TRENDS IN SCIENCES 2026; 23(1): 11556
https://doi.org/10.48048/tis.2025.11556
REVIEW ARTICLE

Zinc in Human Health: A Comprehensive Review of Its Biological Roles and Clinical Implications

Bima Putra Pratama[1], Aswin Rafif Khairullah[2], Dea Anita Ariani Kurniasih[3], Imam Mustofa[4,*], Bantari Wisynu Kusuma Wardhani[5], Mohammad Sukmanadi[6], Riza Zainuddin Ahmad[2], Andi Thafida Khalisa[7], Irma Melati[8], Ulvi Fitri Handayani[9], Sri Mulyati[4], Wita Yulianti[10], Adeyinka Oye Akintunde[11], Ilma Fauziah Maruf[5], Meta Aquarista Galia[12], Hanum Masayu Kirna Sari[13], Arif Nur Muhammad Ansori[14,15,16] and Syahputra Wibowo[17]

[1]Research Center for Process Technology, National Research and Innovation Agency (BRIN), South Tangerang, Banten 15314, Indonesia

[2]Research Center for Veterinary Science, National Research and Innovation Agency (BRIN), Bogor, West Java 16911, Indonesia

[3]Research Center for Public Health and Nutrition, National Research and Innovation Agency (BRIN), Bogor, West Java 16911, Indonesia

[4]Division of Veterinary Reproduction, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, East Java 60115, Indonesia

[5]Research Center for Pharmaceutical Ingredients and Traditional Medicine, National Research and Innovation Agency (BRIN), Bogor, West Java 16911, Indonesia

[6]Division of Basic Veterinary Medicine, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, East Java 60115, Indonesia

[7]Faculty of Military Pharmacy, Universitas Pertahanan, Bogor, West Java 16810, Indonesia

[8]Research Center for Limnology and Water Resources, National Research and Innovation Agency (BRIN), Bogor, West Java 16911, Indonesia

[9]Research Center for Animal Husbandry, National Research and Innovation Agency (BRIN), Bogor, West Java 16911, Indonesia

[10]Research Center for Biota System, National Research and Innovation Agency (BRIN), Bogor, West Java 16911, Indonesia

[11]Department of Agriculture and Industrial Technology, Babcock University, Ogun 121003, Nigeria

[12]D4 Agroindustrial Product Development, Politeknik Negeri Cilacap, Cilacap, Central Java 53212, Indonesia

[13]Undergraduate Program in Biology, Faculty of Mathematics and Natural Sciences, Universitas Brawijaya, Malang, East Java 65145, Indonesia

[14]Postgraduate School, Universitas Airlangga, Kampus B Dharmawangsa, Surabaya, East Java 60286, Indonesia

[15]Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Uttarakhand 248007, India

[16]Medical Biotechnology Research Group, Virtual Research Center for Bioinformatics and Biotechnology, Surabaya, East Java 60493, Indonesia

[17]Eijkman Research Center for Molecular Biology, National Research and Innovation Agency (BRIN), Bogor, West Java 16911, Indonesia

([*]Corresponding author's e-mail: imam.mustofa@fkh.unair.ac.id)

Received: 10 August 2025, Revised: 2 September 2025, Accepted: 12 September 2025, Published: 5 October 2025

Abstract

Zinc (Zn) is an essential micronutrient involved in enzymatic activity, protein and membrane structure, gene regulation, and immune and antioxidant functions. Both excess and deficiency influence health, affecting reproduction, skin, bones, endocrine balance, immunity, and the nervous system. Zinc deficiency remains a major global public health problem, particularly in low-income countries, and is often underdiagnosed due to the lack of reliable biomarkers. This review examines the role of zinc in human health, the clinical consequences of imbalance, and its therapeutic potential in disease prevention and management. Evidence shows that zinc supports antioxidant defense, wound healing, cell proliferation, and immune function. Supplementation may enhance immunity, promote tissue repair, and reduce infection and metabolic risk, especially in vulnerable groups such as children, the elderly, and patients with chronic conditions. Excess intake, however, can be harmful, leading to drug interactions and impaired copper absorption. In summary, zinc plays diverse roles in health and disease and holds promise for evidence-based dietary strategies. Its use should be tailored to individual nutritional needs to maximize benefits and minimize risks.

Keywords: Zinc, Public Health, Immunity, Metabolism, Disease

Introduction

Zinc (Zn) is an indispensable trace element that cannot be synthesized endogenously and must be obtained through the diet [1,2]. It functions as a cofactor for more than 300 enzymes and modulates the activity of over 2,000 transcription factors [3]. Zinc is essential for protein and DNA synthesis [4], cell division [5], wound healing [6], immune regulation [7], and normal growth and development, particularly during pregnancy [8], childhood [9], and adolescence [10].

The recommended dietary intake varies by age, sex, and physiological state. According to the Food and Nutrition Board (FNB) and the World Health Organization (WHO), daily requirements for healthy individuals range from 2 to 11 mg [11,12]. Major dietary sources include oysters, red meat, dairy products, seeds, and nuts [2]. However, phytate-rich plant-based diets can substantially reduce zinc bioavailability by inhibiting intestinal absorption [13].

Globally, approximately 17% of the population is estimated to be at risk of zinc deficiency, with the highest prevalence in South Asia and Sub-Saharan Africa [14]. Clinical consequences include impaired immune function, anorexia, growth retardation, delayed wound healing, dermatological lesions, and reproductive and neurological disorders [15]. Zinc deficiency is also strongly associated with increased morbidity and mortality from diarrhea, pneumonia, and malaria in children under 5 years of age [16].

While deficiency remains a major concern, excessive intake - typically exceeding 40 mg/day - may also be detrimental, leading to gastrointestinal disturbances, immune dysregulation, and impaired copper absorption [17]. Beyond deficiency and toxicity, zinc plays a central role in modulating oxidative stress and inflammation, with relevance to chronic diseases such as diabetes mellitus, cardiovascular disease, neurodegeneration, and cancer [18]. Recent research highlights its immunomodulatory and antiviral properties, including the regulation of T lymphocytes, NK cells, and macrophages [19], as well as its potential role in reducing viral replication in COVID-19 [20]. Furthermore, zinc may contribute to the maintenance of cognitive function and delay neurodegenerative progression in conditions such as Alzheimer's and Parkinson's disease, although current evidence supports association rather than causality [18,20].

Given its multifaceted biological and clinical roles, a comprehensive understanding of zinc metabolism and function remains critical. This review examines zinc's impact across major physiological systems, the health consequences of imbalance, therapeutic applications, and nutrient interactions. It also identifies existing research gaps, providing future directions for elucidating zinc's role in promoting and preserving human health.

Data collection method

Data for this review were collected through a systematic search of PubMed, Scopus, Web of Science, and Google Scholar for publications from January 2000 to June 2025. Keywords included "zinc," "human

health," "immunity," "metabolism," and "disease prevention." Inclusion criteria were English-language articles involving human studies, supported by relevant *in vitro* and *in vivo* research on zinc's biochemical, physiological, or clinical roles. Exclusion criteria were conference abstracts, editorials, duplicate records, and studies lacking sufficient methodological or outcome details. Study quality was assessed based on research design, sample size, and methodological rigor, with priority given to randomized controlled trials and high-quality observational studies. Reference lists of included papers were also screened. Extracted data covered population characteristics, zinc dosage and form, outcomes, and mechanistic insights.

Zinc: Sources, absorption, and metabolism

Zinc (Zn) is an essential trace element present in both plant- and animal-derived foods, with its contribution to human requirements depending on concentration and bioavailability [21]. Animal products - particularly oysters (16 - 182 mg/100 g), liver, chicken, beef, and lamb - contain the highest zinc concentrations [22]. Fortified cereals, dairy products, and eggs also provide substantial amounts [23]. Plant-based sources such as nuts, seeds (sesame, pumpkin, chia), and legumes contribute meaningfully; however, their zinc bioavailability is reduced due to the presence of phytic acid and other mineral-binding compounds [24].

Dietary composition strongly influences zinc absorption [25]. High levels of phytate in cereals and legumes form insoluble complexes with zinc, markedly lowering absorption efficiency [26]. Additional inhibitors include dietary fiber, oxalates, and polyphenols [27]. Conversely, certain amino acids (e.g., histidine, cysteine), citric acid, and animal proteins enhance absorption by forming soluble complexes or stimulating zinc transporters [25]. As a result, omnivorous diets rich in animal products are less likely to cause zinc deficiency compared to predominantly plant-based diets, particularly in low-income populations [28].

Zinc absorption occurs mainly in the jejunum through active transport and facilitated diffusion [29]. The ZIP family of transporters, especially ZIP4, mediate zinc influx into enterocytes, whereas ZnT transporters, notably ZnT1 on the basolateral membrane, export zinc into the bloodstream [30,31]. Within enterocytes, zinc may bind to metallothionein for temporary storage, be utilized locally, or released into circulation. Since the human body lacks a long-term storage system, homeostasis is maintained through tight regulation of intestinal absorption, tissue distribution, and excretion [25]. Most excess zinc is eliminated via feces, with minor amounts excreted in urine and sweat [32]. **Table 1** shows the main dietary sources of zinc together with enhancers and inhibitors of its bioavailability.

After entering the bloodstream, zinc is widely distributed, with approximately 85% stored in skeletal muscle and bone, and smaller fractions present in skin, liver, brain, and plasma [25]. At the cellular level, zinc functions as an enzyme cofactor, a structural stabilizer of proteins, and an intracellular signaling molecule that regulates diverse metabolic pathways [33]. The coordinated expression of ZIP and ZnT transporters, which varies across tissues according to zinc status, is central to maintaining systemic zinc balance [34]. **Figure 1** provides a schematic overview of dietary sources, intestinal absorption mechanisms, and factors affecting zinc bioavailability.

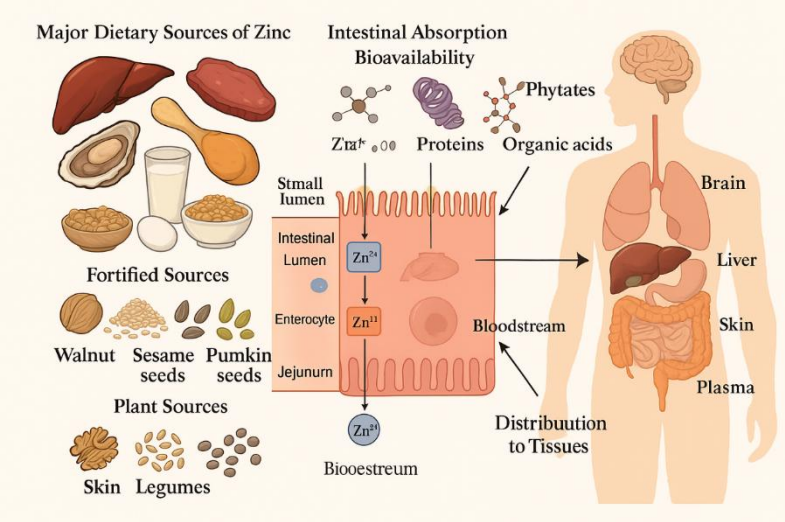

Figure 1 Dietary sources, intestinal absorption, and systemic distribution of zinc.

Table 1 Food sources of zinc and factors affecting bioavailability.

