Chapter

Role of Zinc and Zinc Ionophores in Brain Health and Depression Especially during the COVID-19 Pandemic

Amr Ahmed, Amr Ghit, Asmaa Houjak and Mahmoud Elkazzaz

Abstract

Zinc is a trace metal ion that has a role in both physiological and pathological processes, making it one of the most common and necessary components involved in brain function. Besides, zinc is required for cell proliferation control in a variety of mechanisms, including hormonal regulation of cell division. Also, zinc serves as a biochemical signal to immune cells and transcription factors involved in the synthesis of inflammatory cytokines. On the other hand, zinc has a variety of crucial roles in neurogenesis and also acts as a neuromodulator on a wide range of membrane receptors, ion channels, and transporters. Zinc is produced by neurons under several conditions to activate microglia. The link between zinc dysregulation and psychiatric disorder was that zinc acts as an inhibitory modulator at the N-methyl-D aspartic acid (NMDA) glutamate receptor. Ionophores are ion carrier molecules that reversibly bind and transport ions through biological membranes. Ionophores can be natural or synthetic products. Zinc ionophores such as quercetin, epigallocatechin gallate (EGCG), hinokitol, and proanthocyanidins have been shown to protect brain health, particularly in depression clinically significant depression and depressive symptoms in post-COVID-19 syndrome may have severe implications as it relates to life outcomes quality, herein according to previous research studies, we showed zinc deficiency as a possible risk factor for depression symptoms, which were commonly observed following severe infection of COVID-19.

Keywords: ionophore, zinc, cytokines, quercetin, EGCG, hinokitol, proanthocyanidins

1. Introduction

Zinc is a trace metal ion that has a role in both physiological and pathological processes, making it one of the most common and necessary components involved in brain function. The cortex, amygdala, olfactory bulb, and hippocampus neurons all carry "free ionic zinc" (Zn^{2+}), which appears to have the largest concentration of zinc in the brain. Zinc is involved in the physiochemical function of enzymes, proteins, and signal transcription factors, as well as the maintenance of numerous homeostatic

systems, functioning as structural, regulatory, and catalytic cofactors for enzymes including DNA and RNA polymerases, histone deacetylases, and DNA ligases. Zinc is also required for cell proliferation and genomic integrity [1–5].

As a neuromodulator, zinc is produced during synaptic transmission and attaches to presynaptic or postsynaptic membrane receptors, allowing it to translocate from presynaptic terminals to postsynaptic neurons [6, 7]. Zinc can be found in glutamatergic neurons' synaptic vesicles. Zinc is therefore liberated from glutamatergic synaptic vesicles and then interacts with excitatory and inhibitory amino acid receptors (N-methyl-D aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and γ-aminobutyric acid (GABA) [8–10]. Because of its actions on numerous voltage-gated ion channels, extracellular Zn^{2+} can modify the excitability of nerve cells [11–13].

Besides, zinc is required for cell proliferation control in a variety of mechanisms, including hormonal regulation of cell division. Also, zinc serves as a biochemical signal to immune cells and transcription factors involved in the synthesis of inflammatory cytokines. Zinc supplementation has been proven in trials to reduce rates of infection and proinflammatory cytokine secretion. Zinc also possesses metal-binding characteristics and is widely recognized for its antioxidant qualities [14, 15]. Zinc deficiency causes apoptosis in neurons via the mitochondrial pathway [16, 17]. Zinc has just lately been discovered to have a role in intracellular signaling as a second messenger. It is also used by immune cells as a molecular signal. Zinc controls a variety of transcription factors that control gene expression and are engaged in the signal transduction of inflammatory cytokines and adhesion molecules. Zinc helps to preserve genomic stability by regulating redox homeostasis, DNA repair, synthesis, and methylation [18, 19].

2. Role of zinc in the brain

2.1 Role of zinc in neurogenesis and synaptic transmission

Zinc has a variety of crucial roles in neurogenesis [4]. Zinc deficiency decreases the neurogenesis process and impairs the expression of genes involved in hippocampus proliferation and neuronal development in the postnatal rat cerebellum [20]. Further, zinc deficiency reduces the proliferation of the human neuroblastoma cell line, promotes apoptosis, and inhibits retinoic-acid-induced neuronal development in cultured cells [1, 21].

Of note, zinc is found in the presynaptic glutamatergic vesicles across the brain, including the cerebral cortex, limbic system, hippocampus, and olfactory bulb [22].

