

Zinc: an essential trace element for human health and beyond

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Author contributions

RP, TS and AB conducted the investigation, collected and curated the data, and wrote the original draft of the manuscript. DN contributed to the development of the initial concept of the study and was responsible for the design and implementation of the methodology. Additionally, he reviewed and edited the manuscript, created visualizations and supervised the overall progress of the study. All authors have read and approved the final manuscript.

Competing interests

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Abbreviations

HPA, hypothalamic-pituitary-adrenal; NPase, nucleoside phosphorylase.

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Abstract

Zinc is an essential element that plays a crucial role in the chemistry and biochemistry of living organisms. It serves as a cofactor for numerous enzymes and transcription factors, contributing to DNA synthesis, protein synthesis and cellular metabolism. Additionally, zinc acts as a structural component of proteins and participates in cellular signaling pathways. The chemistry of zinc is determined by its electronic configuration, and it readily forms coordination complexes with various ligands. This review explores the diverse functions of zinc in the body, including its involvement in enzyme activity, immunity, neutrophil function, modulation of allergies, its relationship with COVID-19, antioxidant and anti-inflammatory properties, mental health, pregnancy and wound healing. Zinc has a history of use in traditional medicine systems, and its benefits and applications should be evaluated in the context of current scientific research and medical guidelines. Understanding the roles of zinc in these processes highlights its importance as an essential nutrient for overall health and provides insights into potential therapeutic applications. However, further advancement in understanding the biological function of zinc requires addressing certain limitations. These include overcoming methodological challenges, investigating tissue and cell-type specificity, understanding zinc interactions and redundancy, and employing integrated approaches, advanced imaging techniques, comparative studies, and systems biology approaches to gain a deeper understanding of zinc's implications in health and disease.

Keywords: zinc; biochemistry; deficiency; immune system; enzymes

Background

There are nine trace minerals that are considered nutritionally essential for humans: zinc, iron, selenium, copper, iodide, molybdenum, manganese, cobalt and chromium (Table 1) [1]. Each of these components contributes less than 0.01% to the total body weight. While it is established that the nutritional necessity of certain microminerals (e.g., boron) can be confirmed, and in one case (fluoride), it is partly a matter of semantics. The functional effects of these components as nutrients encompass a wide range, influencing the likelihood and severity of nutrient deficiency or imbalances that have therapeutic and/or public health significance [2].

Zinc and its chemistry and biochemistry

Zinc is a chemical element with the symbol Zn and atomic number 30. It is a transition metal, meaning it has properties of both metals and nonmetals. Zinc is a relatively abundant element in the Earth's crust, and it is essential for the biochemistry of all living organisms.

In terms of biochemistry, zinc acts as a cofactor for numerous enzymes and transcription factors. It plays a crucial role in facilitating the catalytic activity of enzymes involved in DNA synthesis and repair, protein synthesis, and cellular metabolism. Additionally, zinc serves as a structural component of proteins, contributing to the stabilization of their three-dimensional structure. Apart from its involvement in enzymatic and structural functions, zinc participates in cellular signaling pathways. Studies have revealed its ability to modulate the

activity of various signaling molecules, such as kinases and phosphatases. Furthermore, zinc can influence gene expression by binding to specific transcription factors [3].

Zinc's chemistry is largely determined by its electronic configuration, which consists of two electrons in the outermost shell. As a result, zinc exhibits relatively high reactivity, particularly in the presence of acids or oxidizing agents. In its common form, zinc exists in the +2 oxidation state, indicating a loss of two electrons. This particular state renders zinc highly soluble in water and enables it to readily form coordination complexes with various ligands. Additionally, zinc ions have the capability to form insoluble salts when combined with anions like sulfate and carbonate.

In biological systems, zinc typically forms complexes with proteins and other biomolecules, rather than existing in a free ion state. The binding sites for zinc in proteins can be categorized into various types based on the coordination geometry, as well as the number and identity of the ligands involved.

Overall, the chemistry of zinc and its biochemistry are intricately linked, as zinc fulfills crucial functions in a diverse range of cellular processes. Its role as a cofactor, structural component, and signaling molecule makes it an indispensable nutrient for all living organisms (Figure 1) [4].

Zinc and traditional medicine

Traditional medicine refers to the practices and knowledge that have been developed over generations within various cultures and are often based on indigenous beliefs and experiences. Zinc has found its place

Table 1 Organ and processes that play a significant physiological function in sustaining trace mineral homeostasis in the whole body

	Mineral	Iron	Copper	Manganese	Zinc	Iodide	Selenium	Chromium	Molybdenum
Gastrointestinal tract	Absorption	Single major site	Substantial	Major	Major	–	–	–	–
	Endogenous excretion	–	Major (liver)	Major (liver)	Major	–	–	–	–
	Kidneys	–	–	–	Minor	Major	Major	Major	Major