Food category	Examples of food ingredients	Zinc content (mg/100g)	Bioavailability	Factors that increase/decrease absorption
Animal (high in zinc)	Oysters, beef, chicken liver, poultry	Oysters: 25 - 50 mg Meat: 4 - 9 mg	High	↑ Animal protein ↑ Amino acids (histidine, cysteine) ↑ Citric acid
Milk and dairy products	Milk, cheese, yogurt	1 - 5 mg	Medium	↑ Calcium and phosphate have the potential to ↓ absorption, but the effect is still controversial
Vegetable (seeds and nuts)	Pumpkin seeds, sesame, cashews, peanuts	3 - 7 mg	Low-Medium	↓ Phytic acid (high phytate:zinc molar ratio) ↓ Oxalate and polyphenols
Legumes & cereals	Soybeans, lentils, whole wheat, brown rice	1 - 4 mg	Low	↓ Phytate, ↓ Fiber, ↓ Tannin ↑ The fermentation/seeding process can ↑ increase zinc absorption
Fortified foods	Breakfast cereal, fortified wheat flour	Varies (depending on fortification)	Medium-High	↑ Fortified forms (zinc sulfate, zinc gluconate) ↑ Consume with protein

Notes: ↑ = increases zinc absorption; ↓ = decreases zinc absorption; mg/100g = mg per 100 g of food

The role of zinc in biological systems

In the human body, zinc has a wide range of vital biological roles, including molecular and cellular structural, catalytic, and regulatory roles. The 3 primary functions of zinc in biological systems are as an antioxidant that reduces oxidative stress, a cofactor for enzymes, and a modulator of genetic expression [35]. **Table 2** classifies the various biological functions of zinc by molecular category, providing examples of enzymes or pathways involved, and the consequences of zinc deficiency and excess for each role.

Table 2 Classification of zinc biological functions based on molecular categories, pathway examples, and consequences of imbalance.

Molecular category	Biological function	Examples of enzymes/pathways	Consequences of zinc deficiency	Consequences of excess zinc
Enzymatic cofactors	Structural and catalytic activator of > 300 metabolic enzymes	Alcohol dehydrogenase, carbonic anhydrase, DNA/RNA polymerase, carboxypeptidase, Cu/Zn-SOD	Decreased enzyme activity, impaired protein/carbohydrate/lipid metabolism, oxidative stress	Competitive inhibition of other metals (Fe, Cu), other enzymatic metabolic disorders
Genetic expression regulators	Modulation of gene transcription and DNA/RNA/protein synthesis through zinc finger motifs	Metal-responsive transcription factor-1 (MTF-1), p53, DNA repair enzymes	Dysregulation of gene expression, impaired DNA replication and repair, impaired tissue growth	Dysregulation of target gene expression, potential disruption of growth and cellular systems
Antioxidant and anti-inflammatory	Cell membrane stabilizer, inhibits ROS and inflammation	Cu/Zn-SOD, inhibition of Fenton reaction, NF-κB pathway, cytokines (TNF-α, IL-1β, CRP)	Increased ROS, lipid peroxidation, systemic oxidative stress, chronic inflammation	Decreased phagocyte activity, impaired adaptive immune response
Immunity and cell proliferation	T lymphocyte activation, phagocytosis, cytokines, differentiation and wound healing	IL-2, TNF-α, MMPs, collagenase, cell differentiation pathways	Decreased immune response, impaired wound healing, tissue damage	Excessive immune suppression, potential autoimmune disorders or immunodeficiency
Cell homeostasis and apoptosis	Regulation of programmed cell division and death	Caspase, Bcl-2, p53 pathway	Abnormal apoptosis, impaired tissue growth	Inhibition of apoptosis, potential for abnormal cell proliferation

Notes: Cu/Zn-SOD = Copper/zinc superoxide dismutase; Fe = Iron; Cu = Copper; ROS = Reactive oxygen species; NF-κB = Nuclear factor kappa-light-chain-enhancer of activated B cells; TNF-α = Tumor necrosis factor alpha; IL-1β = Interleukin-1 beta; CRP = C-reactive protein; IL-2 = Interleukin-2; MMPs = Matrix metalloproteinases; Bcl-2 = B-cell lymphoma 2.

First, zinc serves as a cofactor for over 300 enzymes that are engaged in different metabolic pathways, such as those that are crucial for the synthesis and breakdown of proteins, the metabolism of carbohydrates and fats, and the detoxification of free radicals [36]. Zinc is necessary, for instance, for the action of DNA and RNA polymerase, alcohol dehydrogenase, carboxypeptidase, and superoxide dismutase (SOD), a crucial enzyme in the body's antioxidant defenses [37]. Zinc is also necessary for metalloenzymes like carbonic anhydrase that control pH and maintain acid-base equilibrium [38].

Second, zinc is essential for the production of macromolecules like proteins, RNA, and DNA as well as for controlling genetic expression [39]. This is accomplished by the way zinc affects transcription factors that have zinc finger motifs, which are protein domain structures that enable particular binding to DNA sequences [40]. Zinc is required for transcription factors like metal-responsive transcription factor-1

(MTF-1) to either activate or inhibit the expression of target genes related to cell development, stress response, and metal homeostasis [41]. Zinc facilitates DNA replication and repair during DNA synthesis and cell division, which is critical for cell proliferation, particularly in tissues with rapid cell turnover like the skin and intestinal mucosa [42].

Third, zinc has anti-inflammatory and oxidative stress-modulating properties that help preserve cell integrity and shield tissues from oxidative damage [43]. Zinc stabilizes cell membranes, prevents the Fenton reaction, which creates hydroxyl radicals from other transition metals like iron and copper, and is an essential component of antioxidant enzymes like Cu/Zn-superoxide dismutase [44]. It has been demonstrated that a zinc deficit raises lipid peroxidation, produces more reactive oxygen species (ROS), and lowers plasma's overall antioxidant capability [35]. On the other hand, zinc supplementation can lower inflammatory biomarkers including TNF-α, IL-1β, and CRP by activating other anti-inflammatory transcription factors and inhibiting the NF-κB pathway [45].

Zinc also has an impact on wound healing, connective tissue creation, apoptosis and cell differentiation, immunological function, and immune cell proliferation [5]. Regarding immunology, zinc is involved in phagocyte function, cytokine synthesis, and T lymphocyte development and activation [46]. Zinc plays a key role in tissue remodeling and wound healing by promoting collagen synthesis and matrix metalloproteinase (MMP) activity [47].

Zinc is a multipurpose micronutrient that is essential for preserving the integrity of the entire biological system, the stability of protein structure, and the effectiveness of enzyme activity [48]. Zinc imbalances, whether deficient or excessive, can lead to increased oxidative stress, genetic transcription abnormalities, enzymatic dysfunction, and eventually the emergence of a number of clinical illnesses [35]. Therefore, to ensure the best possible health and operation of all body systems, zinc homeostasis balance needs to be carefully maintained. **Figure 2** summarizes these biological functions, highlighting representative zinc-dependent enzymes, transcription factors, and antioxidant mechanisms, along with the consequences of zinc deficiency and excess.

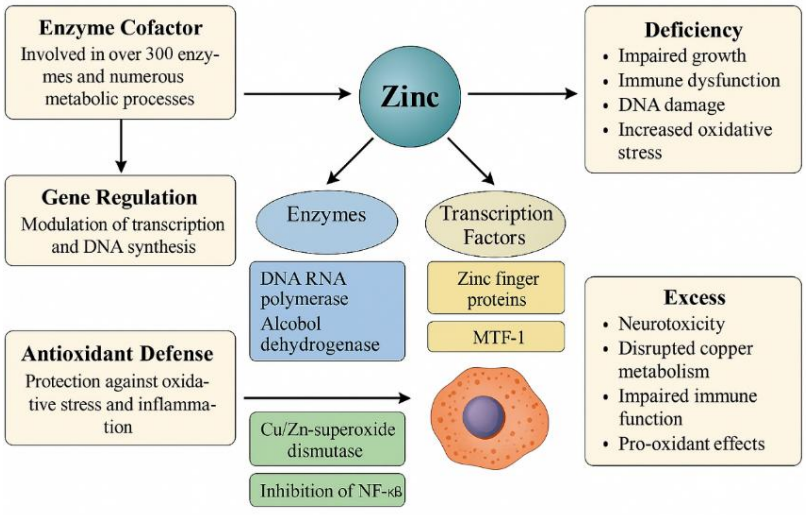

Figure 2 Biological roles of zinc: Enzymatic cofactor, gene regulation, and antioxidant functions.

Zinc levels in physiological and pathological conditions

Serum or plasma zinc concentration is the most widely used indicator of zinc status in humans, although it does not fully reflect tissue zinc stores [49]. Nevertheless, it remains the most practical clinical method. **Table 3** summarizes serum zinc ranges under different physiological and pathological conditions, together with their clinical implications.

Table 3 Comparison of zinc levels in physiological and pathological conditions.

Clinical conditions	Serum zinc levels (normal: 70 - 120 µg/dL)	Clinical description
Normal	90 - 110 µg/dL	Homeostasis is maintained
Mild deficiency	60 - 70 µg/dL	Often asymptomatic, immunosuppression begins to appear
Moderate-severe deficiency	< 60 µg/dL	Recurrent infections, growth disorders, dermatitis
Diabetes Mellitus	↓ (60 - 80 µg/dL)	Increased urinary excretion, oxidative stress
Alzheimer's disease	↓ (50 - 75 µg/dL or varies locally in the brain)	Dysregulation of zinc distribution in the brain
Acute/chronic infection	↓	Redistribution to the liver, use by immune cells
Over-supplementation	> 150 µg/dL	Risk of toxicity, inhibition of Cu absorption

Notes: µg/dL = micrograms per deciliter; ↓ = decreased level compared to normal; Cu = Copper.

Normal condition

In healthy adults, serum zinc levels typically range from 70 to 120 µg/dL, with an average of 90 - 110 µg/dL [50]. Within this range, zinc functions effectively as an immune regulator, cell membrane stabilizer, and enzymatic cofactor. Homeostasis is maintained by adaptive mechanisms in gastrointestinal absorption and excretion [32].

Zinc deficiency

Mild deficiency (60 - 70 µg/dL): Usually asymptomatic or associated with nonspecific symptoms such as fatigue, reduced appetite, and early immune dysfunction [16].

Moderate to severe deficiency (< 60 µg/dL): Associated with systemic manifestations, including dermatitis, impaired wound healing, growth retardation in children, and recurrent infections. This is common in individuals with chronic illness, malabsorption, inadequate intake, or increased requirements (pregnancy, lactation and rapid growth) [51].

Diabetes mellitus

Patients with type 1 or type 2 diabetes mellitus often exhibit serum zinc levels of 60 - 80 µg/dL, due to oxidative stress, chronic inflammation, and urinary zinc loss (zincuria) [52]. Zinc is essential for insulin synthesis and secretion, as well as protection of pancreatic β-cells [53]. Low levels are therefore linked to metabolic inefficiency and increased vascular complications [1].

Alzheimer's disease

Alzheimer's patients show altered zinc distribution, with systemic reduction and depletion in cortical and hippocampal tissues [54]. Although serum zinc may remain unchanged, levels often fall to 50 - 75 µg/dL [55]. Dysregulated zinc contributes to neurodegeneration by promoting β-amyloid aggregation and altering neurotransmitter activity [56].