It acts as a neuromodulator on a wide range of membrane receptors, ion channels, and transporters [23]. Synaptic zinc, in particular, is enhanced via a specialized zinc transporter, ZnT3, and is coreleased with glutamate during action potential-induced exocytosis [24]. These also have an impact on synaptic transmission, which interacts with receptors and channels that regulate auditory processing [25, 26]. Synaptic zinc has been discovered to inhibit NMDA receptors, GABA-A receptors, and calcium channels while activating AMPA and glycine receptors [27–30]. Zinc also has vital effects on other kinds of receptors, including serotonin, dopamine, and acetylcholine receptors, as well as voltage-gated ion channels for sodium, potassium, calcium, and chlorine [29, 31].

Synaptic zinc regulates sensory processing and improves acuity in the discrimination of different sensory stimuli. Synaptic zinc plasticity leads to prolonged adaptations and sense memories. Recently, the mechanism of this long-term synaptic

zinc plasticity has been described as being due to group 1 metabotropic glutamate receptors (G1 mGluRs)-dependent mechanism that triggers a bidirectional long-term change in synaptic zinc signaling [32].

2.2 Role of zinc at depression

No one denies that depression treatment is a gateway to overcoming many social and psychological problems that affect millions of people all over the world. Many factors play a role in depressive-like behaviors, such as impairment of functions of the hippocampus and the prefrontal cortex. These brain parts play an important role in decision-making processes, so any dysfunction at this area can induce a predisposition to negative feelings, and many glucocorticoid receptors are involved in these areas [33].

In terms of both pharmacological and clinical/epidemiological data, recent years have provided additional evidence confirming the role of zinc in depression. Zinc demonstrated antidepressant-like efficacy in preclinical studies and depressive models. Clinical evidence suggested that zinc supplementation might be beneficial in people suffering from depression. Zinc supplementation has been demonstrated to be beneficial as adjuvant therapy or as a stand-alone intervention for depression. Furthermore, zinc consumption has been linked to an increased risk of depression. Dietary zinc restriction was found to be a causal factor in the development of depressive-like symptoms or anhedonia in mouse studies [34]. Some epidemiological studies have reported that reduced nutritional zinc consumption is related to depression in females but not in males [35]. Even though the first prospective study examining the relationship between zinc intake and depression risk found a small but significant inverse correlation between them, a 20-year follow-up study found that a reduced dietary zinc intake protects from depression in men who were not previously depressed. However, because the research participants were all men with a hospital discharge diagnosis of unipolar depression, the findings cannot be applied to women or patients who did not require hospitalization. On the contrary, a reduced nutritional zinc intake was found to be a risk factor for depression in a prospective analysis of both men and women [36]. Mice missing the G-protein-coupled receptor 39 (GPR39), a zinc-activated receptor, show depressive-like behavior [37]. TC-G-1008, a GPR39 agonist, was recently discovered to have antidepressant-like effects [38]. These findings add to the growing body of evidence that zinc is useful in the treatment of depression.

Meta-analyses support the use of zinc as a supplement in the treatment of severe depression, and single research currently supports the use of zinc for psychotic symptoms [39]. Zinc deficiency has also been linked to neuropsychiatric symptoms such as altered behavior and cognition, learning difficulties, and depression [40–42].

The link between zinc dysregulation and psychiatric disorder was that zinc acts as an inhibitory modulator at the NMDA glutamate receptor [43–45]. In addition, the inhibitory effects on the nicotinic acetylcholine receptor (nAChR), GSK3 (glycogen synthase kinase 3beta), and NOS (nitric oxide synthase) are also relevant to depressive processes [46, 47].

Numerous studies show lower zinc blood levels in depressed people compared with healthy people, with a meta-analysis showing depressive symptomatology at zinc serum levels of 1.8 M or below [48]. In several investigations, zinc supplementation enhanced mood in those who were suffering from treatment-resistant depression [41, 49].

Zinc's effect on the brain-derived neurotrophic factor (BDNF), a growth factor that promotes neurogenesis and differentiation, may be connected to depression. The hippocampus is a center of lifelong neurogenesis, and periods of significant

depression are associated with reduced BDNF expression and neuro/synaptogenesis. Rodents on a zinc-deficient diet had lower zinc levels in the hippocampus vesicles, a part of the brain where zinc levels are generally greater, as well as lower amounts of progenitor cells and immature neurons. Zinc-rich diets, on the other hand, increased amounts of progenitor cells [3, 41]. The GPR39 receptor is most likely a critical connection in the interaction between zinc and the serotonergic system, which is required for antidepressants that affect the serotonin pathway to work [34].