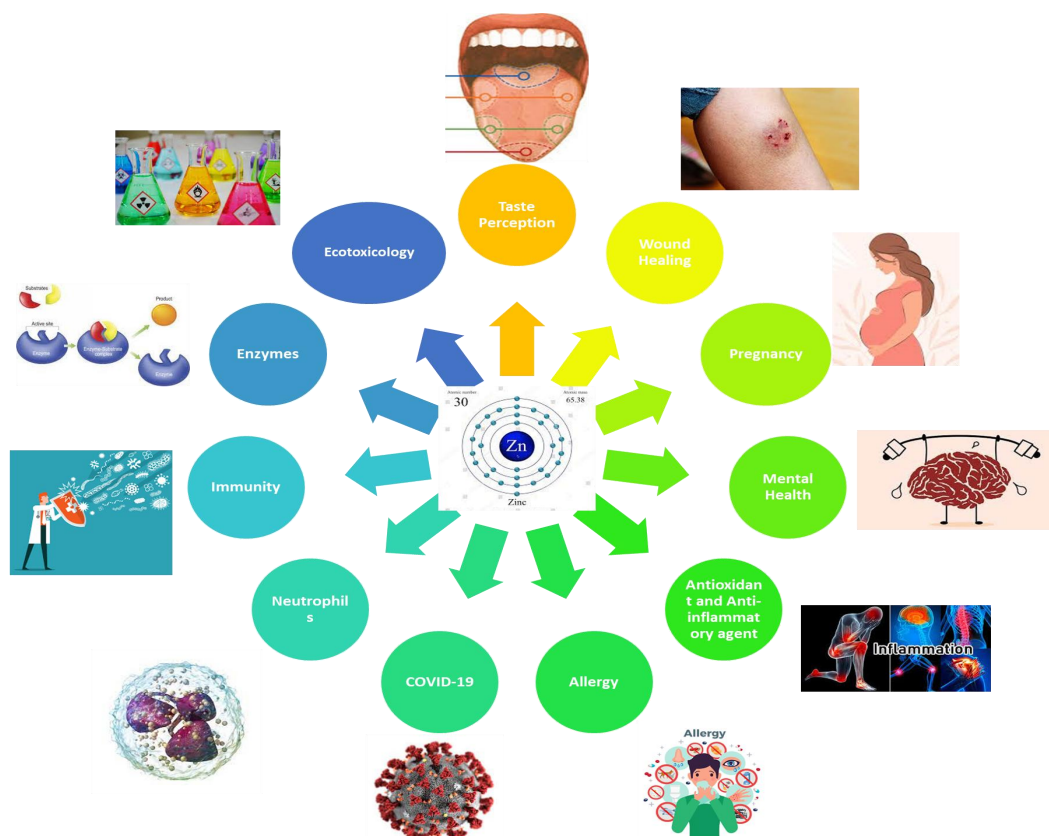


Figure 1 Zinc and its roles in body functions

in traditional medicine systems worldwide, including traditional Chinese medicine, Ayurveda and Unani medicine [5]. In traditional Chinese medicine, zinc is attributed with cooling and astringent properties. It is frequently utilized to eliminate heat and toxins from the body, and it is commonly included in herbal formulas for addressing ailments like diarrhea, skin disorders and fevers [6].

Ayurveda, an ancient holistic healing system from India, recognizes the significance of zinc in maintaining health. According to Ayurvedic principles, zinc helps balance the Pitta dosha, one of the three biological energies, and plays a role in the metabolism of other minerals within the body. It is utilized to support healthy digestion, boost the immune system, and treat conditions such as acne, hair loss, and wound healing [7, 8].

Unani medicine, which originated in ancient Greece and was later adopted and developed in the Arab world, also utilizes zinc in its treatments. It is believed to have a strengthening effect on the body and is employed to address various ailments, including skin conditions, respiratory disorders, and sexual health issues [7]. Indeed, it is crucial to acknowledge that traditional medicine systems may have different perspectives and approaches compared to modern scientific understanding. While traditional medicine recognizes the potential benefits of zinc, it is important to remember that the traditional uses of zinc should not be seen as substitutes for evidence-based medicine or medical advice. When considering any form of treatment, whether traditional or modern, it is always advisable to consult a qualified healthcare professional to ensure the most appropriate and safe approach for individual circumstances.

Zinc and enzymes

Zinc plays a crucial role in the functioning and maintenance of over 200 enzymes [9]. It was hypothesized that the cellular levels of zinc could regulate physiological processes by influencing the development and/or modulation of zinc-dependent enzymes. However, before 1966, there was limited evidence to support this idea in laboratory animals. In 1967, Prasad et al. conducted a study, first time demonstrating that zinc-deficient pigs and rats exhibited reduced tissue function in areas containing zinc and zinc-dependent enzymes compared to pair-fed controls. Additionally, in 1974, Prasad and Oberleas reported that zinc deficiency adversely affected the function of deoxythymidine kinase, an enzyme involved in the rapid regeneration of collagen connective tissue in rats [10]. As zinc-dependent enzymes play crucial roles in cell division and DNA synthesis, their impairment due to zinc deficiency can contribute to growth retardation in both animals and humans. Zinc also stimulates protein metabolic enzymes such as carbonic anhydrase, which is important for immune response and the transportation of carbon dioxide.

