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Zinc in the management of Major Depressive Disorder: Evidence for supplementation and dietary strategies

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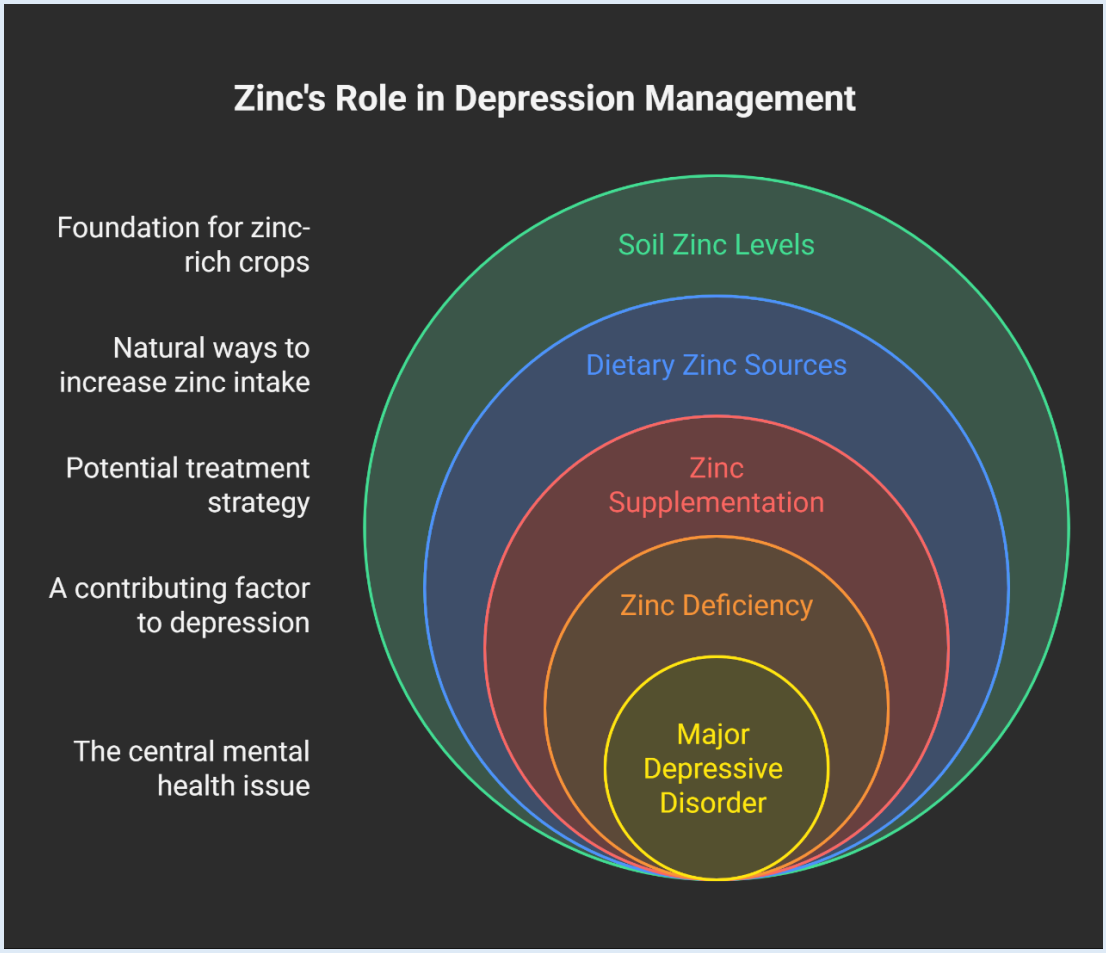
ABSTRACT

Major depressive disorder (MDD) is a mental health disorder that affects almost 1 in 10 Americans. Characterized by lower moods, this disorder can impede a patient's ability to complete everyday tasks like working, sleeping, and more. Antidepressants, the current standard treatment for depression, increase the levels of neurotransmitters like serotonin, dopamine, and norepinephrine in a patient's system. However, there are several known issues surrounding the effectiveness of antidepressants, prompting researchers to explore alternative supplementation through minerals. One such mineral, zinc, has been associated with improving depression symptoms in patients. Many studies have shown a correlation between depression symptoms in patients and low levels of zinc. Recently, more research focusing on the supplementation of zinc with antidepressants for depression patient has been conducted, where it has shown an increased efficacy in lowering depression symptoms. This review establishes zinc as a potential therapeutic supplement for patients with major depressive disorder.