2.3 Zinc and neuroimmunity

Of note, laboratory animal models showed that zinc insufficiency induces thymus and lymphoid tissue atrophy. It lowers the number of spleen cells and the sensitivity to antigens that are both T-cell-dependent and -independent [50]. Microglia is a kind of immune cell found in the central nervous system (CNS) [51]. The link between zinc and microglial activation reflects an undiscovered process that may play a role in neuropathy. However, zinc is produced by neurons under several conditions to activate microglial [52].

3. Zinc ionophores

Ionophores are ion carrier molecules that reversibly bind and transport ions through biological membranes. Many ionophores are lipid-soluble ion transporters that traverse the cell membrane. Ionophores accelerate ion transport through hydrophobic membranes such as liquid polymeric membranes (carrier-based ion-selective electrodes), lipid bilayers in live cells, or synthetic vesicles (liposomes). A hydrophilic core and a hydrophobic section interact with the membrane in the structure of an ionophore [53]. Many microorganisms, fungi, and plants naturally manufacture ionophores, which import ions into their cells and function as a defense against competing or harmful species. Ionophores made from synthetic materials have also been developed. Ionophores that select for cations and anions have a wide range of uses in the analysis [54]. When paired with the ion they bind, these chemicals have been proven to have a variety of biological effects as well as a synergistic impact [55]. Ionophores change the permeability of biological membranes in the direction of certain ions for which they have affinity and selectivity (**Figure 1**). An ionophore has a hydrophilic core and a hydrophobic section that interacts with the membrane in terms of structure. An ionophore-ion complex is formed when ions are bound to the hydrophilic center. X-ray crystallography has confirmed the structure of the ionophore-ion complex [58].

Zinc ionophores (**Table 1**; **Figure 2**) have been shown to inhibit replication of various viruses in vitro, including coxsackievirus [63, 65], equine arteritis virus [68], coronavirus [68], HCV [69], HSV [70], HCoV-229E [71], HIV [72, 73], mengovirus [63, 65], MERS-CoV [71], rhinovirus [65], SARS-CoV-1 [68], and Zika virus [74].

3.1 Examples of zinc ionophores and their role in brain health, depression as an example

3.1.1 Quercetin

Quercetin has attracted the attention of many researchers because of its capacity to pass the blood–brain barrier. It appears in the brain after hours of administration and plays a key function in the central nervous system [75]. Discoveries from animal

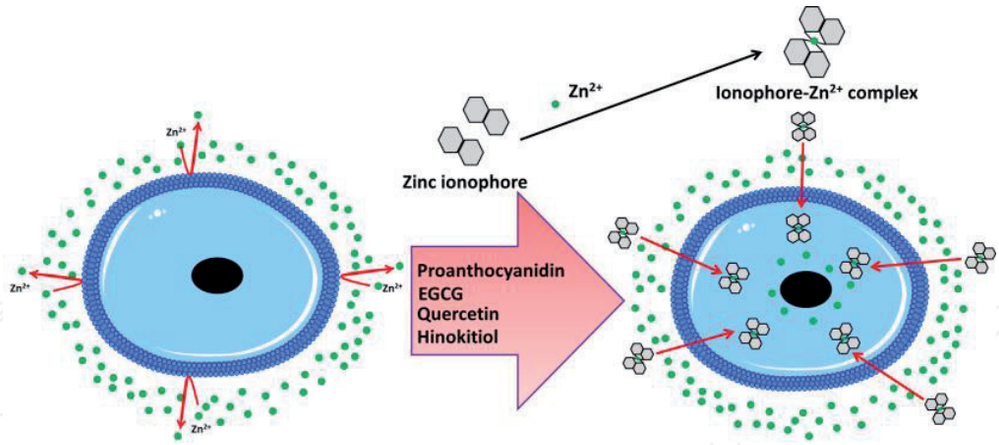

Figure 1.
Zinc ionophores mechanism in penetrating cell membranes. Two ionophore molecules can mediate intracellular zinc accumulation by exchanging extracellular Zn^{2+} with $2H^{+}$ [56]. Then, ionophore-zinc complex is taken up by endocytosis, followed by lysosomal disruption to release zinc into the cytoplasm [57].