Zinc-dependent enzymes are involved in various aspects of cell division. One such enzyme is topoisomerase, which plays a critical role in DNA replication and DNA repair. Topoisomerases help relieve the strain and torsion that occur during DNA unwinding and rewinding processes. Zinc ions assist in stabilizing the structure of topoisomerases, enabling them to carry out their vital functions effectively [11]. In 1975, Giblett et al. documented a case of a 5-year-old girl with significantly deficient immunity to mild B-cells, T-cells and phosphorylase nucleoside deficiency. The nucleoside phosphorylase (NPase) enzyme catalyzes the reaction that converts inosine to hypoxanthine and guanosine, and deoxyguanosine to xanthine. It is calculated that the accumulation of deoxyguanosine is harmful to T cells. In a test model of human zinc insufficiency, it was observed that NPase activity in lymphocytes was diminished in zinc-inadequate subjects and that reduced NPase activity may partly explain abnormal T cell function in zinc insufficiency [12].

Zinc and immunity

Zinc influences several facets of the immune system that are essential for immune function. It is necessary for the normal production and

functioning of neutrophils, natural killer cells and innate immune-mediating cells [13]. Additionally, it affects macrophages, and a deficiency in zinc has negative effects on their development and activity. The deficiency also impacts the development and function of B and T cells. It interferes with cellular activities such as intracellular killing, phagocytosis, and cytokine production. Zinc is required for DNA synthesis, RNA transcription, cell differentiation and cell signaling. Furthermore, zinc deficiency increases the susceptibility to apoptosis (programmed cell death). Zinc deficiency has a detrimental effect on the production and function of cytokines, which are essential messengers in the immune response. In laboratory animals, zinc deficit has been shown to contribute to the atrophy of thymic and lymphoid tissues for several years. In young zinc-deficient mice, thymic atrophy, a decrease in the total number of splenocytes, and a weakened response to both T-cell-dependent and independent antigens were observed [14]. After only 2 weeks, animals on a zinc-deficient diet exhibited a significant impairment in their ability to elicit cytotoxic responses to tumor tests. A decrease in cytotoxic T-killer cell activity in response to allogeneic tumor cells and impaired cell-mediated response to non-H₂ allogeneic tumor cells were also observed in zinc-deficient mice. Studies conducted in the Middle East revealed that most of the zinc deficient dwarfs died by the time they were 25 years old. The cause of death appeared to be related to diseases, indicating that zinc deficiency might have adversely impaired immune functions. Thymulin, a hormone unique to the thymus, is found in serum and requires zinc for its biological function. Thymulin binds to T cells through high-affinity receptors, leading to the induction of multiple T cell markers and promoting T-cell activity, including allogeneic cytotoxicity, suppressor functions and the production of IL-2. Research conducted by Prasad et al. demonstrated decreased production of serum thymulin, reduced expression of IL-2 and IFN mRNAs, diminished generation of IL-2 and IFN, decreased natural killer cell lytic production, and impaired T-cytolytic cell activity in humans with zinc deficiency. No improvements were found in Th2 cytokines. As a result, zinc deficiency shifts the balance from Th1 to Th2 functions, negatively impacting cell-mediated immunity [15].

Zinc and neutrophils

In 1982, Briggs et al. stated that granulocytes exhibited reduced sensitivity in zinc-deficient uremic subjects and displayed decreased chemokinetic and chemotactic activities compared to zinc-supplemented individuals. In a trial model of human zinc inadequacy, it was observed that the movement of NPase in lymphocytes was diminished in zinc-insufficient subjects. This diminished NPase activity may partially account for abnormal T cell function in zinc inadequacy. Therefore, zinc appears to play a significant role in chemotaxis [16].

Additionally, recent research has revealed the crucial role of zinc in the activation and regulation of neutrophils, a type of white blood cell that plays a critical role in the body's immune response to infection and inflammation. Zinc is essential for the proper functioning of enzymes involved in the respiratory burst, a process through which neutrophils generate reactive oxygen species to eliminate invading pathogens [17]. Furthermore, zinc regulates the expression of genes associated with neutrophil activation and cytokine production, which are vital for the recruitment of immune cells to the infection site. Studies have indicated that zinc deficiency can impair neutrophil function, resulting in an increased susceptibility to infections and inflammation. Conversely, both animal models and human studies have demonstrated that zinc supplementation can improve neutrophil function [17].

Zinc and allergy

In a particular study, the effect of zinc during allergic immune reaction on cell development, CD4⁺ regulatory T (Treg) cells and cytokine expression was investigated [18]. Peripheral blood

mononuclear cells from atopic and nonatopic samples was combined with preincubated timothy green allergens without or with (50 μ M) of zinc.

The inclusion of zinc (at a concentration of 50 μ M) along with allergens in CD3+ T cells led to a significant reduction in the proliferation of atopic subjects' peripheral blood mononuclear cells. Furthermore, the combination of zinc and allergen resulted in an improvement in Th1 cytokines, as evidenced by an increased IFN- γ /IL-10 ratio, along with an observed increase in the production of T cells. Zinc tended to downregulate hyperresponsive cells that were not necessary. There has been a major change from IL-10 to Th1 cytokine IFN- γ and enhanced T cell production. This study indicates that zinc supplementation could have beneficial effects as a treatment for allergies, without adversely affecting the immune system.

T lymphocytes play a crucial role in controlling and coordinating immune responses in allergic disorders. Among them, regulatory T cells are responsible for suppressing the activity of CD4+ effector T cells, CD8+ T cells, antigen-presenting cells, natural killer cells and even B cells. In patients with asthma and allergic rhinitis, there is a notable decrease in the production of T cells, leading to the expansion of Th2 cells [19].

