SELF-EMULSIFYING

IMMUNE CHARGE+® ZINC IONOPHORE

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Immune Charge+® Zinc Ionophore contains the essential mineral zinc complexed with the flavonoids quercetin, luteolin, hesperetin, and propolis, designed to support effective cellular uptake of zinc for healthy immune function.

Supplement Facts

Serving Size: 2 Capsules Servings Per Container: 30	Amount Per Serving	% Daily Value
Zinc (as Zinc Acetate)	10mg	91%
Proprietary Zinc Complex Propolis extract, Zinc acetate, Quercetin Dihydrate (from Sophora japonica flower), Luteolin extract, Hesperetin extract	150mg	**

**Daily Value not established

Other Ingredients: Plant-derived cellulose capsule, tocofersolan, medium chain triglycerides, natural mint oil, turmeric oil, phospholipids (from sunflower seed lecithin)

EDUCATION

THE ROLE OF ZINC IN WHOLE-BODY HEALTH BEGINS AT THE CELLULAR LEVEL

Zinc is an essential micronutrient that plays a critical role in numerous physiological processes throughout the body. Zinc is required for the activity of over 300 enzymes, including all six classes of enzymes, including transferases, hydrolases, oxidoreductases, lyases, isomerases and ligases.1 Zinc is also a cofactor for over 50 metalloenzymes, including the alcohol dehydrogenase (ADH) enzyme involved in alcohol detoxification and superoxide dismutase, an enzyme that neutralizes harmful free radicals.[1]

Zinc also aids in the structural maintenance of proteins, including the metallothioneins, small cysteine-rich proteins involved in metal ion homeostasis, the cellular defense against oxidative stress, and heavy metal detoxification.[2]

Zinc also influences gene expression as an intrinsic component of the "zinc finger" proteins involved in an array of molecular functions ranging from the regulation of gene expression to acting as cellular receptors for estrogens, thyroid hormones, vitamin D, and vitamin A.[3]

Through its far-reaching impact on enzymatic activity, protein maintenance, and immune function, zinc mediates whole-body health. For zinc to exert its beneficial systemic health effects, it must first be absorbed from dietary sources and then taken up into cells. However, zinc absorption and entry into cells is tightly regulated, a phenomenon that limits the potential for therapeutic zinc dosing strategies. Zinc ionophores represent an elegant solution to this problem by rapidly enhancing cellular delivery of zinc throughout the body.

THE SCIENCE OF ZINC IONOPHORES

Within cells, most zinc cations are bound to proteins due to their roles as cofactors in enzymatic activity, structural protein maintenance, and gene expression, as mentioned above. A minority of zinc is available as free, or "labile," zinc, present in its free ionic form or loosely bound to proteins. Labile zinc acts as a second messenger molecule, modulating numerous signaling pathways, including those involved in immune function.

Mammalian cells contain an array of zinc transporters from the Znt and ZIP transporter "families" that transport zinc from the extracellular milieu into the cell itself. However, higher doses of zinc decrease zinc uptake from the gut lumen into

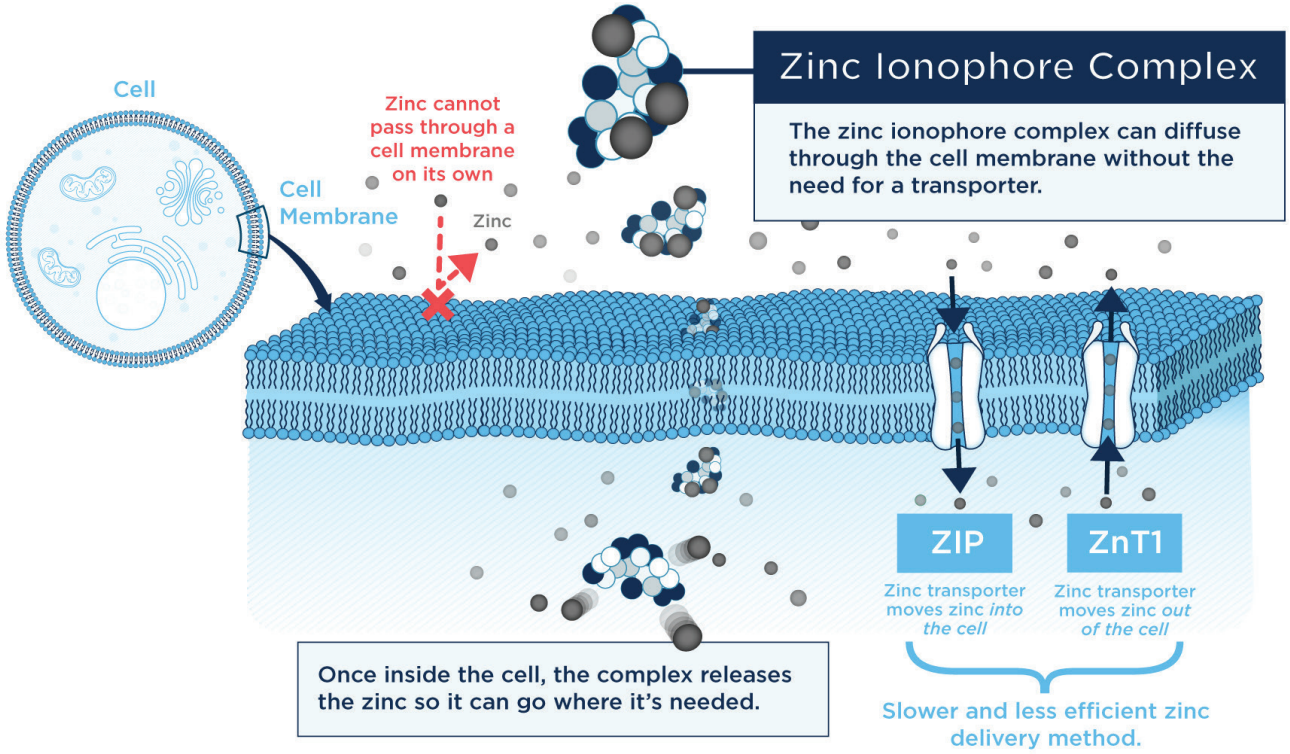
systemic circulation, limiting the utility of therapeutic zinc dosing strategies when zinc is delivered through traditional oral supplements. Zinc ionophores are a sophisticated solution to the bioavailability problem posed by zinc transporters.