Zinc Ionophore	Sources	References
Calcimycin	*Streptomyces chartreusensis*	[59, 60]
Chloroquine	*Cinchona officinalis*	[61]
Clioquinol	Synthetic ionophore	[55]
Diiodohydroxyquinoline	Synthetic ionophore	[62]
Dithiocarbamates	Synthetic ionophore	[63]
EGCG	*Camellia sinensis* (tea plant), apples, plums, onions	[64]
Hinokitiol	*Cupressaceae* species	[65]
Proanthocyanidins	Grape seed	[66]
PBT2	Synthetic analog of 8-hydroxyquinoline	[67]
Pyrithione	*Allium stipitatum*	[65]
Quercetin	Vegetables, fruits, berries, herbs, trees, and other plants	[64]
Zincophorin	*Streptomyces griseus*	[55]

Table 1.
Nature and synthetic zinc ionophores.

model research reported that antioxidant, anti-inflammatory, and neuroprotective effects of quercetin keep neurons in healthy condition by inhibiting the formation of hydroperoxide, reducing free radicals, and restoring antioxidant enzymes. Further, the study of quercetin at rat models proves its antidepressant action [76, 77]. Also, quercetin can reduce stress and depressive-like symptoms [75].

3.1.2 Epigallocatechin gallate (EGCG)

EGCG may act as a new antidepressant by inhibiting neuroinflammation, which may help to alleviate depression. Models of chronic unexpected mild stress (CUMS) in rats have been created in experimental investigations of depression [78]. Although the etiology of depression is not well understood, one popular theory is that depressed

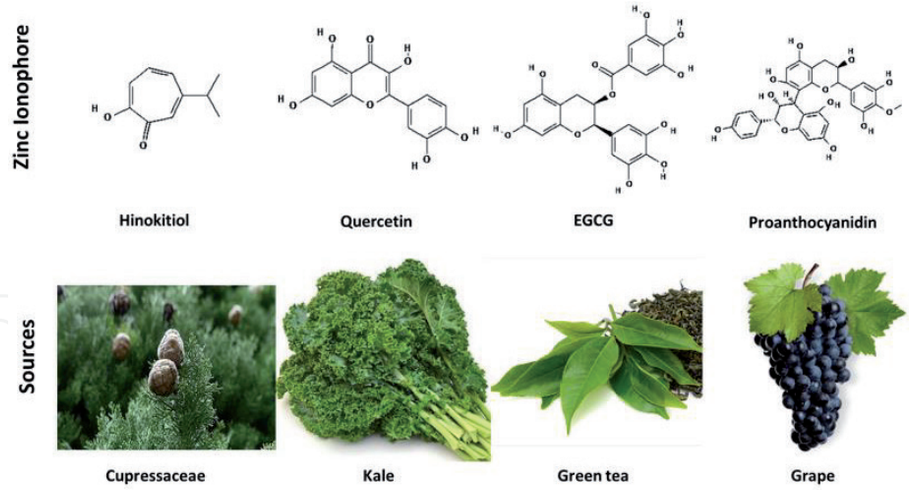

Figure 2.
Natural zinc ionophores and their sources. Chemical structures of ionophores obtained from Pubchem database (Hinokitiol, CID: 3611; quercetin, CID: 5280343; EGCG, CID: 65064; Proanthocyanidin, CID: 108065).

people have greater amounts of cytokines such as IL-6 due to lower levels of amines such as serotonin, noradrenaline, and dopamine [79]. EGCG injection improved depressed behavior in rats by reducing Il-6 levels in the hippocampus. As a result, EGCG was suggested to be used as a new antidepressant to reduce neuroinflammation, which could help to alleviate depression [80].

3.1.3 Hinokitol

Hinokitiol (β-thujaplicin) is a monoterpenoid that occurs naturally in the wood of Cupressaceae plants. It is a natural zinc ionophore that is safe to use. Because of its powerful, broad-spectrum antiviral, antibacterial, antifungal, anti-inflammatory, and anticancer effects, it is frequently employed in oral care and medicinal products. It is also a food additive that does not build up in the body. Throughout years of use, there have been no reports of allergic, poisonous, or adverse consequences in the literature. Hinokitiol is a safe zinc ionophore that increases the intracellular pool of labile zinc by facilitating zinc influx into cells [81].