Allergies are classified as Th2-driven diseases and are frequently followed by a zinc deficiency, making them a target for modulating allergic immune reactions through zinc supplementation. In addition to Th2 cells, Th1 and Th17 cells also contribute to hyperresponsiveness and allergic inflammation. Treg inhibits T-cell activation upon sensitivity to allergens but in atopic individuals this mechanism is not optimum. Patients with allergic asthma often exhibit impaired Treg-mediated suppression, which correlates with reduced serum zinc levels, as reported in multiple studies. Supplementation with zinc can help restore Treg function. Furthermore, zinc deficiency during breastfeeding has been linked to an increased risk of allergies in children.

Zinc and COVID-19

Since the onset of the COVID-19 pandemic, numerous studies have investigated the potential role of zinc in combating the virus. Zinc has been proposed to possess antiviral properties and may hinder viral replication. One study demonstrated that zinc ionophores could aid in inhibiting the replication of SARS-CoV-2. Additionally, zinc may assist in preventing cytokine storms, which are associated with severe cases of the disease. Zinc is crucial for the production and activation of T cells, which are integral to the immune response against COVID-19 [20].

Several clinical trials have been conducted to assess the effectiveness of zinc supplementation in patients with COVID-19. One randomized controlled trial indicated that high-dose zinc supplementation was linked to a reduced hospitalization duration and a decreased need for intensive care unit admission [21]. Another study demonstrated that combining zinc supplementation with hydroxychloroquine and azithromycin improved clinical outcomes in COVID-19 patients. However, further research is necessary to determine the optimal dosage and duration of zinc supplementation for COVID-19 patients. Overall, zinc seems to play a significant role in the immune response against COVID-19 and shows promise as a preventive and therapeutic agent.

Zinc as a functions of antioxidant and anti-inflammatory agent

Oxidative stress and systemic inflammation are major risk factors in various chronic illnesses, such as atherosclerosis and related arterial conditions, mutagenesis and cancer, neurodegeneration, immunological disturbances and the aging process. Zinc deficiency itself has been associated with an increased production of IL-1 β by monocytes-macrophages in experimental human models. In elderly individuals and patients with sickle cell disease who are deficient in zinc, elevated oxidative stress and higher levels of inflammatory cytokines have been observed, which can be reduced with zinc

supplementation. In cell culture experiments using HL-60, a promyelocytic leukemia cell line, it was found that zinc enhanced mRNA upregulation and the specific binding of A-20 DNA, a transactivating agent that prevents NF-KB activation. A study has indicated that zinc supplementation can reduce the levels of inflammatory cytokines by upregulating the negative feedback loop A-20, thereby preventing the activation of NF-KB. It showed that zinc in human monocytic leukemia THP-1 cells and human aortic endothelial cells decreased the production of TNF- α average, IL-1 β average, VCAM-1, and MDA+HAE and the activation of NF-KB average and increased A-20 and peroxisome proliferator-activated receptors. These findings suggest that zinc may have a protective effect in chronic diseases involving oxidative stress and systemic inflammation [22, 23].

In addition to its antioxidant and anti-inflammatory properties, recent studies have shown that zinc has been found to have a significant impact on immune responses by regulating oxidative stress and inflammation. Zinc functions as a cofactor for antioxidant enzymes like superoxide dismutase, which aids in reducing oxidative stress within cells. It also inhibits the production of reactive oxygen species and nitric oxide, both of which contribute to inflammation. Taken together, these findings highlight the crucial role of zinc in modulating oxidative stress, inflammation, and immune responses. Consequently, zinc may hold therapeutic potential for the treatment of various chronic diseases [24].

Zinc and mental health

Recent research suggests that zinc may also have a significant impact on mental health. Zinc deficiency has been associated with various mental health disorders, including depression, anxiety, attention deficit hyperactivity disorder and Alzheimer's disease. Zinc is involved in numerous processes that affect the brain and its functioning. It is necessary for the proper functioning of neurotransmitters, including serotonin, dopamine and norepinephrine, which are essential for regulating mood, cognition and behavior. Zinc is also involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is responsible for the body's response to stress. The HPA axis regulates the production of cortisol, a hormone that is involved in the body's response to stress. Zinc deficiency can lead to dysregulation of the HPA axis and an increase in cortisol levels, which can lead to anxiety and depression [25].

Studies have found that zinc supplementation can have beneficial effects on mental health. In a study published in the Journal of Affective Disorders, Swardfager et al. (2013) found that zinc supplementation improved mood and reduced symptoms of depression in patients with major depressive disorder [26]. Another study found that zinc supplementation improved cognitive function and reduced symptoms of depression in patients with Alzheimer's disease.

In contrast, zinc deficiency has been associated with various mental health disorders. In a study published in the Journal of Affective Disorders, researchers found that zinc levels were significantly lower in patients with major depressive disorder compared to healthy controls. In another study published in the Journal of Child Psychology and Psychiatry, researchers found that children with attention deficit hyperactivity disorder had lower levels of zinc in their blood than healthy controls [27].

The evidence linking zinc deficiency to mental health disorders emphasizes the significance of sufficient zinc intake for optimal mental well-being. However, it is essential to be aware that excessive zinc intake can be harmful and potentially toxic. Therefore, maintaining a balanced and healthy diet that provides adequate zinc intake is crucial. It is recommended to consult with a healthcare professional or a registered dietitian to determine the appropriate zinc intake and ensure a well-rounded nutritional approach to support mental health.

