritious healthy food containing lots of vitamins, antioxidants and Zinc-rich food sources. During this pandemic, keen inclination to dietary supplements to assist and enhance the immune system has increased. Although no specific diet, food or supplement can prevent Covid infection, but specific nutrients can help support and boost the immune system and hence the body will be able to fight the virus efficiently [[14],[15],[31]]. Vitamin C, Vitamin D, Selenium and Zinc (trace element), Glutamine (nonessential amino acid) plays a vital role in supporting and enhancing the immune system [[14]].

In this review, the role of Zinc as an immune-boosting agent has been studied, especially in children with post covid symptom management and recovery.

2. Zinc- an essential trace element

Zinc is one of the vital/ essential trace elements in our body with catalytic, structural and regulatory functions. It has a wide array of roles in immune response, homeostasis, oxidative stress, apoptosis and ageing. Metallothioneins, the zinc-binding proteins has a protective role in combating toxic metal exposure, infections and stress. The protein also plays a key role in Zn related cell homeostasis, required against both oxidative stress and immune responses, especially in natural killer cell activity. Zinc also helps in preventing ageing-related problems. Zinc is not stored in the body as excess intakeof zinc led to its reduced absorption and increased excretion [[16],[17]].

The vital importance of Zinc in children can be understood by the below points:

Growth and regulatory function: Zinc as micronutrients that support cellular growth-differentiation and metabolism among children, especially under 12 years of age. It supports linear growth in children who are below 5 years of age. Zinc is vital forthe synthesis of certain enzymes required for the normal production of RNA and DNA. Zinc has a binding affinity to proteins present in the brain, thereby helps in the structure and function of the brain. Its deficiency is associated with growth retardation and hypogonadism in children and results in decreased growth rate, decreased differentiation, decreased metabolism and structural malformation within the brain. [[17],[18],[19],[22]].

Immune and inflammatory response: Zincinfluences multiple aspects of the immune system. The normal development and functioning of cell-mediated innate immunity, natural killer cells and neutrophils requires Zinc. Macrophages also require zinc for their functioning. Zinc deficiency can highly affect the process of intracellular killing, phagocytosis and production of cytokines. It can also adversely affect T cells and B cells growth and function. Since zinc can function as an anti-oxidant, stabilizing membrane, it suggests its role in preventing free radical-induced injury due to inflammatory processes. It was observed that zinc supplement course during shigellosis in children, increase the proliferation of lymphocyte response and Ipa-specific immunoglobulin G response. Zinc helps in enhancing the defence system of the body, in order to fight various infections [[20],[21]].

Structural and catalytic function: Zinc is essential for the activity of many enzymes. Enzymes have various zinc-binding sites which has a high affinity for Zinc. Therefore, Zinc plays a critical role in triggering chemical reactions within the body. Zinc is a vital cofactor for more than 10% of the protein encoded by the genome of human.These zinc-dependent proteins play various indispensable roles in the human body like DNA repair, transcriptional regulation, metabolic process, ECM regulationantioxidant defence and apoptosis. It is therefore required for the normal functioning of enzymes that are required for DNA and RNA synthesis. Thereby it helps the body creating new DNA, RNA and proteins and also in folic acid utilization. It also helps in regulating some signal transduction. [[22], [23], [41]].

Cognitive development: Zinc is associated with the structural and functional development of the brain; hence its deficiency is associated with the structural malformation of the brain. These further effects normal activity, short term memory and also spatial learning. Its deficiency results in abnormal cerebellar function and also impact behavioural and emotional response. Zinc is also required for normal motor and cognitive development in children. Its deficiency therefore led to an alteration in attention, locomotory skills and activity, impaired neuropsychologic functioning, low confidence and increased dependency. [[22]]

Wound healing: Zinc plays a key role in human physiology. It acts as a cofactor for many metalloenzymes which are vital for membrane repair, growth, cell differentiation, cell proliferation and normal functioning of immune functioning. Zinc helps in modulating innate and adaptive immune responses in the case of myeloid-derived cells and also in inflammatory signalling, resulting in lymphocyte differentiation and antibody production.It has a vital role in wound repair, by involving platelet cells and homeostasis, defence via inflammation, re-epithelization and ECM re-modelling using matrix metalloproteinases and tripartite motif family protein. It assists to promote healthy skin and mucous membranes, thereby enhances wound healing. [[23]]

Healthy ocular tissue: Zinc is involved in many physiological metabolic processes. It is present in high concentration within the ocular tissue, especially in the choroid and retina. It is required for the normal development and function of ocular tissues. Zinc deficiency is associated with impaired ocular development, cataracts, age-specific macular degeneration and even diabetic retinopathy [[24]].