Acute and chronic infections

During infections, zinc redistributes from plasma to the liver as part of the acute-phase response mediated by cytokines such as IL-6 [57]. Consequently, serum levels decrease despite adequate intake, reflecting tissue sequestration and heightened immune demand [58]. This transient response may worsen zinc deficiency in vulnerable individuals.

Over-supplementation

Serum zinc concentrations exceeding 150 µg/dL are generally associated with prolonged intake of high-dose supplements without medical supervision [59]. Toxicity at this level can lower HDL cholesterol, cause gastrointestinal disturbances, and impair copper absorption, potentially leading to immune dysfunction, neuropathy, and anemia [16].

Zinc and the immune system

Zinc (Zn) is a critical mineral required for the maintenance and regulation of both innate and adaptive immunity [60]. It regulates immune gene expression,

cytokine production, and inflammatory signaling pathways, while serving structural and functional roles in multiple immune cells [61].

In the innate immune system, zinc supports epithelial barrier integrity in the respiratory and gastrointestinal tracts, thereby reducing susceptibility to microbial invasion [62,63]. It also influences neutrophil and macrophage function, including phagocytosis, reactive oxygen species (ROS) generation, and clearance of intracellular pathogens [64]. Moreover, zinc is necessary for the activation and degranulation of natural killer (NK) cells, which eliminate virus-infected and malignant cells [18].

In adaptive immunity, zinc is essential for T and B cell development, maturation, and function [6]. Deficiency can cause thymic atrophy, reduced T lymphocyte numbers, and imbalance between T helper (Th1/Th2/Th17) and regulatory T (Treg) cells [65,66]. It also impairs antibody synthesis and B cell activation, thereby weakening immune responses to novel antigens, including vaccines [67,68].

Zinc further modulates inflammation by inhibiting nuclear factor kappa B (NF-κB) activation, thereby reducing the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [69]. It also promotes the expression of A20, a cytoprotective protein that suppresses inflammatory signaling, and inhibits phosphodiesterase activity [70]. These mechanisms contribute to limiting excessive immune activation and preventing autoimmunity in diseases such as systemic lupus erythematosus, inflammatory bowel disease, and rheumatoid arthritis [71-74]. Zinc thus promotes immune tolerance and prevents inappropriate recognition of self-antigens [75]. **Figure 3** illustrates zinc's immunomodulatory functions, including effects on epithelial barriers, phagocytes, NK cells, T and B lymphocytes, as well as its regulation of NF-κB and A20.

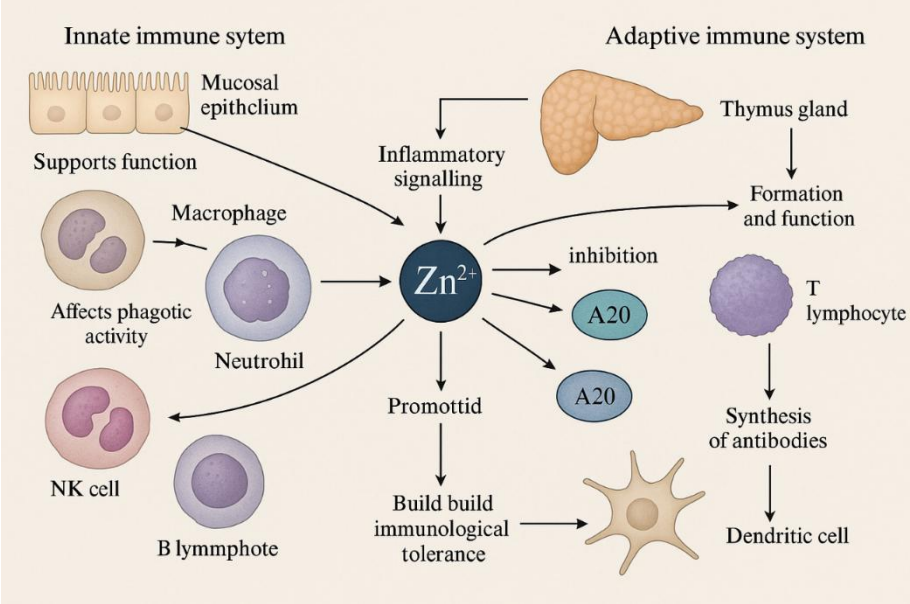

Figure 3 Role of zinc in the immune system: Regulation of innate and adaptive immunity.

The association between zinc status and infection outcomes has been confirmed by numerous clinical and epidemiological studies. Supplementation has been shown to shorten the duration of upper respiratory tract infections [76], reduce the severity of acute diarrhea [77], and lower pneumonia incidence [78]. Zinc also exhibits direct antiviral effects by enhancing interferon responses, inhibiting viral RNA replication, and blocking viral proteases [79]. *In vitro*, increased intracellular zinc concentrations inhibit the replication of RNA viruses such as hepatitis C virus, coronaviruses, and rhinoviruses [80-82].

During the COVID-19 pandemic, zinc received particular attention as a supportive therapy. Several clinical studies reported that patients with low zinc levels experienced more severe symptoms, longer hospitalizations, and higher mortality [83-86]. Zinc may enhance immune responses, augment endogenous

antiviral activity, and inhibit SARS-CoV-2 replication through suppression of RNA-dependent RNA polymerase [87]. Although evidence remains inconclusive, zinc supplementation continues to be recommended as supportive therapy, particularly for individuals at risk of deficiency such as the elderly and patients with chronic conditions [88].

Overall, zinc contributes to immunological homeostasis by balancing effective immune activation against infections with the prevention of tissue damage and excessive inflammation [62,89]. Adequate zinc status is therefore essential for resistance to infection, recovery from illness, and protection against autoimmunity and chronic inflammatory disorders.

Zinc in development and reproduction

Zinc is an essential micronutrient required for human growth, reproduction, and development [90]. Requirements increase markedly during growth, pregnancy, and lactation due to heightened metabolic activity, rapid cell division, and the demand for protein and DNA synthesis [91]. Zinc deficiency during these critical periods is associated with increased morbidity, reproductive complications, and long-term consequences for organ development and physiological function [92].

Zinc and child growth

Zinc plays a central role in linear growth and tissue development during infancy, childhood, and adolescence [8]. It stimulates growth hormone and insulin-like growth factor-1 (IGF-1), key regulators of bone and soft tissue growth [93], and supports bone formation by enhancing osteoblast activity and mineralization [94]. Deficiency in children results in growth retardation, weight loss, and delayed puberty [95]. Clinical trials and meta-analyses consistently demonstrate that zinc supplementation improves height and weight in children with poor nutritional status, particularly in low-income countries [96-98]. Zinc also strengthens immunity, reducing the incidence of diarrhea, pneumonia, and respiratory tract infections, thereby indirectly supporting growth [99].

Zinc in pregnancy and fetal development

During pregnancy, zinc is required for fetal organogenesis, placental growth, and maternal immune function [91]. It contributes to angiogenesis, DNA synthesis, embryonic cell proliferation, and antioxidant defense, protecting fetal tissues from oxidative stress [100]. Adequate zinc is also necessary for hormonal regulation, placental enzyme activity, and folate metabolism, which is vital for neural tube formation [101]. Zinc deficiency during pregnancy is associated with adverse outcomes, including low birth weight, preterm delivery, intrauterine growth restriction (IUGR), preeclampsia, and perinatal infections [102]. Moreover, insufficient maternal zinc impairs fetal immune and neurological development, increasing the risk of long-term immunological and cognitive dysfunction [103]. Supplementation during pregnancy is therefore recommended to improve maternal and child health, particularly in populations at risk [104].

Zinc and fertility

Zinc is critical for gametogenesis, reproductive hormone regulation, and the quality of sperm and oocytes [90]. In men, zinc supports spermatogenesis, testosterone metabolism, and protection against oxidative damage to sperm DNA [105]. High concentrations of zinc in the prostate and seminal fluid stabilize sperm membranes and enhance motility [106]. Deficiency is linked to reduced semen volume, impaired motility, and abnormal morphology, leading to decreased fertility [107]. In women, zinc influences endometrial development, ovulation, and embryo implantation [91], partly through its regulation of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [108]. Zinc deficiency is associated with disrupted ovulation, poor oocyte quality, and reduced fertilization rates [109]. Evidence from *in vitro* fertilization (IVF) studies further demonstrates that adequate zinc concentrations in culture media improve embryo viability and implantation success [110].

Zinc and degenerative diseases

Zinc (Zn) is an essential micronutrient that supports the structure and function of the brain and central nervous system (CNS) [111]. It contributes to enzymatic activity, neurogenesis, antioxidant defense, and synaptic transmission [20]. Altered zinc homeostasis has been associated with mood disorders, such as depression, and with neurodegenerative diseases, including Alzheimer's and Parkinson's [112].

Evidence suggests that zinc may exert both protective and potentially harmful effects in the CNS, depending on its concentration and distribution [113].

Zinc in brain health and neuroprotection

Zinc is concentrated in the hippocampus, cortex, and amygdala, regions crucial for memory, emotion, and behavior [114]. Within glutamatergic neurons, zinc is stored in synaptic vesicles and released during neurotransmission, where it modulates GABA, AMPA, and NMDA receptors [115]. Through these mechanisms, zinc acts as a neuromodulator that influences synaptic plasticity, memory, and neuronal excitability. As a cofactor of superoxide dismutase (Cu/Zn-SOD), zinc contributes to antioxidant defense and protection against reactive oxygen species (ROS) [10]. It may also limit neuroinflammation by suppressing proinflammatory cytokines and regulating microglial activity [116]. Collectively, these processes highlight zinc's role in maintaining neural homeostasis and resilience. **Figure 4** illustrates zinc localization in specific brain regions, its involvement in synaptic signaling, and its potential relevance to neurodegenerative disorders.

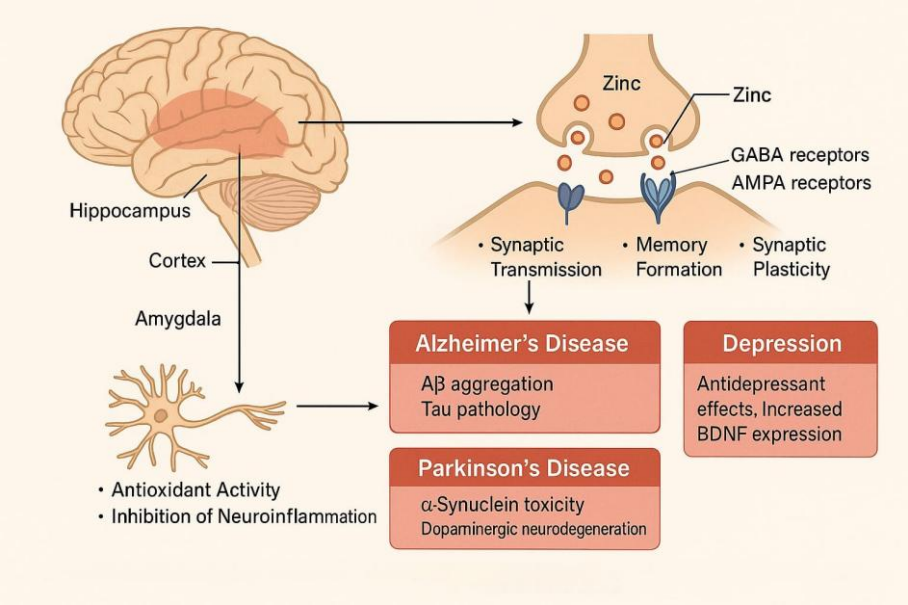

Figure 4 Role of zinc in brain health, neuroprotection, and neurological disorders.