Zinc ionophores are chemical compounds that reversibly bind zinc ions, transporting zinc across cell membranes independently of zinc transporters. Several natural substances function as zinc ionophores. Quercetin, a plant flavonoid found in onions, green tea, apples, and berries, demonstrates remarkable zinc ionophore activity. It chelates zinc cations, facilitating their transport across lipid membranes and enhancing intracellular zinc levels.[4] While quercetin enhances total zinc levels inside cells, it also inhibits zinc toxicity, maintaining optimal intracellular levels of this vital micronutrient.[5]

Quercetin also demonstrates beneficial effects independent of its role as a zinc ionophore. It exerts antiviral activity and balances immune function, dampening unproductive immune responses.[6,7] It also promotes glucose uptake into cells, thereby improving glucose homeostasis, through activation of the AMPK pathway.[8] Complexation of quercetin with zinc in zinc ionophores enhances quercetin bioavailability, allowing greater amounts of the beneficial polyphenol to enter cells.

Luteolin is a flavonoid found in various fruits, vegetables, and medicinal herbs that also demonstrates zinc ionophore activity.[9] Complexation with zinc may increase this flavonoid's bioavailability within cells, where it can exert additional beneficial effects, including direct antiviral, anti-inflammatory, and brain-supportive properties.[10,11]

Hesperetin is a flavonoid found in the peels of citrus fruits, such as oranges and tangerines. Like its flavonoid cousins, quercetin and luteolin, it acts as a zinc ionophore and supports the immune system. Hesperidin, a glycosylated form of hesperetin, interferes with the binding of viral invaders to host cells, enhancing host resilience to infection.[12] The multi-ringed chemical structure of hesperitin is strikingly similar to that of quercetin and may also make it an effective zinc ionophore for enhancing intracellular zinc levels.[13]



ZINC IONOHORES SUPPORT THE IMMUNE SYSTEM

Zinc plays a vital role in the immune system.[14] It is crucial for the normal development of innate white blood cells, which comprise the body's frontline defenses against microbial invaders.[15] Cytokine production is also significantly influenced by zinc availability, with zinc insufficiency compromising cytokine mobilization in response to pathogens.

Zinc also fortifies mucosal immune defenses in the upper respiratory and gastrointestinal tracts by inducing beneficial structural changes in tight junction complexes, the proteins that bind epithelial cells together.[16] These changes strengthen membrane barrier integrity, creating a more robust physical defense barrier against external invaders.[17]

Quercetin provides additional mucosal barrier support by activating AMPK, an evolutionarily conserved pathway that is a central regulator of metabolism, growth, and energy production. AMPK activation is known to regulate the apical junctions and barrier integrity of the intestinal mucosal epithelium. The pharynx (throat) represents the very beginning of

the gastrointestinal tract, and there is reason to believe that AMPK activation may support barrier integrity and immune resilience in this critical location as well.[18]

The body's response to infection involves the production of free radicals. In appropriate amounts, these free radicals effectively target and eliminate pathogens; however, when free radical production exceeds the body's capacity to neutralize these molecules, an unproductive inflammatory response may result, distracting the immune system from the pathogens at hand. Hesperetin counteracts the damaging effects of pathogen-triggered free radical production, allowing the immune system to prioritize infection management.[12]

Pathogens have a more challenging time invading host cells and causing disease when the body's internal terrain is immunologically resilient. Propolis, a resinous mixture produced by honeybees, offers powerful immunomodulatory effects in addition to antibacterial, antiviral, and antifungal properties, improving the resilience of the body's internal terrain.[19,20]

ZINC AND QUERCETIN FORTIFY THE GASTROINTESTINAL TRACT

Approximately 70 percent of the human immune system resides in the gastrointestinal tract, making maintaining a healthy gastrointestinal milieu essential for optimal immune function. Zinc exerts powerful, overlapping effects on immune and gastrointestinal function through its impact on epithelial cells, which comprise the interface between the intestinal lumen, the immune cell-rich mucosal barrier of the gut, and systemic circulation.