Zinc and pregnancy

Pregnant women face an increased risk of zinc deficiency due to the greater demand for this nutrient by the developing fetus. Extensive research has shown that zinc deficiency during pregnancy is associated with various adverse outcomes, including preterm birth, low birth weight and congenital abnormalities. Adequate zinc intake during pregnancy is crucial for the prevention of these adverse outcomes. Studies have reported that zinc supplementation during pregnancy can lead to a reduced risk of preterm birth, low birth weight, and congenital abnormalities [28, 29]. This is because zinc plays a vital role in regulating DNA synthesis, cell proliferation, and differentiation, all of which are critical for fetal growth and development. Therefore, it is important for pregnant women to ensure they have adequate zinc intake through a well-balanced and nutrient-rich diet or, if necessary, through zinc supplementation under the guidance of a healthcare professional. As with any supplement, it is important to follow the recommended dosage and avoid excessive zinc intake, as excessive levels can be harmful to both the mother and the developing fetus [30].

Zinc and wound healing

Zinc plays a crucial role in all stages of the wound healing process, including inflammation, proliferation, and remodeling. It affects the immune system, protein synthesis and collagen formation, all of which are essential for wound healing. Zinc deficiency can impair the healing process, while zinc supplementation has been proposed to accelerate wound healing. Numerous studies have explored the impact of zinc on wound healing, with promising findings. For instance, a study on burn patients found that zinc supplementation led to faster wound healing, reduced hospitalization duration, and improved overall outcomes of the patients [31]. Another study focused on diabetic foot ulcers and revealed that zinc supplementation significantly shortened the healing time and enhanced the patients' quality of life [32]. Zinc possesses antimicrobial properties, has been shown to inhibit the growth of various microorganisms that could cause wound infections. Due to its antimicrobial effects and wound healing promotion, zinc oxide is commonly used in wound dressings.

Zinc and taste perception

One important role of zinc is in the proper functioning of taste buds. Zinc is required for the maturation and differentiation of taste receptor cells, and it contributes to the maintenance of taste bud structure and function [33]. Inadequate zinc levels can result in taste disorders, including a reduced ability to perceive bitter, sweet, sour and salty tastes. This can lead to a loss of appetite, potentially resulting in malnutrition and other health problems.

Indeed, studies have demonstrated that zinc supplementation can be beneficial in improving taste perception, particularly in individuals with zinc deficiency. For example, in a study involving elderly individuals with zinc deficiency, zinc supplementation was found to enhance taste acuity, highlighting the role of zinc in maintaining proper taste perception [34]. Moreover, zinc has shown potential in enhancing the effectiveness of chemotherapy drugs that may cause taste alterations as a side effect. By improving taste perception, zinc supplementation can contribute to enhancing the quality of life for cancer patients undergoing chemotherapy [35]. These findings suggest that zinc supplementation can have positive effects on taste perception and may be beneficial in specific clinical contexts.

Zinc and ecotoxicology

Zinc is naturally found throughout the world in various forms, such as rocks, dirt, water and air. Over the course of evolution, all living organisms have relied on the presence of zinc in their ecosystem to carry out vital metabolic functions. As a result, zinc is considered an essential element within all ecosystems, playing a crucial role in the functioning of all living organisms. The living species are sensitive to their ecosystem's normal abundance of zinc. In fact, they established

methods for preserving optimal living conditions as this degree of focus differs from the normal norm. However, any significant fluctuations in zinc production can disrupt these conditions, consequently affecting the overall balance of the environment.

Fortunately, amounts of zinc in European environments, resulting either through human actions (such as ambient degradation of rolled zinc and galvanized steel, wear and tear of car tyres, fertilizers and animal feed, etc.) or from natural pollution (mainly from volcanic activity on Earth), stay beyond the limits of optimum life. A clear example of this is the existing zinc amounts in the Rhine (extreme values between 3 and 25 µg/L) that are below the ideal zinc amount.

However, it is important to acknowledge that zinc pollution can occur in specific industrial and agricultural settings, which raises concerns regarding ecotoxicology. Excessive amounts of zinc in aquatic environments, for instance, can prove toxic to fish and other aquatic organisms, disrupting the dynamics of the food chain within the ecosystem. Similarly, zinc pollution in soils can result in reduced crop yields and impact the composition of soil microbial communities. Moreover, human exposure to high levels of zinc can lead to health issues such as nausea, vomiting, and diarrhea, and can have long-term effects on the liver and kidneys. Therefore, it is crucial to actively monitor and regulate zinc pollution to ensure a healthy environmental balance and safeguard the well-being of both humans and ecosystems [36].

Zinc enriched food source

Zinc is an essential mineral that plays a crucial role in maintaining overall health and well-being. While zinc can be obtained through supplements, it is always recommended to obtain nutrients from natural food sources whenever possible. Fortunately, there are several food sources that are naturally enriched with zinc, making it easier to incorporate this important mineral into your diet.