Zinc and Alzheimer's disease

Alzheimer's disease (AD), the most common form of dementia, is characterized by beta-amyloid (Aβ) plaques and tau neurofibrillary tangles [117]. Zinc can bind to Aβ and promote oligomer formation, which may contribute to neurotoxicity [118]. At the same time, adequate zinc levels may inhibit β- and γ-secretase activity, thereby reducing Aβ generation [119]. Post-mortem studies have revealed both regional zinc accumulation and depletion in the hippocampus and cortex of AD patients [120]. Animal studies using zinc supplementation or chelation have shown mixed results, suggesting that therapeutic outcomes depend on disease stage and zinc distribution [21,54].

Zinc and Parkinson's disease

Parkinson's disease (PD) is marked by dopaminergic neuron loss in the substantia nigra and α-synuclein aggregation [121]. Zinc has been detected in α-synuclein aggregates and may influence their toxicity [122]. However, physiological zinc levels can support antioxidant activity and protect neurons from oxidative and mitochondrial damage [123]. Dysregulation may also promote microglial activation and release of proinflammatory cytokines such as TNF-α and IL-1β [124]. Preclinical evidence suggests that zinc supplementation at appropriate levels may help maintain dopaminergic neuron survival, although further clinical validation is required [125].

Zinc and depressive disorders

Depression is a multifactorial condition associated with neurotransmitter imbalance, oxidative stress, and systemic inflammation [126]. Patients with major depressive disorder often show reduced serum zinc concentrations, which are inversely related to symptom severity [127]. Zinc may support antidepressant effects by modulating NMDA receptor activity, enhancing brain-derived neurotrophic factor (BDNF) expression, and reducing inflammatory signaling [128]. Clinical studies indicate that adjunctive zinc supplementation with selective serotonin reuptake inhibitors (SSRIs) can accelerate symptom improvement and enhance treatment outcomes [129]. Zinc also contributes to regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is frequently altered in chronic depression [130].

Zinc and chronic disease

Zinc plays a multifaceted role in chronic disease pathogenesis, particularly in obesity, metabolic syndrome [131], cardiovascular disease [132], and diabetes mellitus (DM) [133]. Its functions extend beyond structural and enzymatic support to include antioxidant, anti-inflammatory, and gene-regulatory effects influencing blood pressure, cholesterol, and glucose metabolism [45]. Both zinc deficiency and excess are associated with increased disease risk and severity.

Zinc and diabetes mellitus

Diabetes mellitus, particularly type 2 (T2DM), is characterized by impaired insulin secretion and resistance [134]. Zinc is essential for insulin production, storage, and release, and protects β cells from oxidative and inflammatory damage [45]. Within β cells, zinc stabilizes insulin crystals in secretory granules and enhances insulin sensitivity in target tissues [135]. It also regulates PI3K/Akt signaling, which is central to glucose metabolism [136]. Serum and pancreatic zinc levels are typically reduced in diabetic patients, while hyperglycemia and renal dysfunction accelerate zinc loss via urine [137]. Deficiency further exacerbates oxidative stress and β-cell dysfunction [10]. Clinical trials suggest that zinc supplementation can lower HbA1c, improve insulin sensitivity, and reduce inflammatory biomarkers, though outcomes vary by diabetes type and baseline zinc status [138,139].

Zinc and cardiovascular disease

Cardiovascular disease (CVD), the leading cause of global mortality, is strongly linked to endothelial dysfunction, atherosclerosis, and hypertension [140]. Zinc exerts cardioprotective effects by stabilizing endothelial membranes, inhibiting LDL oxidation, and reducing pro-oxidant enzyme activity [35]. It also suppresses vascular adhesion molecules (VCAM-1, ICAM-1), thereby limiting plaque formation [141]. In addition, zinc regulates vascular tone through calcium homeostasis and modulation of angiotensin-converting enzyme (ACE) activity [142]. Observational studies link low zinc status to increased risks of stroke [143], ischemic heart disease [144], and hypertension [145], particularly in diabetic and renal disease patients [146]. While clinical trial findings remain inconsistent, adequate zinc status appears important for cardiovascular protection, primarily through anti-inflammatory and antioxidative mechanisms.

Zinc and metabolic disorders

In obesity and metabolic syndrome, zinc contributes to lipid and energy homeostasis [45]. It regulates adipokines such as leptin and adiponectin, which influence appetite, lipolysis, and insulin sensitivity [147]. Obese individuals often exhibit reduced serum zinc and heightened systemic inflammation [131]. At the molecular level, zinc modulates transcription factors including SREBP and PPAR-γ, which regulate lipid biosynthesis and hepatic lipogenesis [148,149]. Experimental studies report that zinc supplementation can raise HDL and lower LDL and triglyceride concentrations, though human outcomes remain variable depending on baseline nutritional status [150-152].

Zinc toxicity and supplementation risks

Although zinc is vital for metabolic health, excessive intake can be harmful. At the cellular level, excess zinc may disrupt mitochondrial function, induce oxidative stress, and impair signaling pathways involved in insulin and lipid metabolism [153]. Chronic high-dose supplementation (> 40 mg/day) reduces copper absorption, leading to anemia,

neutropenia, and immune dysfunction [16]. Clinically, toxicity may manifest as gastrointestinal distress, lowered HDL cholesterol, and increased infection risk. The elderly and patients with chronic diseases are particularly vulnerable to such adverse effects due to altered zinc metabolism and polypharmacy interactions [154]. Careful dosage regulation and individualized supplementation strategies are therefore essential to maximize benefits while avoiding toxicity.

Zinc toxicity and drug interactions

Zinc is an essential micronutrient crucial for health and physiological function, but excessive intake or prolonged supplementation without medical supervision can have harmful consequences and interact with medications and other minerals [1]. Therefore, it is important to consider the safe limits of zinc intake, its potential toxicity, and its interactions in the context of therapy and nutrition, in addition to understanding its role in maintaining biological activities.

Zinc toxicity and safe intake limits

The World Health Organization (WHO) and the Food and Nutrition Board (FNB) have established the tolerable upper intake level (UL) for zinc at 40 mg/day for adults, which is higher than the recommended daily allowance (RDA) [11]. Intakes exceeding this threshold, particularly from supplements or fortified foods, may lead to both acute and chronic adverse effects [153]. Acute zinc poisoning can occur with very high doses (> 200 mg) taken at once, such as from accidental industrial exposure or high-dose supplements. Clinical case reports describe symptoms including headaches, diarrhea, nausea, vomiting, abdominal pain, and dysgeusia (abnormal taste perception) [154]. In more severe cases, metabolic disturbances such as reduced plasma high-density lipoprotein (HDL) levels have been observed, along with gastrointestinal distress [155].

Chronic zinc toxicity may develop when intake consistently exceeds 50 mg/day, leading to impaired activity of copper-dependent enzymes (e.g., ceruloplasmin, cytochrome oxidase) and secondary copper deficiency [156]. Case studies have documented conditions such as peripheral neuropathy, neutropenia, and normocytic hypochromic anemia as consequences of prolonged high zinc intake [158]. This occurs because elevated zinc induces enterocytes to overexpress metallothionein, which binds copper ions (Cu^{2+}) with higher affinity, reducing systemic copper absorption [157].

Interaction of zinc with other nutrients

Zinc interacts antagonistically and competitively with copper (Cu) and iron (Fe) [159]. Excess zinc can impair absorption of these minerals, while concurrent high-dose iron intake may reduce zinc bioavailability [160]. Clinical practice therefore recommends separating zinc and iron supplementation by at least 2 h [161]. Furthermore, zinc absorption is influenced by dietary factors, as it can form insoluble complexes with phytates, fiber, and polyphenols present in plant-based diets [2]. Such interactions must be considered in designing fortification and supplementation strategies [162].

Zinc interactions with drugs

Zinc also interacts pharmacokinetically with several drugs, influencing absorption, distribution, and therapeutic efficacy. Notably, zinc can chelate with quinolone antibiotics (e.g., ciprofloxacin, levofloxacin) and tetracyclines (e.g., doxycycline), leading to reduced absorption. Clinical guidance advises separating intake of these antibiotics and zinc supplements by at least 2 to 3 h [163]. Patients on long-term thiazide diuretics (e.g., hydrochlorothiazide) may experience zinc depletion due to increased urinary excretion, warranting monitoring of zinc status [164]. Similarly, zinc can interact with penicillamine, a chelating agent used for rheumatoid arthritis and heavy metal poisoning, by forming complexes that lower the drug's bioavailability [165]. Monitoring zinc levels is recommended in such patients. In addition, potential interactions with certain antihypertensives, immunosuppressants, and anticonvulsants have been suggested, although further clinical studies are required to confirm these findings [166].

Further research directions

Numerous studies have demonstrated the critical role of zinc in immune function, growth, reproduction, and the prevention of degenerative and chronic diseases, but it is also important to acknowledge

several scientific and methodological limitations. These limitations create opportunities for more comprehensive and systematic research, particularly to clarify zinc's molecular mechanisms and to optimize its therapeutic applications in clinical settings.

At present, most zinc research remains observational, which limits the ability to establish clear causal relationships between zinc status and specific clinical disorders. For instance, it is often difficult to determine whether low zinc levels in individuals with chronic illnesses are a cause or a consequence of the condition [21]. Moreover, methodological inconsistencies in assessing zinc status - such as reliance on serum or plasma zinc concentrations, which are influenced by disease, hydration status, and timing of sampling - further complicate comparisons across studies.

There are also relatively few randomized controlled clinical trial (RCT) data on zinc supplementation, and the existing trials vary considerably in design, dose, duration, and study population [167]. In addition, dietary interactions, genetic polymorphisms in zinc transporters, and poorly controlled comorbid variables contribute to the heterogeneity of findings [168]. Based on these gaps, the following recommendations can be made for future research:

Large-scale, standardized clinical trials

Multicenter RCTs with rigorous designs are needed to evaluate the preventive and therapeutic effects of zinc supplementation. Such studies should determine optimal dosage, zinc form (organic or inorganic), timing, and carefully account for confounding factors such as phytate intake, micronutrient status, and immune response [169].

Mechanistic and molecular studies

Further research is required to investigate the molecular pathways of zinc, including its roles in gene expression, epigenetic regulation, and the modulation of immune and inflammatory signaling. In particular, studies on zinc transporters (ZIP and ZnT) and their relevance to cancer, neurological diseases, and metabolic disorders would advance understanding of zinc deficiency and excess [170].

Improved biomarkers of zinc status

The development of more sensitive and specific biomarkers beyond serum zinc is essential. Integrating metabolomic, proteomic, and molecular imaging approaches could allow more accurate mapping of zinc distribution and biological function [171].

Interactions with nutrients and drugs

More studies are needed to examine zinc's interactions with other micronutrients (e.g., copper, iron, vitamin A, selenium) and with medications. Such interactions may affect nutritional status and therapeutic efficacy, particularly in populations with chronic disease, polypharmacy, or advanced age [172].