3. Components of Immune system

The immune system of the body is a defence mechanism against any invasions by foreign elements or antigens, therefore is critical for survival. The immune system has a complex mechanism of identifying and distinguishing between the self and non-self molecules. It specifically targets the foreign body or external invaders like pathogenic bacteria, viruses, fungi etc. and destroys them. [[14]]

Cells of the immune system can be divided broadly into innate and adaptive immune response. The innate response is the very first response to an invading germ or pathogen. Phagocytes (macrophages, monocytes), neutrophils, eosinophils, mast cells, dendritic cells etc. are associated with innate immunity. The response though not specific, but

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is very rapid. Whereas adaptive immune response has Lymphocytes as the responding cell, having a highly specific response to a particular microbe, as it has the ability to not only recognize a pathogen but also remember it if exposed to it again. T cell and B cells both are involved in the adaptive immune response. T cells recognize antigens and further coordinates immune response. Cytotoxic T cells (CD8 receptor) directly kill infected damaged cells or tumour cells. T helper cells (CD4 receptor) has two subtypes Th1 and Th2, based on the cytokines they produce. Th1 produces Interferon-gamma (IFN- γ) and Interleukin 2 (IL-2) plays a key role in the antiviral and cellular immune response. However, Th2produces IL-4, IL-5 and IL-3 and is vital for humoral (antibody), anti-parasitic and allergic responses. Some other types of Th subtypes are also there which fight against bacteria and fungi etc. Regulatory T cells maintain immune tolerance against non-harmful non-self particles like food, pollen etc. B cells produce antibody or immunoglobulins and specifically respond to a particular antigen. They either differentiate into short-lived plasma cells (produces Igs) or long-lived plasma cells IgM, IgD, IgG, IgA, IgE). Each class of Ig has a specific role and can bind to an antigen, identifying it for destruction by other cells of the immune system. IgG is predominant, stays for a longer time while IgA has a protective role against bacteria and viruses. B cells become active by the cytokines (IL-4, IL-6, IFN- γ) secreted by T helper cells. T and B cells have the ability to turn into memory cells and persist permanently and are able to identify the pathogen if encounter a second time and elicit an immune response specific to the pathogen [[14]]

4. Effect of Zinc on Immune System during viral infections, including Covid-19

Zinc has multiple influences on the immune system, as it regulates proliferation, differentiation and maturation of leukocytes and lymphocytes. It is essential for the normal development and function of both cell-mediated innate immunity as well as adaptive immunity, as it regulates intracellular signalling pathways in both the immune response. Zinc is also involved in zinc homeostasis and has anti-inflammatory and anti-oxidant property. Zinc has a key signalling role in the modulation of inflammatory responses. The deficiency of zinc alters immune response and results in the increased susceptibility to both inflammatory and infectious diseases. Therefore, all kinds of immune cells show a decreased/ impairedfunction in case of zinc deficiency like monocytes functions are impaired, cytotoxicity of the natural killer cell was reduced, phagocytosis in neutrophil granulocytes is reduced. It also impaired the normal function of T cells and results in the apoptosis of B cell. The entire immune system undergoes impairment due to deficiency of zinc, while it can be reversed with adequate zinc supplement and then switching to a zinc-rich source of food. [[14], [28], [31]]

Zinc not only helps in the immune response against infections but also assist in bringing back the immune system to normal after an infection. Theinflammatory response is mandatory and vital while fighting an infection, however overproduction of pro-inflammatory cytokines early in infection is associated with some of the worst symptoms in many infections, including Covid 19. Zinc has a significant role in the regulation of inflammation after infection. Zinc might block the replication of rhinoviruses responsible for respiratory infections, including the common cold in humans. Higher levels of zinc in cells assist block the reproduction of rhinoviruses and stimulate interferon α production, this signalling molecule forces nearby cells to initiate their anti-viral defence mechanism. One study suggested that zinc blocks the enzyme responsible for replicating the coronavirus that led to the SARS outbreak of 2002.[[14], [20], [21], [25], [26], [27], [28], [29], [30], [31]]

In context to the current Covid-19 pandemic due to the SARS-CoV-2 virus, there is a requirement to the search for possible protective and therapeutic antiviralstrategies. Zinc can modulate both antiviral and antibacterial immune response, which can be beneficial in fighting covid infection. The antiviral activity of zinc is because of the fact that it inhibits SARS-CoV RNA polymerase and decreases angiotensin-convertingenzyme-2 (ACE2) receptors for SARS-CoV-2, while it up-regulates interferon αproduction. Also, the anti-inflammatory activity of zinc limits the high production of cytokine in Covid-19, by inhibiting NF-kB signallingand modulation of the regulatory function of T cell.Zinc also minimises the risk of secondary infection due to bacteria and fungi by enhancing the mucociliary clearance along with barrier function of the epithelium of respiratory tract and hence posses a direct antibacterial effect on S. pneumoniae. The high-risk groups like old age, immunocompromised individuals, obesity, atherosclerosis, diabetes etc shows zinc deficiency. Also, children with zinc deficiency show a reduced immune response against any infection and hence are at a risk in context to Covid infection. However adequate zinc supplement increases immune reactivity and lowers the risk of upper and lower respiratory infection. Hence, zinc may have a protective effect as preventive and adjuvant therapy for Covid-19 management [[31]]