One of the most well-known sources of zinc is meat, particularly red meat and poultry. Beef, lamb and pork are excellent sources of zinc, as they contain high levels of this mineral [37]. Similarly, chicken and turkey also provide a significant amount of zinc. When consuming meat, it is important to choose lean cuts and opt for healthier cooking methods, such as grilling or baking, to minimize the intake of unhealthy fats. Seafood, especially shellfish, is another category of food known for its zinc content. Oysters, in particular, are considered a zinc powerhouse, containing one of the highest concentrations of this mineral among all food sources. Other shellfish like crab and shrimp also provide a good amount of zinc. Additionally, fish such as salmon and sardines contribute to zinc intake, although in smaller quantities compared to shellfish [38].

Plant-based sources of zinc are abundant and include legumes, nuts, and seeds. Chickpeas, lentils, kidney beans, and black beans are excellent choices for vegetarians and vegans seeking to enhance their zinc intake. Nuts such as almonds, cashews, and peanuts, as well as seeds like pumpkin seeds and sesame seeds, also offer notable amounts of zinc [39]. Incorporating these foods into your daily diet can be advantageous in meeting your zinc requirements. Certain dairy products, such as milk, cheese, and yogurt, provide moderate levels of zinc. Additionally, fortified cereals and whole grains can serve as good sources of zinc. Opting for whole grain bread, brown rice and oatmeal can contribute to your daily zinc intake [40].

It is worth noting that the bioavailability of zinc can vary depending on the source. Animal-based sources, such as meat and seafood, contain zinc that is more easily absorbed by the body compared to plant-based sources. However, consuming a diverse range of foods and combining different sources of zinc can help ensure adequate intake. Incorporating zinc-enriched foods into your diet is essential for maintaining optimal health. However, it is important to remember that individual zinc requirements may vary, and it is always advisable to consult with a healthcare professional or registered dietitian for personalized advice.

Limitations of current studies about the biological function of zinc

The study of the biological function of zinc has made significant progress in recent years. However, like any field of scientific research, there are limitations to our current understanding. Recognizing these limitations is crucial for further advancements in the field. Here, we discussed some of the limitations of current studies on the biological function of zinc and provide suggestions for future development directions.

Methodological challenges

One of the limitations in studying zinc's biological function is the complexity of zinc biology and the challenges associated with accurately measuring zinc levels and dynamics within cells and tissues. Current techniques for quantifying zinc often rely on indirect measurements, which may introduce potential errors and limitations in data interpretation. Developing more precise and sensitive methods for measuring zinc levels, localization, and dynamics will enhance our understanding of its biological functions.

Tissue and cell-type specificity

Zinc's biological function can vary across different tissues and cell types. Many studies have focused on a limited range of tissues or cell types, which may not fully represent the diversity of zinc's functions throughout the body. Expanding research efforts to include a broader range of tissues, cell types, and model organisms will provide a more comprehensive understanding of zinc's biological roles.

Zinc interactions and redundancy

Zinc interacts with various other minerals, ions, and molecules in complex ways. These interactions can influence zinc's biological functions and complicate the interpretation of experimental results. Investigating the interplay between zinc and other essential elements and understanding their synergistic or antagonistic effects will contribute to a more nuanced understanding of zinc's biological functions.

Functional redundancy

Zinc is involved in multiple cellular processes, and many biological functions are regulated by a network of molecules rather than a single factor. Disentangling the specific roles of zinc in these complex networks is a challenge. Identifying specific zinc-dependent pathways and dissecting their contributions to cellular processes will provide insights into zinc's precise functions and its interplay with other regulatory mechanisms.

To overcome these limitations and further advance the field, several suggestions can be considered

Integrated approaches

Employing integrated approaches, such as combining molecular biology, genetics, proteomics, and metabolomics, will enable a comprehensive analysis of zinc's biological functions. By integrating multiple levels of information, we can gain a more holistic understanding of zinc's roles in cellular processes.

Advanced imaging techniques

Developing advanced imaging techniques that allow for real-time visualization of zinc dynamics within living cells and tissues will greatly enhance our understanding of zinc's spatial and temporal distribution and its functional implications.

Comparative studies

Conducting comparative studies across different organisms and species will help identify conserved zinc-dependent pathways and shed light on the evolutionarily conserved roles of zinc in biological processes.

Systems biology approaches

Applying systems biology approaches, such as mathematical modeling and network analysis, will aid in deciphering the complex interactions

and regulatory networks involving zinc. Such approaches can uncover emergent properties and predict the consequences of zinc perturbations on cellular functions.

Conclusion

Zinc is a versatile element that plays critical roles in various cellular processes, making it essential for the biochemistry and overall health of living organisms. Its functions as a cofactor for enzymes, structural component of proteins, and signaling molecule underline its significance in DNA synthesis, protein synthesis, cellular metabolism and immune responses. Zinc deficiency has been associated with impaired enzyme activity, compromised immunity, dysfunctional neutrophils, allergic reactions, and mental health disorders. Furthermore, zinc has been explored in the context of COVID-19, where it may have antiviral properties and aid in immune response regulation. Additionally, zinc exhibits antioxidant and anti-inflammatory properties, making it relevant for chronic disease management. During pregnancy, adequate zinc intake is crucial for fetal growth and development. Moreover, zinc plays a vital role in the wound healing process. Overall, understanding the multifaceted roles of zinc sheds light on its importance as a micronutrient and its potential therapeutic applications in various health conditions. While significant progress has been made in understanding the biological function of zinc, there are limitations that need to be addressed for further advancement. Overcoming methodological challenges, investigating tissue and cell-type specificity, understanding zinc interactions and redundancy, and employing integrated approaches, advanced imaging techniques, comparative studies, and systems biology approaches will contribute to a deeper understanding of zinc's biological functions and its implications in health and disease.