Novelty: This review examines the potential for zinc as a supplement for patients with depression, an area that has received limited attention in the scientific field. By reviewing the fallbacks of antidepressants, the potential for agricultural changes to decrease zinc deficiency, and the effect of excessive zinc on human health, this review extensively addresses all aspects of zinc deficiency and its connection to depression.

Keywords: major depressive disorder (MDD), zinc, depression, NMDA, serotonin, supplementation, antioxidant, zinc deficiency, trace minerals



Graphical Abstract: Zinc's role in reducing symptoms in patients with major depressive disorder

Retrieval of Published Studies: To review published literature on zinc's effects on depression, an electronic search of the PubMed and Functional Food Center databases was conducted. Keywords for the search included zinc, depression, NMDA, serotonin, supplementation, antioxidant, zinc deficiency, trace minerals, and more.

INTRODUCTION

Depression is a group of common mental health disorders characterized by an elevation or lowering in a patient's moods [1]. There are three common types of depressive disorders that patients are typically diagnosed with: dysthymia, manic depression/bipolar disorder, and major depressive disorder. Dysthymia is a disorder characterized by long-term, chronic symptoms that do not altogether disable a patient from functioning. Instead, it slows, obstructing the patient's regular functioning, preventing them from functioning at 100% efficiency. Manic depression, or bipolar disorder, is distinguished by extreme mood swings, segmented between manic and depressive episodes. Finally, major

depressive disorder, the focus of this review, is associated with a variety of symptoms that impede a patient's ability to complete daily tasks like working, sleeping, eating, and much more [2].

As of 2020, major depressive disorder has affected almost 1 in 10 Americans and 1 in 5 adolescents and young adults. In addition, this trend seems to be on the rise, increasing every year [3]. Because of this, it is essential to find proper methods of alleviating major depressive disorder symptoms and preventing them before they arise.

One such method could be the use of zinc supplementation. Zinc is a trace element required by many different animals and organisms. In humans, it plays a role in over 300 biological processes. Zinc is necessary for proper cellular function, including DNA replication, transcription, protein synthesis, maintenance of cell membranes, cellular transport, and endocrine, immunological, and neuronal systems, making it essential to the human body [4]. Studies have shown that proper consumption of zinc for 1-2 months can improve immune responses, decrease the incidence of infections, and increase survival rates [5].

The first case of zinc deficiency was reported in 1969 in a Puerto Rican subject with dwarfism, hypogonadism, hypogammaglobulinemia, giardiasis, strongyloidiasis, and schistosomiasis, and it has become a prevalent problem ever since. Zinc deficiency is common in many Americans and can cause many health issues including reduced immunological functioning, stunted tissue regeneration, impaired growth, gastrointestinal complaints, and ocular and sensory disturbances [4,6]. The diet's most abundant sources of zinc come from oysters, meat, poultry, crab, clams, beans, and nuts [7]. Because there is a high zinc concentration in many meats, people who follow vegan and vegetarian diets are especially at risk of falling to zinc deficiency [7]. Neurologically, zinc deficiency is associated with neuropsychiatric manifestations that can present as altered behavior and cognition, reduced ability to learn, and depression [4,6].