Zinc applications in precision medicine

Future work should also explore zinc's role in precision medicine, especially its impact on individual genetic and epigenetic profiles. This may enable the development of zinc-based personalized therapies - for example, in neurodegeneration, oncology, or autoimmune regulation [173].

Long-term safety studies

Finally, further research is required to establish the long-term safety of high-dose zinc intake, whether from supplementation or fortification. Chronic toxicity studies in both animal and human models are needed to define safe intake thresholds for the general and vulnerable populations [17].

Conslusions

An important micronutrient, zinc is crucial for many bodily biological processes, such as enzyme activity, gene expression regulation, membrane stability, immunity, and oxidative stress defense. According to this study, zinc is crucial for immune system integrity, neurological and endocrine system development, wound healing, bone growth, and reproductive health. It has been demonstrated that zinc shortage affects several physiological systems both clinically and subclinically, with symptoms ranging from reduced cognitive function to growth retardation, metabolic problems, and increased susceptibility to infection. However, high zinc intake, particularly from supplements or unregulated fortification, can be harmful, interfere with the balance of other

micronutrients like copper and iron, and have adverse drug interactions. Therefore, it is strongly advised to check zinc levels in the general population, particularly in susceptible populations including children, pregnant women, the elderly, and patients with chronic illnesses. Zinc supplementation interventions should be administered judiciously, evidence-based, and with consideration for dosage, duration, and any interactions. A critical step in preventing and treating a number of disorders linked to micronutrient deficiencies is the incorporation of zinc status monitoring into public health policies and nutrition-based therapeutic practices, given the significance of zinc in systemic health. Optimizing the safe and effective use of zinc requires more research and advancements in the areas of diagnosis, treatment, and nutrition education.

Acknowledgements

The authors would like to express their sincere gratitude to the National Research and Innovation Agency (BRIN) and the Research Organization for Agriculture and Food (ORPP BRIN) for the financial and facility support provided through the 2025 Research Activity Budget under the Research Program on Downstreaming Agricultural Innovation Products, as stated in the official letter Number B-34668/III.11/TK.01.02/12/2024. The authors also extend their appreciation to the Research Center for Mineral Technology, BRIN, for their valuable support in the preparation and completion of this manuscript. This support has significantly contributed to the successful implementation of this research and paper.

This work was supported by the National Research and Innovation Agency (BRIN) and the Research Organization for Agriculture and Food (ORPP BRIN) through the 2025 Research Activity Budget under the Research Program on Downstreaming Agricultural Innovation Products, as stated in the official letter Number B-34668/III.11/TK.01.02/12/2024. The funding body had no role in the design of the study, the collection, analysis, or interpretation of data, or in writing the manuscript.

Declaration of Generative AI in Scientific Writing

Generative AI tools were not used for scientific content, data, analysis, or conclusions. They were used only for language editing and improving grammar and clarity. All text was reviewed and approved by the authors, who take full responsibility for the manuscript.

CRediT author statement

Bima Putra Pratama led the conceptualization, supervision, project administration, funding acquisition, and original draft writing. **Aswin Rafif Khairullah and Imam Mustofa** contributed to conceptualization and draft preparation, with **Imam Mustofa** serving as the corresponding author. **Adeyinka Oye Akintunde and Ilma Fauziah Ma'ruf** developed the methodology and refined the study scope. **Bantari Wisynu Kusuma Wardhani, Andi Thafida Khalisa, and Riza Zainuddin Ahmad** conducted the literature search, data curation, and visualization, with additional support from **Meta Aquarista Galia. Dea Anita Ariani Kurniasih and Arif Nur Muhammad Ansori** performed formal analysis and interpretation. **Mohammad Sukmanadi and Sri Mulyati** were responsible for major revisions, validation, and substantive editing. **Irma Melati and Ulvi Fitri Handayani** contributed to resources and investigation, while **Wita Yulianti** supported visualization and review. **Hanum Masayu Kirna Sari and Syahputra Wibowo** contributed to critical review and editing. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

References

[1] DP Kiouri, E Tsoupra, M Peana, SP Perlepes, ME Stefanidou and CT Chasapis. Multifunctional role of zinc in human health: An update. *EXCLI Journal* 2023; **22(1)**, 809-827.

[2] J Tokarczyk and W Koch. Dietary Zn - recent advances in studies on its bioaccessibility and bioavailability. *Molecules* 2025; **30(13)**, 2742.

[3] M Yan, Y Song, CP Wong, K Hardin and E Ho. Zinc deficiency alters DNA damage response genes in normal human prostate epithelial cells. *Journal of Nutrition* 2008; **138(4)**, 667-673.

[4] RS MacDonald. The role of zinc in growth and cell proliferation. *Journal of Nutrition* 2000; **130(5)**, 1500S-1508S.

[5] PH Lin, M Sermersheim, H Li, PHU Lee, SM Steinberg and J Ma. Zinc in wound healing modulation. *Nutrients* 2017; **10(1)**, 16.

[6] I Wessels, M Maywald and L Rink. Zinc as a gatekeeper of immune function. *Nutrients* 2017; **9(12)**, 1286.

[7] BW Chaffee and JC King. Effect of zinc supplementation on pregnancy and infant outcomes: A systematic review. *Paediatric and Perinatal Epidemiology* 2012; **26(S1)**, 118-137.

[8] F Padoan, E Piccoli, A Pietrobelli, LA Moreno, G Piacentini and L Pecoraro. The role of zinc in developed countries in pediatric patients: A 360-degree view. *Biomolecules* 2024; **14(6)**, 718.

[9] R Kawade. Zinc status and its association with the health of adolescents: A review of studies in India. *Global Health Action* 2012; **5(1)**, 7353.

[10] DD Marreiro, KJ Cruz, JB Morais, JB Beserra, JS Severo and AR de Oliveira. Zinc and oxidative stress: Current Mechanisms. *Antioxidants* 2017; **6(2)**, 24.

[11] World Health Organization and Food and Agriculture Organization of the United Nations. *Vitamin and mineral requirements in human nutrition.* 2nd ed. WHO, Geneva, Switzerland, 2004.

[12] Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for micronutrients.* National Academies Press, Washington, D.C., United States, 2001.

[13] AG Hall and JC King. The molecular basis for zinc bioavailability. *International Journal of Molecular Sciences* 2023; **24(7)**, 6561.

[14] S Gupta, AKM Brazier and NM Lowe. Zinc deficiency in low- and middle-income countries: Prevalence and approaches for mitigation. *Journal of Human Nutrition and Dietetics* 2020; **33(5)**, 624-643.

[15] T Bellini, M Bustaffa, B Tubino, B Giordano, C Formigoni, E Fueri, F Casabona, B Vanorio, A Pastorino, A Herzum, C Matucci-Cerinic, S Arrigo, G Viglizzo and E Piccotti. Acquired and inherited zinc deficiency-related diseases in children: A case series and a narrative review. *Pediatric Reports* 2024; **16(3)**, 602-617.

[16] MT Schulz and L Rink. Zinc deficiency as possible link between immunosenescence and age-related diseases. *Immun and Ageing* 2025; **22(1)**, 19.

[17] H Schoofs, J Schmit and L Rink. Zinc toxicity: Understanding the limits. *Molecules* 2024; **29(13)**, 3130.

[18] D Skrajnowska and B Bobrowska-Korczak. Role of zinc in immune system and anti-cancer defense mechanisms. *Nutrients* 2019; **11(10)**, 2273.

[19] D Jin, X Wei, Y He, L Zhong, H Lu, J Lan, Y Wei, Z Liu and H Liu. The nutritional roles of zinc for immune system and COVID-19 patients. *Frontiers in Nutrition* 2024; **11(1)**, 1385591.

[20] Z Li, Y Liu, R Wei, VW Yong and M Xue. The important role of zinc in neurological diseases. *Biomolecules* 2022; **13(1)**, 28.

[21] N Roohani, R Hurrell, R Kelishadi and R Schulin. Zinc and its importance for human health: An integrative review. *Journal of Research in Medical Sciences* 2013; **18(2)**, 144-157.

[22] N Bilandžić, M Sedak, M Đokić, I Varenina, BS Kolanović, Đ Božić, M Brstilo and B Šimić. Determination of zinc concentrations in foods of animal origin, fish and shellfish from Croatia and assessment of their contribution to dietary intake. *Journal of Food Composition and Analysis* 2014; **35(2)**, 61-66.

[23] B Shkembi and T Huppertz. Influence of dairy products on bioavailability of zinc from other food products: A review of complementarity at a meal level. *Nutrients* 2021; **13(12)**, 4253.

[24] AA Ranini, AM Ayu, G Anjani, A Syauqy, ER Noer and F Ayustaningwarno. The role of malting in grains and legumes for the development of high-functionality medical foods. *Journal of Agriculture and Food Research* 2025; **22(1)**, 102031.

[25] M Maares and H Haase. A guide to human zinc absorption: General overview and recent advances of *in vitro* intestinal models. *Nutrients* 2020; **12(3)**, 762.

[26] NK Morgan, DV Scholey and EJ Burton. Use of Zn concentration in the gastrointestinal tract as a

measure of phytate susceptibility to the effect of phytase supplementation in broilers. *Poultry Science* 2017; **96(5)**, 1298-1305.

[27] S Abera, W Yohannes and BS Chandravanshi. Effect of processing methods on antinutritional factors (oxalate, phytate, and tannin) and their interaction with minerals (calcium, iron, and zinc) in red, white, and black kidney beans. *International Journal of Analytical Chemistry* 2023; **2023(1)**, 6762027.

[28] E Łuszczki, F Boakye, M Zielińska, K Dereń, A Bartosiewicz, Ł Oleksy and A Stolarczyk. Vegan diet: Nutritional components, implementation, and effects on adults' health. *Frontiers in Nutrition* 2023; **10(1)**, 1294497.

[29] UNS Prakash and K Srinivasan. Enhanced intestinal uptake of iron, zinc and calcium in rats fed pungent spice principles - Piperine, capsaicin and ginger (*Zingiber officinale*). *Journal of Trace Elements in Medicine and Biology* 2013; **27(3)**, 184-90.

[30] B Chen, P Yu, WN Chan, F Xie, Y Zhang, L Liang, KT Leung, KW Lo, J Yu, GMK Tse, W Kang and KF To. Cellular zinc metabolism and zinc signaling: From biological functions to diseases and therapeutic targets. *Signal Transduction and Targeted Therapy* 2024; **9(1)**, 6.

[31] Y Nishito and T Kambe. Zinc transporter 1 (ZNT1) expression on the cell surface is elaborately controlled by cellular zinc levels. *Journal of Biological Chemistry* 2019; **294(43)**, 15686-15697.

[32] Y Wan and B Zhang. The impact of zinc and zinc homeostasis on the intestinal mucosal barrier and intestinal diseases. *Biomolecules* 2022; **12(7)**, 900.

[33] MI Costa, AB Sarmento-Ribeiro and AC Gonçalves. Zinc: From biological functions to therapeutic potential. *International Journal of Molecular Sciences* 2023; **24(5)**, 4822.

[34] T Kambe, A Hashimoto and S Fujimoto. Current understanding of ZIP and ZnT zinc transporters in human health and diseases. *Cellular and Molecular Life Sciences* 2014; **71(17)**, 3281-3295.

[35] AS Prasad and B Bao. Molecular mechanisms of zinc as a pro-antioxidant mediator: Clinical therapeutic implications. *Antioxidants* 2019; **8(6)**, 164.