References

1. Hambidge M. Biomarkers of Trace Mineral Intake and Status. *J Nutr* 2003;133(3):948S–955S. Available at: <http://doi.org/10.1093/jn/133.3.948S>
2. Saunders J, Smith T. Malnutrition: causes and consequences. *Clin Med* 2010;10(6):624–627. Available at: <http://doi.org/10.7861/clinmedicine.10-6-624>
3. Skrajnowska D, Bobrowska-Korczak B. Role of Zinc in Immune System and Anti-Cancer Defense Mechanisms. *Nutrients* 2019;11(10):2273. Available at: <http://doi.org/10.3390/nu11102273>
4. Kambe T, Taylor KM, Fu D. Zinc transporters and their functional integration in mammalian cells. *J Biol Chem* 2021;296:100320. Available at: <http://doi.org/10.1016/j.jbc.2021.100320>
5. Patwardhan B, Warude D, Pushpangadan P, Bhatt N. Ayurveda and Traditional Chinese Medicine: A Comparative Overview. *Evid Based Complement Alternat Med* 2005;2(4):465–473. Available at: <http://doi.org/10.1093/ecam/neh140>
6. Leung P-C, Xue CC-L. Chinese Medicine – Modern Practice. *World Sci* 2005. Available at: <http://doi.org/10.1142/5633>
7. Rizvi SAA, Einstein GP, Tulp OL, Sainvil F, Branly R. Introduction to Traditional Medicine and Their Role in Prevention and Treatment of Emerging and Re-Emerging Diseases. *Biomolecules* 2022;12(10):1442. Available at: <http://doi.org/10.3390/biom12101442>
8. Rastogi S. Building bridges between Ayurveda and Modern Science. *Int J Ayurveda Res* 2010;1(1):41. Available at: <http://doi.org/10.4103/0974-7788.59943>
9. Cuajungco M, Ramirez M, Tolmasky M. Zinc: Multidimensional Effects on Living Organisms. *Biomedicines* 2021;9(2):208. Available at: <http://doi.org/10.3390/biomedicines9020208>
10. Prasad AS. Discovery of Human Zinc Deficiency: Its Impact on