Table 1 below presents Dietary Reference Intakes (DRIs), developed by the Food and Nutrition Board at the National Academies of Sciences, Engineering, and Medicine, which provide intake recommendations for zinc and other nutrients based on age and sex. The table below presents the Recommended Dietary Allowance, a key component of the DRIs, representing the average daily intake sufficient to meet the nutrient needs of nearly all (97–98 %) healthy individuals [8]. The table shows that the RDA for zinc consumption increases as age increases, staying consistent after 19 years. However, many people do not meet these zinc consumption requirements, even at a young age when it is most vital.

Table 1. Recommended Dietary Allowances (RDAs) for various age groups for zinc consumption (mg).

Age	Male	Female
Birth to 6 months	2 mg	2 mg
7-12 months	3 mg	3 mg
1-3 years	3 mg	3 mg
4-8 years	5 mg	5 mg
9-13 years	8 mg	8 mg
14-18 years	11 mg	9 mg
19+ years	11 mg	8 mg

Regarding depressive symptoms, zinc deficiency is associated with major depression in many clinical and research trials [9]. Thus, it has become increasingly researched in terms of its potential benefits for patients with depression. This review aims to identify the beneficial relationship of supplementing zinc for patients diagnosed with MDD and help establish zinc as a possible supplement for patients with MDD.

Aim and Source of Journal and Literature Review: A comprehensive literature review was conducted electronically to explore the role of zinc in helping patients manage MDD symptoms using PubMed®, ScienceDirect, and relevant journals from the Functional Food Center's database. These databases were selected for their extensive collection of pertinent studies. 50 research and review articles about zinc were used to write this review. Published from 1979 to 2025, this review portrays how zinc research has changed over time, becoming increasingly extensive.

The selected articles provided insights into zinc's role in lowering MDD symptoms and the neurobiology behind this phenomenon. Studies were selected based on their examination of how zinc is related to MDD. Articles that investigated a range of topics like effects of zinc deficiency, MDD and its current treatments, zinc's role in reducing MDD, zinc's neurobiological effects related to MDD, excess zinc consumption, and zinc levels with current agricultural practices were all included in this review. Articles not published in English or zinc or MDD articles unrelated to the review topic were excluded from this review.

Keywords that were used during the search to find relevant articles included "zinc," "depression," "Major Depressive Disorder -MDD," "NMDA," "serotonin," "SSRIs," "supplementation," "antioxidant," "zinc-deficiency," "trace minerals," and

Current Depression Treatments: The monoamine-deficiency theory is the most relevant theory on the cause of MDD. This theory indicates that the underlying pathophysiological cause of depression is the depletion of neurotransmitters like serotonin, norepinephrine, or dopamine in the central nervous system [10].

Currently, the main form of treatment for patients with mild to severe depression is antidepressants, which are common medications used to either prevent the reuptake or mimic the effects of neurotransmitters such as serotonin and dopamine [11]. There are three commonly used antidepressants to treat major depressive disorder: monoamine oxidase inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs). Monoamine oxidase inhibitors block the degradation of the monoamine neurotransmitters serotonin, norepinephrine, and dopamine by inhibiting the enzyme monoamine oxidase. Tricyclic antidepressants prevent the reuptake of various neurotransmitters, including serotonin, norepinephrine, and, to a much lesser extent, dopamine. Finally, SSRIs avoid serotonin reuptake, increasing the brain's active serotonin level [2]. SSRIs are the most commonly used as they are more selective and offer improved safety and tolerability [12].

Though the three described are the most common types of antidepressants, many more varieties can be prescribed by doctors, all with their benefits. Table 2 below gives an extensive list of the antidepressants and their fallbacks in terms of side effects. As we can see in the table below, there are many side effects associated with all the antidepressants prescribed by doctors for patients with depression. Some of these side effects, like increased risk of hypertension caused by monoamine oxidase inhibitors, are severe, raising the importance of finding natural supplements that can potentially decrease the patient's need for these antidepressants.

Table 2. A table displaying different types of antidepressants used to treat MDD, as well as their unwanted side effects.