3.1.4 Proanthocyanidins

Proanthocyanidins (GSPs), which comprise dimers, trimers, oligomers, and oligomers of catechin and epicatechin, are known to have antidepressant properties. Recent research has demonstrated the mechanism of GSPs' antidepressant effects in female juvenile prenatally stressed offspring rats. The main pathway was that GSPs work synergistically to inhibit oxidative stress and inflammatory response activator proteins [66].

4. Cross talk between zinc deficiency and depression caused by COVID-19

High rates of neuropsychiatric symptoms (e.g., depression) have been observed among patients affected by COVID-19, suggesting an effect of COVID-19 on the human central nervous system (CNS) [82–85]. It was showed globally that depression is a leading cause of disability [86]. Accordingly, clinically significant depression and

depressive symptoms in post-COVID-19 syndrome may have severe implications as it relates to life outcomes quality [86]. Herein according to previous research studies, we showed zinc deficiency as a possible risk factor for depression symptoms, which were commonly observed following severe infection of COVID-19. A meta-analysis of 17 observational studies found that blood Zn^{2+} concentrations were lower in depressed subjects than in control subjects [48]. Interestingly, a recent study showed that a significant number of patients with COVID-19 were zinc-deficient [87], and a higher number of zinc-deficient COVID-19 patients had prolonged hospital stay when compared with those with normal zinc levels and required intensive care unit (ICU) [87]. A significant positive correlation was observed between the prevalence of zinc deficiency and COVID-19 cases [88]. A pooled analysis of 1532 COVID-19 patients suggested that zinc deficiency was associated with a sixfold increased risk of severe disease and 16-fold increased risk of death via elevating LDH [89] The elevated LDH in the present study was probably indicative of severe disease [87].Because zinc has a critical role in regulating functions of the human brain, many disorders have been linked with Zn^{2+} deficiency, including neurological diseases, such as psychiatric disorders, (depression) [48, 89] and schizophrenia [90]. Consequently, the clinical picture, which is common in severe COVID-19 patients and is referred to as "Depression" [82–85], is nothing more than depression seen in zinc deficiency [48, 87–89]. Most likely, depression and other mental problems in these patients also develop due to zinc deficiency in nerve cells in the brain.

The first study revealing a relationship between depression and dietary zinc deficiency was conducted by Amani et al. [90]. This study included 23 young females diagnosed with moderate and severe depression and 23 healthy volunteers who were age-matched. The findings revealed that the depressive group's daily zinc consumption and serum zinc concentration were both lower than the healthy women's. Moreover, an inverse correlation between serum zinc concentration and the depression scores was obtained [90]. According to the World Health Organization (WHO), zinc deficiency affects at least one-third of the world's population [91]. The fact that zinc deficiency is linked to the risk of infection and severe advancement of COVID-19 [91] gives a first significant clue on a link between zinc deficiency and the risk of infection as well as its symptoms with unknown etiology such as depression and suggests possible benefits of zinc supplementation. Owing to Zn^{2+} neuroprotective properties, it is not surprising that Zn^{2+} supplementation could be effective not only on COVID-19-related symptoms but also on virus replication, as well as on COVID-19-related inflammation and neurological damage [92]. In vitro, Zn^{2+} inhibits Coronavirus and Arter virus RNA polymerase activity, and zinc ionophores prevent these viruses from replicating in cell culture [93]. Zinc ionophore may play a role in therapeutic management for COVID-19 [94].

5. Conclusions

Zinc deficiency has been linked to different nervous system disorders. Because zinc is not fat-soluble, it requires transporters called zinc ionophores, which facilitate the entrance of zinc in cytoplasm increasing its level of concentration in the body after consumption. The role of zinc in protecting brain cells has been extensively studied recently particularly in depression treatment. Therefore, natural zinc ionophores plus zinc supplements, which are commercially available, could be a new way to treatment of many neuropsychiatric disorders. Zinc ionophore may play a role in therapeutic management for COVID-19 and postcovid-19 depression.

Abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	brain-derived neurotrophic factor
CUMS	chronic unexpected mild stress
EGCG	Epigallocatechin gallate
G1 mGluRs	group 1 metabotropic glutamate receptors
GABA	γ-aminobutyric acid, gamma-Aminobutyric acid
GPR39	G-protein coupled receptor 39
GSK3	glycogen synthase kinase 3beta
GSPs	Proanthocyanidins
nAChR	nicotinic acetylcholine receptor
NMDA	N-methyl-D aspartic acid
NOS	nitric oxide synthase
LDH	Lactate dehydrogenase

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