[36] M Temnik, S Gurin, A Balakin, R Byshovets, O Kalmukova, T Vovk, T Halenova, N Raksha, T Falalyeyeva and O Savchuk. Therapeutic potential of zinc ^{64}Zn aspartate for obesity management: impact on oxidative stress, lipid metabolism, pancreas and liver in high-calorie diet model. *Frontiers in Pharmacology* 2025; **16(1)**, 1543166.

[37] C Andreini and I Bertini. A bioinformatics view of zinc enzymes. *Journal of Inorganic Biochemistry* 2012; **111(1)**, 150-156.

[38] C Tu, L Foster, A Alvarado, R McKenna, DN Silverman and SC Frost. Role of zinc in catalytic activity of carbonic anhydrase IX. *Archives of Biochemistry and Biophysics* 2012; **521(1-2)**, 90-94.

[39] RL Medida, AK Sharma, Y Guo, L Johnston, PE Urriola, A Gomez and M Saqui-Salces. Dietary zinc restriction affects the expression of genes related to immunity and stress response in the small intestine of pigs. *Journal of Nutritional Science* 2022; **11(1)**, e104.

[40] C Bach, W Sherman, J Pallis, P Patra and H Bajwa. Evaluation of novel design strategies for developing zinc finger nucleases tools for treating human diseases. *Biotechnology Research International* 2014; **2014(1)**, 970595.

[41] U Lindert, M Cramer, M Meuli, O Georgiev and W Schaffner. Metal-responsive transcription factor 1 (MTF-1) activity is regulated by a nonconventional nuclear localization signal and a metal-responsive transactivation domain. *Molecular and Cellular Biology* 2009; **29(23)**, 6283-93.

[42] P Xia, S Lian, Y Wu, L Yan, G Quan and G Zhu. Zinc is an important inter-kingdom signal between the host and microbe. *Veterinary Research* 2021; **52(1)**, 39.

[43] G Briassoulis, P Briassoulis, S Ilia, M Miliaraki and E Briassouli. The anti-oxidative, anti-inflammatory, anti-apoptotic, and anti-necroptotic role of zinc in COVID-19 and sepsis. *Antioxidants* 2023; **12(11)**, 1942.

[44] M Jarosz, M Olbert, G Wyszogrodzka, K Młyniec and T Librowski. Antioxidant and anti-inflammatory effects of zinc. Zinc-dependent NF-κB signaling. *Inflammopharmacology* 2017; **25(1)**, 11-24.

[45] J Olechnowicz, A Tinkov, A Skalny and J Suliburska. Zinc status is associated with inflammation, oxidative stress, lipid, and glucose metabolism. *The Journal of Physiological Sciences* 2018; **68(1)**, 19-31.

[46] AH Shankar and AS Prasad. Zinc and immune function: The biological basis of altered resistance to infection. *The American Journal of Clinical Nutrition* 1998; **68(2 Suppl)**, 447S-463S.

[47] M Kandhwal, T Behl, S Singh, N Sharma, S Arora, S Bhatia, A Al-Harrasi, M Sachdeva and S Bungau. Role of matrix metalloproteinase in wound healing. *American Journal of Translational Research* 2022; **14(7)**, 4391-4405.

[48] RB Saper and R Rash. Zinc: An essential micronutrient. *American Family Physician* 2009; **79(9)**, 768-772.

[49] FT Wieringa, MA Dijkhuizen, M Fiorentino, A Laillou and J Berger. Determination of zinc status in humans: Which indicator should we use? *Nutrients* 2015; **7(5)**, 3252-3263.

[50] LI Stiles, K Ferrao and KJ Mehta. Role of zinc in health and disease. *Clinical and Experimental Medicine* 2024; **24(1)**, 38.

[51] AS Prasad. Discovery of human zinc deficiency: Its impact on human health and disease. *Advances in Nutrition* 2013; **4(2)**, 176-190.

[52] M Kubota, S Matsuda, M Matsuda, K Yamamoto and Y Yoshii. Association of serum zinc level with severity of chronic kidney disease in diabetic patients: A cross-sectional study. *BMC Nephrology* 2022; **23(1)**, 407.

[53] P Ranasinghe, S Pigera, P Galappatthy, P Katulanda and GR Constantine. Zinc and diabetes mellitus: Understanding molecular mechanisms and clinical implications. *Daru* 2015; **23(1)**, 44.

[54] J Rivers-Auty, VS Tapia, CS White, MJD Daniels, S Drinkall, PT Kennedy, HG Spence, S Yu, JP Green, C Hoyle, J Cook, A Bradley, AE Mather, R Peters, TC Tzeng, MJ Gordon, JH Beattie, D Brough and CB Lawrence. Zinc status alters Alzheimer's disease progression through NLRP3-dependent inflammation. *Journal of Neuroscience* 2021; **41(13)**, 3025-3038.

[55] JW Kim, MS Byun, D Yi, JH Lee, MJ Kim, G Jung, JY Lee, KM Kang, CH Sohn, YS Lee, YK Kim, DY Lee and KBASE Research Group. Serum zinc levels and *in vivo* beta-amyloid deposition in the human brain. *Alzheimer's Research & Therapy* 2021; **13(1)**, 190.

[56] G Lyubartseva and MA Lovell. A potential role for zinc alterations in the pathogenesis of Alzheimer's disease. *Biofactors* 2012; **38(2)**, 98-106.

[57] NZ Gammoh and L Rink. Zinc in infection and inflammation. *Nutrients* 2017; **9(6)**, 624.

[58] JC King, KH Brown, RS Gibson, NF Krebs, NM Lowe, JH Siekmann and DJ Raiten. Biomarkers of nutrition for development (BOND) - zinc review. *Journal of Nutrition* 2015; **146(4)**, 858S-885S.

[59] H Schoofs, J Schmit and L Rink. Zinc toxicity: Understanding the limits. *Molecules* 2024; **29(13)**, 3130.

[60] A Stefanache, II Lungu, IA Butnariu, G Calin, C Gutu, C Marcu, C Grierosu, ERB Goroftei, LD Duceac, MG Dabija, F Popa and D Damir. Understanding how minerals contribute to optimal immune function. *Journal of Immunology Research* 2023; **2023(1)**, 3355733.

[61] E Mocchegiani and M Malavolta. Zinc-gene interaction related to inflammatory/immune response in ageing. *Genes and Nutrition* 2008; **3(2)**, 61-75.

[62] M Maywald and L Rink. Zinc in human health and infectious diseases. *Biomolecules* 2022; **12(12)**, 1748.

[63] E Scarpellini, LM Balsiger, V Maurizi, E Rinninella, A Gasbarrini, N Giostra, P Santori, L Abenavoli and C Rasetti. Zinc and gut microbiota in health and gastrointestinal disease under the COVID-19 suggestion. *Biofactors* 2022; **48(2)**, 294-306.

[64] H Gao, W Dai, L Zhao, J Min and F Wang. The role of zinc and zinc homeostasis in macrophage function. *Journal of Immunology Research* 2018; **2018(1)**, 6872621.

[65] T Kido, K Ishiwata, M Suka and H Yanagisawa. Inflammatory response under zinc deficiency is

exacerbated by dysfunction of the T helper type 2 lymphocyte-M2 macrophage pathway. *Immunology* 2019; **156(4)**, 356-372.

[66] CM Sergi. The role of zinc in the T-cell metabolism in infection requires further investigation - an opinion. *Frontiers in Immunology* 2022; **13(1)**, 865504.

[67] D Jin, X Wei, Y He, L Zhong, H Lu, J Lan, Y Wei, Z Liu and H Liu. The nutritional roles of zinc for immune system and COVID-19 patients. *Frontiers in Nutrition* 2024; **11(1)**, 1385591.

[68] AF Gombart, A Pierre and S Maggini. A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. *Nutrients* 2020; **12(1)**, 236.

[69] M Foster and S Samman. Zinc and regulation of inflammatory cytokines: Implications for cardiometabolic disease. *Nutrients* 2012; **4(7)**, 676-694.

[70] AA Oyagbemi, TO Ajibade, YG Aboua, IT Gbadamosi, ADA Adedapo, AO Aro, OA Adejumobi, E Thamahane-Katengua, TO Omobowale, OO Falayi, TO Oyagbemi, BS Ogunpolu, FO Hassan, IO Ogunmiluyi, OE Ola-Davies, AB Saba, AA Adedapo, SM Nkadimeng, LJ McGaw, …, MA Yakubu. Potential health benefits of zinc supplementation for the management of COVID-19 pandemic. *Journal of Food Biochemistry* 2021; **45(2)**, e13604.

[71] A Sanna, D Firinu, P Zavattari and P Valera. Zinc status and autoimmunity: A systematic review and meta-analysis. *Nutrients* 2018; **10(1)**, 68.

[72] EM Pedro, LF da Rosa Franchi Santos, BM Scavuzzi, TMV Iriyoda, TS Peixe, MAB Lozovoy, EMV Reiche, I Dichi, ANC Simão and MJ Santos. Trace elements associated with systemic lupus erythematosus and insulin resistance. *Biological Trace Element Research* 2019; **191(1)**, 34-44.

[73] S Siva, DT Rubin, G Gulotta, K Wroblewski and J Pekow. Zinc deficiency is associated with poor clinical outcomes in patients with inflammatory bowel disease. *Inflammatory Bowel Disease* 2017; **23(1)**, 152-157.

[74] A Mierzecki, D Strecker and K Radomska. A pilot study on zinc levels in patients with rheumatoid arthritis. *Biological Trace Element Research* 2011; **143(2)**, 854-862.

[75] AS Prasad. Zinc in human health: Effect of zinc on immune cells. *Molecular Medicine* 2008; **14(5-6)**, 353-357.

[76] AV Skalny, L Rink, OP Ajsuvakova, M Aschner, VA Gritsenko, SI Alekseenko, AA Svistunov, D Petrakis, DA Spandidos, J Aaseth, A Tsatsakis and AA Tinkov. Zinc and respiratory tract infections: Perspectives for COVID-19 (Review). *International Journal of Molecular Medicine* 2020; **46(1)**, 17-26.

[77] MA Barffour, GM Hinnouho, KR Wessells, S Kounnavong, K Ratsavong, D Sitthideth, B Bounheuang, K Sengnam, B Chanhthavong, CD Arnold, KH Brown, CP Larson and SY Hess. Effects of therapeutic zinc supplementation for diarrhea and 2 preventive zinc supplementation regimens on the incidence and duration of diarrhea and acute respiratory tract infections in rural Laotian children: A randomized controlled trial. *Journal of Global Health* 2020; **10(1)**, 010424.

[78] T Sakulchit and RD Goldman. Zinc supplementation for pediatric pneumonia. *Canadian Family Physician* 2017; **63(10)**, 763-765.

[79] SA Read, S Obeid, C Ahlenstiel and G Ahlenstiel. The role of zinc in antiviral immunity. *Advances in Nutrition* 2019; **10(4)**, 696-710.

[80] S Kumar, S Ansari, S Narayanan, CT Ranjith-Kumar and M Surjit. Antiviral activity of zinc against hepatitis viruses: current status and future prospects. *Frontiers in Microbiology* 2023; **14(1)**, 1218654.