Antidepressant	Drug	Therapeutic action	Unwanted pharmacological action	Side effect
Tricyclic antidepressants (TCAs)	Clomipramine, imipramine, amitriptyline, desipramine, trimipramine, nortriptyline, protriptyline, maprotiline, amoxapine, doxepine	Block reuptake transporters for serotonin and norepinephrine, and to a lesser extent, dopamine	Muscarinic receptor blockade (anticholinergic)	Dry mouth, tachycardia, blurred vision, glaucoma, constipation, urinary retention. Sexual dysfunction, cognitive impairment
			α1-Adrenoceptor blockade	Drowsiness, postural hypotension, and sexual dysfunction
			Histamine H1 receptor blockade	Drowsiness, weight gain
Monoamine oxidase inhibitors (MAOIs)	Irreversible: phenelzine, tranylcypromine, isocarboxazid	Irreversible and nonselective inhibition of monoamine oxidase (MAO)	Irreversible blockade of monoamine oxidase	Risk of hypertension from dietary amines – tyramine must be avoided, risk of intracerebral hemorrhage
	Reversible: moclobemide	Reversible and selective inhibition of MOA	N/A	N/A
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine, paroxetine sertraline, fluvoxamine citalopram, escitalopram	Selective inhibition of 5-HT reuptake transporter	Agonist of 5HT2C receptor	Gastrointestinal: reduced appetite, nausea, constipation, dry mouth Central nervous system: headache, insomnia, anxiety, fatigue, tremor Other: delayed orgasm, anorgasmia
Norepinephrine and dopamine reuptake inhibitors (NDRIs)	Bupropion	Blockade of NE and DA reuptake transporters	N/A	Increased risk of seizures
Dual serotonin and norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine, duloxetine	Blockade of 5HT and NE reuptake transporters	N/A	Nausea, dizziness, headache, dry mouth, insomnia, and increases in blood pressure
Dual 5HT-2 receptor antagonist/5HT reuptake inhibitors SARIs)	Trazodone	Powerfully blocks serotonin-2 receptors with less potent inhibition of 5HT reuptake	Histamine H1 receptor blockade	Sedation, cognitive impairment
			α1-Adrenoceptor blockade	Lowers blood pressure, postural hypotension
				Other: priapism (prolonged erections)
	Nefazodone	N/A	Histamine H1 receptor blockade	Sedating (less so than Trazodone)
Noradrenaline and serotonin-specific antidepressant (NASSA)	Mianserin, mirtazepine	5HT2 antagonism α1-Adrenoceptor antagonism	Histamine H1 receptor blockade	Drowsiness, dry mouth, sedation, weight gain
Noradrenergic reuptake inhibitor (NARI)	Reboxetine	Selective inhibition of NA reuptake	Muscarinic receptor blockade	Dry mouth, constipation, headaches

The four most commonly used drugs include Desvenlafaxine, Vortioxetine, Vilazodone, and Levomilnacipran [13]. Desvenlafaxine, an active metabolite of venlafaxine, was approved by the FDA for the treatment of patients with depression in 2009 [14]. Desvenlafaxine selectively inhibits serotonin (5-HT) and norepinephrine (NE) reuptake, with a higher affinity for 5-HT transporters than NE transporters and minimal impact on dopamine levels. It also influences hypothalamic regulation of essential biological functions such as mood, sleep, stress response, and pain perception [15]. Desvenlafaxine's treatment-emergent adverse effects (AEs) are dose-related and the leading cause of treatment discontinuation, with common AEs including nausea, headache, dizziness, insomnia, and dry mouth [16].

Approved for treatment of depression in 2013, vortioxetine exerts its antidepressant effects through multimodal activity by modulating serotonin receptors and inhibiting 5-HT transporters. It also increases extracellular neurotransmitters such as dopamine, histamine, noradrenaline, and acetylcholine [17-18]. Vortioxetine's side effects contribute to treatment discontinuation rates of 3-11%, with nausea being the most frequently reported adverse event [18-20]. Common side effects include headache, diarrhea, dry mouth, and sexual dysfunction, with men experiencing a higher incidence of adverse effects compared to women [19].