- Human Health and Disease. *Adv Nutr* 2013;4(2):176–190. Available at: <http://doi.org/10.3945/an.112.003210>
11. McKie SJ, Neuman KC, Maxwell A. DNA topoisomerases: Advances in understanding of cellular roles and multi-protein complexes via structure-function analysis. *Bioessays* 2021;43(4): 2000286. Available at: <http://doi.org/10.1002/bies.202000286>
 12. Giblett EloiseR, Ammann ArthurJ, Sandman R, Wara DianeW, Diamond LouisK. NUCLEOSIDE-PHOSPHORYLASE DEFICIENCY IN A CHILD WITH SEVERELY DEFECTIVE T-CELL IMMUNITY AND NORMAL B-CELL IMMUNITY. *Lancet* 1975;305(7914): 1010–1013. Available at: [http://doi.org/10.1016/S0140-6736\(75\)91950-9](http://doi.org/10.1016/S0140-6736(75)91950-9)
 13. Wessels I, Maywald M, Rink L. Zinc as a Gatekeeper of Immune Function. *Nutrients* 2017;9(12):1286. Available at: <http://doi.org/10.3390/nu9121286>
 14. Bonaventura P, Benedetti G, Albarède F, Miossec P. Zinc and its role in immunity and inflammation. *Autoimmun Rev* 2015;14(4): 277–285. Available at: <http://doi.org/10.1016/j.autrev.2014.11.008>
 15. Prasad AS, Bao B. Molecular Mechanisms of Zinc as a Pro-Antioxidant Mediator: Clinical Therapeutic Implications. *Antioxidants* 2019;8(6):164. Available at: <http://doi.org/10.3390/antiox8060164>
 16. Briggs WA, Pedersen MM, Mahajan SK, Sillix DH, Prasad AS, McDonald FD. Lymphocyte and granulocyte function in zinc-treated and zinc-deficient hemodialysis patients. *Kidney Int* 1982;21(6):827–832. Available at: <http://doi.org/10.1038/ki.1982.106>
 17. Kuźmicka W, Manda-Handzlik A, Cieloch A, et al. Zinc Supplementation Modulates NETs Release and Neutrophils' Degranulation. *Nutrients* 2020;13(1):51. Available at: <http://doi.org/10.3390/nu13010051>
 18. Rosenkranz E, Hilgers R-D, Uciechowski P, Petersen A, Plümäkers B, Rink L. Zinc enhances the number of regulatory T cells in allergen-stimulated cells from atopic subjects. *Eur J Nutr* 2015;56(2):557–567. Available at: <http://doi.org/10.1007/s00394-015-1100-1>
 19. Zhang J, Zou Y, Chen L, et al. Regulatory T Cells, a Viable Target Against Airway Allergic Inflammatory Responses in Asthma. *Front Immunol* 2022;13. Available at: <http://doi.org/10.3389/fimmu.2022.902318>
 20. Wessels I, Rolles B, Rink L. The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis. *Front Immunol* 2020;11. Available at: <http://doi.org/10.3389/fimmu.2020.01712>
 21. Boretti A, Banik BK. Zinc role in Covid-19 disease and prevention. *Vacunas* 2022;23(2):147–150. Available at: <http://doi.org/10.1016/j.vacun.2021.08.003>
 22. Wessels I, Haase H, Engelhardt G, Rink L, Uciechowski P. Zinc deficiency induces production of the proinflammatory cytokines IL-1 β and TNF α in promyeloid cells via epigenetic and redox-dependent mechanisms. *J Nutr Biochem* 2013;24(1): 289–297. Available at: <http://doi.org/10.1016/j.jnutbio.2012.06.007>
 23. Guo J, He L, Li T, Yin J, Yin Y, Guan G. Antioxidant and Anti-Inflammatory Effects of Different Zinc Sources on Diquat-Induced Oxidant Stress in a Piglet Model. *BioMed Research International* 2020;2020:1–10. Available at: <http://doi.org/10.1155/2020/3464068>
 24. Marreiro D, Cruz K, Morais J, Beserra J, Severo J, de Oliveira A. Zinc and Oxidative Stress: Current Mechanisms. *Antioxidants* 2017;6(2):24. Available at: <http://doi.org/10.3390/antiox6020024>
 25. Takeda A, Tamano H, Nishio R, Murakami T. Behavioral Abnormality Induced by Enhanced Hypothalamo-Pituitary-Adrenocortical Axis Activity under Dietary Zinc Deficiency and Its Usefulness as a Model. *Int J Mol Sci* 2016;17(7):1149. Available at: <http://doi.org/10.3390/ijms17071149>
 26. Swardfager W, Herrmann N, McIntyre RS, et al. Potential roles of zinc in the pathophysiology and treatment of major depressive disorder. *Neurosci Biobehav Rev* 2013;37(5):911–929. Available at: <http://doi.org/10.1016/j.neubiorev.2013.03.018>
 27. Hu Q, Liu F, Yang L, et al. Lower serum nicotinamide N-methyltransferase levels in patients with bipolar disorder during acute episodes compared to healthy controls: a cross-sectional study. *BMC Psychiatry* 2020;20(1):33. Available at: <http://doi.org/10.1186/s12888-020-2461-4>
 28. Ota E, Mori R, Middleton P, et al. Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database Syst Rev* 2015. Available at: <http://doi.org/10.1002/14651858.CD000230.pub5>
 29. Carducci B, Keats EC, Bhutta ZA. Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database Syst Rev* 2021;2021(3). Available at: <http://doi.org/10.1002/14651858.CD000230.pub6>
 30. Maxfield L, Shukla S, Crane JS. Zinc Deficiency. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2023. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK493231/>
 31. Lin P-H, Sermersheim M, Li H, Lee P, Steinberg S, Ma J. Zinc in Wound Healing Modulation. *Nutrients* 2017;10(1):16. Available at: <http://doi.org/10.3390/nu10010016>
 32. Momen-Heravi M, Barahimi E, Razzaghi R, Bahmani F, Gilasi HR, Asemi Z. The effects of zinc supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial. *Wound Rep Reg* 2017;25(3):512–520. Available at: <http://doi.org/10.1111/wrr.12537>
 33. Luo R, Zhang Y, Jia Y, et al. Molecular basis and homeostatic regulation of Zinc taste. *Protein Cell* 2021;13(6):462–469. Available at: <http://doi.org/10.1007/s13238-021-00845-8>
 34. Mozaffar B, Ardavani A, Muzafar H, Idris I. The Effectiveness of Zinc Supplementation in Taste Disorder Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Nutr Metab* 2023;2023:6711071. Available at: <http://doi.org/10.1155/2023/6711071>
 35. Najafizade N, Hemati S, Gookizade A, et al. Preventive effects of zinc sulfate on taste alterations in patients under irradiation for head and neck cancers: A randomized placebo-controlled trial. *J Res Med Sci* 2013;18(2):123–126. Available at: <https://pubmed.ncbi.nlm.nih.gov/23914214/>
 36. Nalage D, Sontakke T, Patil R, Biradar A. Environmental Impact Assessment. Mumbai: Gaurang Publishing Globalize Private Limited; 2023. Available at: <http://doi.org/10.5281/zenodo.7816944>
 37. Roohani N, Hurrell R, Kelishadi R, Schulin R. Zinc and its importance for human health: An integrative review. *J Res Med Sci* 2013;18(2):144–157. Available at: <https://pubmed.ncbi.nlm.nih.gov/23914218/>
 38. National Institutes of Health. Zinc – Fact Sheet for Health Professionals; 2022. Available at: <https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/>
 39. Saunders AV, Craig WJ, Baines SK. Zinc and vegetarian diets. *Med J Aust* 2013;199(S4). Available at: <http://doi.org/10.5694/mja11.11493>
 40. Silva ARA, Silva MMN, Ribeiro BD. Health issues and technological aspects of plant-based alternative milk. *Food Res Int* 2020;131:108972. Available at: <http://doi.org/10.1016/j.foodres.2019.108972>