5. Zinc supplements versus Zinc from Resilient agri-food system

Zinc deficiency particularly in children has taken a shape of a public health threat, especially in many zinc-deficient regions globally. One way of dealing with this deficiency is via the use of zinc supplements, while the other is the consumption of naturally occurring nutritious biofortified crops that plays a key role in providing much micronutrient-rich food, including Zinc, vitamin A, Iron etc. [[37]]

Zinc deficiency is a common micronutrient deficiency problem at the global level, particularly in cereal grain crops which is a dominant food source in the majority of developing countries, including India. As nearly 50%-60% of cultivated soil contains a lower amount of zinc, plant growing in this zinc-deficient soils will have not only reducing productivity but also contain low zinc concentration in edible parts of the crop, thereby resulting in zinc deficiency within the mass.[[33],[34]] Agri-food or Biofortified food essentially address the nutrient deficiency problem. It helps in building the micronutrient resiliency within the nutrition deprived mass and surely is a way to healthy living even during current as well as future pandemic crisis if any. Biofortified crops if well integrated within the local food production system, can affordably and efficiently deliver key micronutrients along with basic calories, strengthening this resilience. An effort is the need of the hour to increase and enhance the development and deployment of the present 350 variety (11 key staples) of biofortified cropsincluding the development of new varieties. Over the last ten years, CGIAR's HarvestPlus along with CIP and other partners has ensured almost 15 million households to grow a different variety of biofortified crops like sweet potatoes, oranges etc across Asia, Africa and Latin America[[32],[38],[39],[40]].

Foodsources rich in zinc

Zinc containing biofortified food can play an essential role in combating zinc deficiency within the population, especially in children. Various methods including the use of biofertilizers etc. in crop field nutrient-deprived soil ensure a high yield of fortified crops. Resilient agri-food or Biofortified food can be certain cash crops, including wheat and rice, legumes, pulses, sweet potatoes, potatoes, oranges etc.

A Few of the high source of zinc-containing foods are: [[35], [36], [37]].

- **Eggs**

Whole eggs contain a great amount of zinc that can help one meet the daily requirement. Eggs also give a host of other healthful nutrients like vitamin B, healthy fats, proteins, selenium, and many more.

- **Chicken and meat**

Both red meat and chicken are a great source of zinc. They are also filled with vitamin B12 and protein that can keep the nervous system healthy and assist in cell regeneration. However, animal-based food products are also rich in cholesterol and fat.

- **Dairy Products**

Dairy products such as milk, cheese, paneer are excellent sources of several nutrients and minerals including zinc. Most of the zinc content present in milk and cheese can be easily absorbed by the body.

- **Legumes**

Chickpeas, beans, and lentils are filled with zinc. Legumes are low in calories and packed with healthy nutrients such as protein, vitamins, iron, copper, magnesium, manganese, and phosphorus.

- **Pumpkin Seeds and Cashews**

The super versatile pumpkin seeds and cashews are amongst the most zinc-rich nut and seeds. Apart from zinc, they also have iron, magnesium, copper, vitamin K, vitamin A and folate.

6. Conclusion

Zinc plays a key role in the functioning of the human immune system, especially boosting immunity in children. Zincmodulatesthe antiviral and antibacterial immune response, which is beneficial in fighting Covid infection. It minimizes the risk of secondary infections by mucociliary clearance and also brings down inflammatory reactions. If included in a regular diet asresilient agri-food or biofortified food, the zinc concentration in the body will be maintained naturally and more efficiently at a normal level, ensuring immunity against various infections, including lowering down the risk of covid-19 infection and associated secondary infections, particularly in children.

Pandemic has pushed every country and its government to invest billions of dollars in medical infrastructure, bio-research, vaccination and promotion to create preventive awareness among people. However, there can be an additional strategy that can boost our economy, employment and possibly can impact the coronavirus spread and death percentages. A small budget can be allotted to subsidized zinc-rich or zincresilient agri-food or biofortified food in the country and support resilient agri-food producing farmers including running communication campaigns for people to adopt zinc-rich Agri-products in their daily diet. Such a preventive strategy can prove a good bet, with no risk, rather will not only boost the general health of the mass but also increase and enhance the employment and economy of our country.

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