Quercetin provides additional support for mucosal barrier integrity by acting as an agonist at aryl hydrocarbon (AhR) receptors in the intestine.[21] Aryl hydrocarbon receptors are transcription factors that link environmental stimuli to cellular responses, including immune responses, within the body. AhR activation defends the respiratory and gut barriers against environmental stressors, such as infectious agents. Since the throat sits at the crossroads of the respiratory and gastrointestinal system, AhR activation may fortify immune defenses in this vital tissue.[22,23]

ZINC SUPPORTS THE BODY'S REDOX SYSTEM

The body's redox system refers to its balance between reactive oxygen species (ROS), reactive nitrogen species (RNS), and scavenging by antioxidant compounds. The cellular redox state influences the immune defense against foreign invaders, brain function, and metabolic health. Emerging research indicates that zinc plays an essential role in maintaining the body's redox system, an effect that may bolster immune function and mitigate inflammation.[24]

ZINC, FLAVONOIDS, AND QUERCETIN ATTENUATE UNPRODUCTIVE INFLAMMATORY SIGNALING

Zinc homeostasis is crucial for regulating the body's inflammatory response.[25] It is truly a "Goldilocks" nutrient; either too little or too much zinc can pose a problem for regulating the body's inflammatory balance. Pairing zinc with flavonoids may help the body maintain a "just right" level of zinc required for a healthy inflammatory balance by delivering zinc to cells' interior while helping to prevent zinc toxicity.

Quercetin induces the expression of antioxidant enzymes that balance inflammatory and anti-inflammatory signaling pathways in the body. It activates the Nrf2 pathway to increase the activity of antioxidant enzymes such as superoxide dismutase (SOD) and inhibiting the pro-inflammatory signaling pathway NF-kappa B. Luteolin suppresses the expression of inflammatory mediators, inhibiting pathogen-triggered respiratory inflammation.[26] It also stabilizes mast cells, which are immune cells implicated in airway reactivity.[27] Propolis may also attenuate inflammasome activation in acute viral infections, inhibiting unproductive signaling while allowing the immune system to efficiently target foreign invaders.[28]

ZINC SUPPORTS METABOLIC HEALTH

Zinc plays several regulatory roles in metabolic health. It stimulates glucose oxidation and supports the activity of insulin, improving glucose homeostasis.[29] Dysfunctional zinc transporter mechanisms are associated with the pathogenesis of metabolic diseases, such as type 2 diabetes.[30] Replenishment of bodily zinc levels with a delivery system that bypasses zinc transporters may be beneficial for correcting zinc insufficiency and supporting healthy glucose homeostasis in individuals heading down a trajectory towards metabolic dysfunction.

ZINC AND FLAVONOIDS PROTECT BRAIN FUNCTION

Zinc regulates neuronal growth and signaling, and a lack of zinc is implicated in decreased neurogenesis and increased neuronal death.[31,32] Supplemental zinc may improve memory and attention in older adults and positively impact aspects of mental health, such as mood.[33,34]

Excitingly, hesperetin also shows promise as a brain-supportive compound. It has been found to attenuate neuroinflammation triggered by pro-inflammatory bacterial byproducts.[35] It may also protect the brain during the aging process by enhancing the generation of neural growth factors and endogenous antioxidant balance in the brain.[36]

ZINC AND HORMONAL BALANCE

Zinc plays several crucial roles in the body's hormonal balance. It is a vital cofactor for the deiodinases, enzymes involved in the synthesis of thyroid hormones.[37] Low zinc intakes can thus adversely impact thyroid function.

Zinc is essential for testosterone synthesis, with zinc supplementation improving testosterone levels in zinc-deficient men.[38] Zinc is also essential for female reproductive hormone balance; it may normalize aromatase activity in women with PCOS, reduce hyperandrogenism symptoms, and improve fertility by attenuating inflammation and oxidative stress.[39]

Supporting optimal bodily levels of zinc may also balance the hypothalamic-pituitary-adrenal (HPA) axis, a complex network of hormones and other signaling molecules that regulate the body's stress response and overall hormone balance.[40] A balanced HPA axis is crucial for healthy thymic function; by supporting hormones, zinc may exert further positive effects on immune function.

SEDS DELIVERY TECHNOLOGY Self-emulsifying delivery systems (SEDS) represent a new frontier in nutraceutical delivery systems. SEDS are formulations of oils and surfactants that quickly dissolve in the stomach upon contact with gastric juices, creating emulsified nanoparticles that quickly diffuse across cellular membranes and enter the bloodstream. SEDS improve the oral absorption of lipophilic ("fat-loving") compounds, including fat-soluble vitamins and phytonutrients, which are notorious for their poor bioavailability. SEDS delivery systems can help overcome significant bioavailability challenges, allowing powerful natural compounds to exert systemic benefits.*

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References available at quicksilverscientific.com/zincionophorereferences

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