[81] V Chinni, J El-Khoury, M Perera, R Bellomo, D Jones, D Bolton, J Ischia and O Patel. Zinc supplementation as an adjunct therapy for COVID-19: Challenges and opportunities. *British Journal of Clinical Pharmacology* 2021; **87(10)**, 3737-3746.

[82] D Hulisz. Efficacy of zinc against common cold viruses: An overview. *Journal of the American Pharmacists Association* 2004; **44(5)**, 594-603.

[83] D Jothimani, E Kailasam, S Danielraj, B Nallathambi, H Ramachandran, P Sekar, S Manoharan, V Ramani, G Narasimhan, I

Kaliamoorthy and M Rela. COVID-19: Poor outcomes in patients with zinc deficiency. *International Journal of Infectious Diseases* 2020; **100(1)**, 343-349.

[84] V Perestiuk, T Kosovska, L Volianska and O Boyarchuk. Association of zinc deficiency and clinical symptoms, inflammatory markers, severity of COVID-19 in hospitalized children. *Frontiers in Nutrition* 2025; **12(1)**, 1566505.

[85] GI Alhajjaji, N Alotaibi, N Abutaleb, MM Alotaibi, A Alhajjaji, AS Alotaibi, B Alshehail and ME Alotaibi. Effect of zinc supplementation on symptom reduction and length of hospital stay among pediatric patients with Coronavirus disease 2019 (COVID-19). *Saudi Pharmaceutical Journal* 2023; **31(4)**, 585-591.

[86] KY Chen, CK Lin and NH Chen. Effects of vitamin D and zinc deficiency in acute and long COVID syndrome. *Journal of Trace Elements in Medicine and Biology* 2023; **80(1)**, 127278.

[87] AS Prasad, A Malysa, G Bepler, A Fribley and B Bao. The mechanisms of zinc action as a potent anti-viral agent: The clinical therapeutic implication in COVID-19. *Antioxidants* 2022; **11(10)**, 1862.

[88] JP Mossink. Zinc as nutritional intervention and prevention measure for COVID-19 disease. *BMJ Nutrition, Prevention and Health* 2020; **3(1)**, 111-117.

[89] D Kumari, S Garg and P Bhawrani. Zinc homeostasis in immunity and its association with preterm births. *Scandinavian Journal of Immunology* 2022; **95(4)**, e13142.

[90] S Vickram, K Rohini, S Srinivasan, DN Veenakumari, K Archana, K Anbarasu, P Jeyanthi, S Thanigaivel, G Gulothungan, N Rajendiran and PS Srikumar. Role of zinc (Zn) in human reproduction: A journey from initial spermatogenesis to childbirth. *International Journal of Molecular Sciences* 2021; **22(4)**, 2188.

[91] TB Garner, JM Hester, A Carothers and FJ Diaz. Role of zinc in female reproduction. *Biology of Reproduction* 2021; **104(5)**, 976-994.

[92] A Imdad, J Rogner, RN Sherwani, J Sidhu, A Regan, MR Haykal, O Tsistinas, A Smith, XHS Chan, E Mayo-Wilson and ZA Bhutta. Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years. *Cochrane Database of Systematic Reviews* 2023; **3(3)**, CD009384.

[93] CX Alves, SH Vale, MM Dantas, AA Maia, MC Franca, JS Marchini, LD Leite and J Brandao-Neto. Positive effects of zinc supplementation on growth, GH, IGF1, and IGFBP3 in eutrophic children. *Journal of Pediatric Endocrinology and Metabolism* 2012; **25(9-10)**, 881-887.

[94] JP O'Connor, D Kanjilal, M Teitelbaum, SS Lin and JA Cottrell. Zinc as a therapeutic agent in bone regeneration. *Materials* 2020; **13(10)**, 2211.

[95] JM Cho, JY Kim and HR Yang. Effects of oral zinc supplementation on zinc status and catch-up growth during the first 2 years of life in children with non-organic failure to thrive born preterm and at term. *Pediatrics and Neonatology* 2019; **60(2)**, 201-209.

[96] E Liu, L Pimpin, M Shulkin, S Kranz, CP Duggan, D Mozaffarian and WW Fawzi. Effect of zinc supplementation on growth outcomes in children under 5 years of age. *Nutrients* 2018; **10(3)**, 377.

[97] MF Escobedo-Monge, G Ayala-Macedo, G Sakihara, S Peralta, A Almaraz-Gómez, E Barrado and JM Marugán-Miguelsanz. Effects of zinc supplementation on nutritional status in children with chronic kidney disease: A randomized trial. *Nutrients* 2019; **11(11)**, 2671.

[98] GF Ahmad, HS Ahmed and ES Abbas. Systematic review and meta-analysis of zinc supplementation and stunting in children under 5 years of age. *Bulletin of the National Nutrition Institute of the Arab Republic of Egypt* 2022; **59(1)**, 55-83.

[99] ZS Lassi, A Moin and ZA Bhutta. Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months. *Cochrane Database of Systematic Reviews* 2016; **12(12)**, CD005978.

[100] CP Wong, LM Beaver and E Ho. Protective role of dietary zinc on DNA damage, oxidative stress, and metal toxicity. *Frontiers in Molecular Biosciences* 2025; **12(1)**, 1618318.

[101] SS Ballestín, MIG Campos, JB Ballestín and MJL Bartolomé. Is supplementation with

micronutrients still necessary during pregnancy? A review. *Nutrients* 2021; **13(9)**, 3134.

[102] B Carducci, EC Keats and ZA Bhutta. Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database of Systematic Reviews* 2021; **3(3)**, CD000230.

[103] KC Kadosh, L Muhardi, P Parikh, M Basso, HJJ Mohamed, T Prawitasari, F Samuel, G Ma and JM Geurts. Nutritional support of neurodevelopment and cognitive function in infants and young children-an update and novel insights. *Nutrients* 2021; **13(1)**, 199.

[104] D Shah and HP Sachdev. Zinc deficiency in pregnancy and fetal outcome. *Nutrition Reviews* 2006; **64(1)**, 15-30.

[105] H Akbari, L Elyasi, AA Khaleghi and M Mohammadi. The effect of zinc supplementation on improving sperm parameters in infertile diabetic men. *The Journal of Obstetrics and Gynecology of India* 2023; **73(4)**, 316-321.

[106] A Kaltsas. Oxidative stress and male infertility: The protective role of antioxidants. *Medicina* 2023; **59(10)**, 1769.

[107] A Fallah, A Mohammad-Hasani and AH Colagar. Zinc is an essential element for male fertility: A review of Zn roles in men's health, germination, sperm quality, and fertilization. *Journal of Reproduction and Infertility* 2018; **19(2)**, 69-81.

[108] M Nasiadek, J Stragierowicz, M Klimczak and A Kilanowicz. The role of zinc in selected female reproductive system disorders. *Nutrients* 2020; **12(8)**, 2464.

[109] WJ Liu, LS Li, MF Lan, JZ Shang, JX Zhang, WJ Xiong, XL Lai and X Duan. Zinc deficiency deteriorates ovarian follicle development and function by inhibiting mitochondrial function. *Journal of Ovarian Research* 2024; **17(1)**, 115.

[110] LK Wooldridge, ME Nardi and AD Ealy. Zinc supplementation during *in vitro* embryo culture increases inner cell mass and total cell numbers in bovine blastocysts. *Journal of Animal Science* 2019; **97(12)**, 4946-4950.

[111] SD Gower-Winter and CW Levenson. Zinc in the central nervous system: From molecules to behavior. *Biofactors* 2012; **38(3)**, 186-193.

[112] B Szewczyk. Zinc homeostasis and neurodegenerative disorders. *Frontiers in Aging Neuroscience* 2013; **5(1)**, 33.

[113] SD Portbury and PA Adlard. Zinc signal in brain diseases. *International Journal of Molecular Sciences* 2017; **18(12)**, 2506.

[114] LJ Blakemore and PQ Trombley. Zinc as a neuromodulator in the central nervous system with a focus on the olfactory bulb. *Frontiers in Cellular Neuroscience* 2017; **11(1)**, 297.

[115] LJ Blakemore and PQ Trombley. Mechanisms of zinc modulation of olfactory bulb AMPA receptors. *Neuroscience* 2019; **410(1)**, 160-175.

[116] C Gao, J Jiang, Y Tan and S Chen. Microglia in neurodegenerative diseases: Mechanism and potential therapeutic targets. *Signal Transduction and Targeted Therapy* 2023; **8(1)**, 359.

[117] S Sadigh-Eteghad, B Sabermarouf, A Majdi, M Talebi, M Farhoudi and J Mahmoudi. Amyloid-beta: A crucial factor in Alzheimer's disease. *Medical Principles and Practice* 2015; **24(1)**, 1-10.

[118] N Rezaei-Ghaleh, K Giller, S Becker and M Zweckstetter. Effect of zinc binding on β-amyloid structure and dynamics: Implications for Aβ aggregation. *Biophysical Journal* 2011; **101(5)**, 1202-1211.

[119] B Wang, T Fang and H Chen. Zinc and central nervous system disorders. *Nutrients* 2023; **15(9)**, 2140.

[120] M Rychlik and K Mlyniec. Zinc-mediated neurotransmission in alzheimer's disease: A potential role of the GPR39 in dementia. *Current Neuropharmacology* 2020; **18(1)**, 2-13.

[121] M Gómez-Benito, N Granado, P García-Sanz, A Michel, M Dumoulin and R Moratalla. Modeling parkinson's disease with the alpha-synuclein protein. *Frontiers in Pharmacology* 2020; **11(1)**, 356.

[122] SP Banik, D Bagchi, P Banerjee, S Chakraborty, M Bagchi, C Bose, D De, S Saha and S Chakraborty. Subtle concentration changes in zinc hold the key to fibrillation of α-synuclein: An updated insight on the micronutrient's role in prevention of neurodegenerative disorders. *Frontiers in Molecular Biosciences* 2025; **12(1)**, 1603364.

[123] HC Kung, KJ Lin, CT Kung and TK Lin. Oxidative stress, mitochondrial dysfunction, and neuroprotection of polyphenols with respect to resveratrol in Parkinson's disease. *Biomedicines* 2021; **9(8)**, 918.

[124] S Fakorede, OM Lateef, WA Garuba, PO Akosile, DA Okon and AT Aborode. Dual impact of neuroinflammation on cognitive and motor impairments in Alzheimer's disease. *Journal of Alzheimer's Disease Reports* 2025. https://doi.org/10.1177/25424823251341870

[125] K Wojtunik-Kulesza, A Oniszczuk and M Waksmundzka-Hajnos. An attempt to elucidate the role of iron and zinc ions in development of Alzheimer's and Parkinson's diseases. *Biomedicine & Pharmacotherapy* 2019; **111(1)**, 1277-1289.

[126] AS Correia, A Cardoso and N Vale. Oxidative stress in depression: The link with the stress response, neuroinflammation, serotonin, neurogenesis and synaptic plasticity. *Antioxidants* 2023; **12(2)**, 470.

[127] AH Abdelmoneam, GM Khafagy, KA Elbeh and MDA Hasan. The inverse correlation between serum zinc levels and depression severity in Egyptian adolescent students: A case-control study. *The Egyptian Journal of Neurology, Psychiatry and Neurosurgery* 2024; **60(1)**, 139.

[128] B Iring-Varga, M Baranyi, F Gölöncsér, P Tod and B Sperlágh. The antidepressant effect of short- and long-term zinc exposition is partly mediated by P2X7 receptors in male mice. *Frontiers in Pharmacology* 2023; **14(1)**, 1241406.

[129] E Ranjbar, MS Kasaei, M Mohammad-Shirazi, J Nasrollahzadeh, B Rashidkhani, J Shams, SA Mostafavi and MR Mohammadi. Effects of zinc supplementation in patients with major depression: A randomized clinical trial. *Iranian Journal of Psychiatry* 2013; **8(2)**, 73-79.

[130] H Tendilla-Beltrán, P Aguilar-Alonso, CA Hernández-González, E Baltazar-Gaytán, AA Orduña, H Nicolini, F García-Dolores and G Flores. Dysregulated zinc homeostasis and microadenomas in the anterior pituitary: Pathological insights into suicide risk. *Frontiers in Psychiatry* 2024; **15(1)**, 1446255.

[131] C Franco and LMT Canzoniero. Zinc homeostasis and redox alterations in obesity. *Frontiers in Endocrinology* 2024; **14(1)**, 1273177.

[132] H Zhang and L Cai. Zinc homeostasis plays an important role in the prevention of obesity-induced cardiac inflammation, remodeling and dysfunction. *Journal of Trace Elements in Medicine and Biology* 2020; **62(1)**, 126615.

[133] Y Tamura. The role of zinc homeostasis in the prevention of diabetes mellitus and cardiovascular diseases. *Journal of Atherosclerosis and Thrombosis* 2021; **28(11)**, 1109-1122.

[134] U Galicia-Garcia, A Benito-Vicente, S Jebari, A Larrea-Sebal, H Siddiqi, KB Uribe, H Ostolaza and C Martín. Pathophysiology of type 2 diabetes mellitus. *International Journal of Molecular Sciences* 2020; **21(17)**, 6275.

[135] K Lemaire, F Chimienti and F Schuit. Zinc transporters and their role in the pancreatic β-cell. *Journal of Diabetes Investigation* 2012; **3(3)**, 202-211.

[136] X Tang and NF Shay. Zinc has an insulin-like effect on glucose transport mediated by phosphoinositol-3-kinase and Akt in 3T3-L1 fibroblasts and adipocytes. *The Journal of Nutrition* 2001; **131(5)**, 1414-1420.

[137] R Ahmad, R Shaju, A Atfi and MS Razzaque. Zinc and diabetes: A connection between micronutrient and metabolism. *Cells* 2024; **13(16)**, 1359.

[138] GS Chhina, A Chhabra, SR Luthra, S Khattar, P Singh and S Luthra. Effect of zinc supplementation on glycemic control in newly diagnosed patients with type 2 diabetes mellitus. *Cureus* 2024; **16(9)**, e69180.

[139] R El Dib, OL Gameiro, MS Ogata, NS Módolo, LG Braz, EC Jorge, P do Nascimento and V Beletate. Zinc supplementation for the prevention of type 2 diabetes mellitus in adults with insulin resistance. *Cochrane Database of Systematic Reviews* 2015; **2015(5)**, CD005525.

[140] W Frąk, A Wojtasińska, W Lisińska, E Młynarska, B Franczyk and J Rysz. Pathophysiology of cardiovascular diseases: New insights into molecular mechanisms of

atherosclerosis, arterial hypertension, and coronary artery disease. *Biomedicines* 2022; **10(8)**, 1938.

[141] M Gholizadeh, SAG Saeedy, PB Roodi and A Saedisomeolia. The association between zinc and endothelial adhesion molecules ICAMs and VCAM-1 and nuclear receptors PPAR-α and PPAR-γ: A systematic review on cell culture, animal and human studies. *Microvascular Research* 2021; **138(1)**, 104217.

[142] AH Betrie, JA Brock, OF Harraz, AI Bush, GW He, MT Nelson, JA Angus, CE Wright and S Ayton. Zinc drives vasorelaxation by acting in sensory nerves, endothelium and smooth muscle. *Nature Communications* 2021; **12(1)**, 3296.

[143] AA Ahangar, P Saadat, S Niroomand, S Alijanpour, R Sohrabnezhad, A Firozejahi, MA Biani, F Arab, H Hosseinzadeh, S Faraji and J Niroomand. Increased zinc serum level: New clues in babol stroke patients, Northern Iran. *Stroke Research and Treatment* 2018; **2018(1)**, 7681682.

[144] T Tsuruoka, A Kodama, S Yamaguchi, T Masutomi, A Koyama, T Murohara, K Komori and R Shibata. Zinc deficiency impairs ischemia-induced angiogenesis. *JVS-Vascular Science* 2021; **3(1)**, 30-40.

[145] J Kim. Dietary zinc intake is inversely associated with systolic blood pressure in young obese women. *Nutrition Research and Practice* 2013; **7(5)**, 380-384.

[146] S Nakatani, K Mori, T Shoji and M Emoto. Association of zinc deficiency with development of CVD events in patients with CKD. *Nutrients* 2021; **13(5)**, 1680.

[147] M Banaszak, I Górna and J Przysławski. Zinc and the innovative zinc-α2-glycoprotein adipokine play an important role in lipid metabolism: A critical review. *Nutrients* 2021; **13(6)**, 2023.

[148] N Li, X Li, Y Ding, X Liu, K Diggle, T Kisseleva and DA Brenner. SREBP regulation of lipid metabolism in liver disease, and therapeutic strategies. *Biomedicines* 2023; **11(12)**, 3280.

[149] Y Li, Y Pan, X Zhao, S Wu, F Li, Y Wang, B Liu, Y Zhang, X Gao, Y Wang and H Zhou. Peroxisome proliferator-activated receptors: A key link between lipid metabolism and cancer progression. *Clinical Nutrition* 2024; **43(2)**, 332-345.

[150] S Younes. The role of micronutrients on the treatment of diabetes. *Human Nutrition & Metabolism* 2024; **35(1)**, 200238.

[151] Age-Related Eye Disease Study Research Group. The effect of 5-year zinc supplementation on serum zinc, serum cholesterol and hematocrit in persons randomly assigned to treatment group in the age-related eye disease study: AREDS Report No. 7. *Journal of Nutrition* 2002; **132(4)**, 697-702.

[152] J Roozbeh, P Hedayati, MM Sagheb, M Sharifian, AH Jahromi, S Shaabani, H Jalaeian, GA Raeisjalali and S Behzadi. Effect of zinc supplementation on triglyceride, cholesterol, LDL, and HDL levels in zinc-deficient hemodialysis patients. *Renal Failure* 2009; **31(9)**, 798-801.

[153] M Ceballos-Rasgado, NM Lowe, S Mallard, A Clegg, VH Moran, C Harris, J Montez and M Xipsiti. Adverse effects of excessive zinc intake in infants and children aged 0-3 years: A systematic review and meta-analysis. *Advances in Nutrition* 2022; **13(6)**, 2488-2518.

[154] AM Uwitonze, N Ojeh, J Murererehe, A Atfi and MS Razzaque. Zinc adequacy is essential for the maintenance of optimal oral health. *Nutrients* 2020; **12(4)**, 949.

[155] M Foster, P Petocz and S Samman. Effects of zinc on plasma lipoprotein cholesterol concentrations in humans: A meta-analysis of randomised controlled trials. *Atherosclerosis* 2010; **210(2)**, 344-352.

[156] RG Barber, ZA Grenier and JL Burkhead. Copper toxicity is not just oxidative damage: Zinc systems and insight from Wilson disease. *Biomedicines* 2021; **9(3)**, 316.

[157] A Krężel and W Maret. The functions of metamorphic metallothioneins in zinc and copper metabolism. *International Journal of Molecular Sciences* 2017; **18(6)**, 1237.

[158] N Chun, S Aman, D Xu, J Wang, C Zuppan and A Kheradpour. Anemia due to unexpected zinc-induced copper deficiency. *Hematology Reports* 2025; **17(4)**, 35.

[159] C Doguer, JH Ha and JF Collins. Intersection of iron and copper metabolism in the mammalian intestine and liver. *Comprehensive Physiology* 2018; **8(4)**, 1433-1461.

[160] A Takahashi. Role of zinc and copper in erythropoiesis in patients on hemodialysis. *Journal of Renal Nutrition* 2022; **32(6)**, 650-657.

[161] NU Stoffel, HK von Siebenthal, D Moretti and MB Zimmermann. Oral iron supplementation in iron-deficient women: How much and how often? *Molecular Aspects of Medicine* 2020; **75(1)**, 100865.

[162] IR Gunanti, A Al-Mamun, L Schubert and KZ Long. The effect of zinc supplementation on body composition and hormone levels related to adiposity among children: A systematic review. *Public Health Nutrition* 2016; **19(16)**, 2924-2939.

[163] K Eljaaly, A Helal, T Almandeel, R Algarni and S Alshehri. Multivalent cations interactions with fluoroquinolones or tetracyclines: A cross-sectional study. *Saudi Journal of Biological Sciences* 2021; **28(12)**, 6929-6932.

[164] J Suliburska, K Skrypnik, M Szulińska, J Kupsz, L Markuszewski and P Bogdański. Diuretics, Ca-antagonists, and angiotensin-converting enzyme inhibitors affect zinc status in hypertensive patients on monotherapy: A randomized trial. *Nutrients* 2018; **10(9)**, 1284.

[165] AT Jan, M Azam, K Siddiqui, A Ali, I Choi and QMR Haq. Heavy metals and human health: Mechanistic insight into toxicity and counter defense system of antioxidants. *International Journal of Molecular Sciences* 2015; **16(12)**, 29592-29630.

[166] LA Braun and F Rosenfeldt. Pharmaco-nutrient interactions - a systematic review of zinc and antihypertensive therapy. *International Journal of Clinical Practice* 2013; **67(8)**, 717-725.

[167] MX Wang, SS Win and J Pang. Zinc supplementation reduces common cold duration among healthy adults: A systematic review of randomized controlled trials with micronutrients supplementation. *American Journal of Tropical Medicine and Hygiene* 2020; **103(1)**, 86-99.

[168] KJ Day, MM Adamski, AL Dordevic and C Murgia. Genetic variations as modifying factors to dietary zinc requirements - a systematic review. *Nutrients* 2017; **9(2)**, 148.

[169] NM Lowe, AG Hall, MR Broadley, J Foley, E Boy and ZA Bhutta. Preventing and controlling zinc deficiency across the life course: A call to action. *Advances in Nutrition* 2024; **15(3)**, 100181.

[170] Z Pan, S Choi, H Ouadid-Ahidouch, JM Yang, JH Beattie and I Korichneva. Zinc transporters and dysregulated channels in cancers. *Frontiers in Bioscience* 2017; **22(4)**, 623-643.

[171] MC Carpenter, MN Lo and AE Palmer. Techniques for measuring cellular zinc. *Archives of Biochemistry and Biophysics* 2016; **611(1)**, 20-29.

[172] E Mocchegiani, J Romeo, M Malavolta, L Costarelli, R Giacconi, LE Diaz and A Marcos. Zinc: Dietary intake and impact of supplementation on immune function in elderly. *Age* 2013; **35(3)**, 839-860.

[173] R Sharif, P Thomas, P Zalewski and M Fenech. The role of zinc in genomic stability. *Mutation Research* 2012; **733(1-2)**, 111-121.