Vilazodone is a drug used to treat depression that enhances serotonergic activity by selectively inhibiting serotonin reuptake through SERT blockade and partially agonizing 5-HT1A receptors [14]. Vilazodone treatment is associated with higher discontinuation rates due to adverse effects compared to a placebo, with nausea being the most common AE leading to discontinuation. Other frequently reported AEs include diarrhea, insomnia, vomiting, dizziness, and dry mouth [14, 21].

Levomilnacipran extended release (ER) is a serotonin-norepinephrine reuptake inhibitor with a higher potency for norepinephrine reuptake inhibition than serotonin [22]. Unlike other SNRIs, it does not significantly affect other receptors, ion channels, or transporters, including serotonergic (5-HT1-7), adrenergic (α- and β-), muscarinic, or histaminergic receptors, as well as Ca^{2+}, Na^{+}, K^{+}, or Cl^{-} channels [23]. In randomized controlled trials evaluating levomilnacipran ER at 40, 80, and 120 mg, the most common treatment-emergent AEs included headache, nausea, constipation, dry mouth, increased heart rate, and hyperhidrosis. Serious AEs were infrequent, with isolated cases such as chest pain, deep vein thrombosis, aggression, and cytomegalovirus mononucleosis reported. Other AEs included increases in liver transaminases and mild increases in blood pressure [24]. Similar AE profiles were observed in studies assessing 40 and 80 mg doses, with some patients discontinuing due to serious AEs like intussusception and asthma. Additionally, AEs such as urinary hesitation and erectile dysfunction occurred at an incidence of 5% or more and at least twice the rate of placebo in both levomilnacipran ER groups [25].

Apart from various adverse effects that arise from each drug, several other issues arise with the currently used antidepressants. About 19-34% of patients with depression do not respond to antidepressants, and 15-50% of them have recurring symptoms even after the use of medications. In addition to intolerance and relapse issues, problems like delayed therapeutic onset and limited effectiveness are also common [26-27]. The limited efficacy of many antidepressants is likely because currently used antidepressants target monoamine levels, like serotonin, even though people with depression don't necessarily have lower levels of these neurotransmitters. While antidepressants quickly increase monoamine levels, their therapeutic effects often take time because they rely on later changes in the brain, like adjusting receptor levels, activating enzyme pathways, and increasing proteins like brain-derived neurotrophic factor (BDNF), which supports brain health. Current

medications might focus on the wrong or indirect targets, limiting their effectiveness [26]. Therefore, the use of zinc as a supplement to antidepressants in patients with depressive symptoms has become an increasingly studied topic, with many promising results.

Zinc's Role in Neurobiology: Studies have shown that, in general, zinc has a beneficial role in human neurobiology. Zinc modulates synaptic activity, neuronal metabolism, and plasticity, and dysregulated zinc homeostasis has been linked to several neurological disorders, including depression [28]. In addition, zinc has a role in the antioxidative and anti-inflammatory functions of the brain, which not only leads to decreased depressive disorders, but also plays a role in neurological disorders such as Alzheimer's disease and dementia. Zinc's antioxidant and anti-inflammatory properties help to balance glutamate levels in the brain. At lower concentrations, it increases glutamate release. Since inflammation, oxidative stress, and glutamate imbalance are all connected, they play a role in the development of depression [29].

In a study, rats with low levels of zinc in their blood showed higher levels of corticosterone (a stress hormone), which is linked to depressive-like behaviors. This suggests that overactivation of the hypothalamic-pituitary-adrenal (HPA) axis—a system that regulates stress—plays a role in depression. Reducing this overactivation might help improve depressive-like behaviors in rats exposed to chronic mild stress [28].

As we can see in Figure 1, zinc affects the nervous system and can also benefit many parts of the body. This emphasizes the importance of consuming adequate amounts of zinc to ensure that all parts of the body function to their maximum potential.

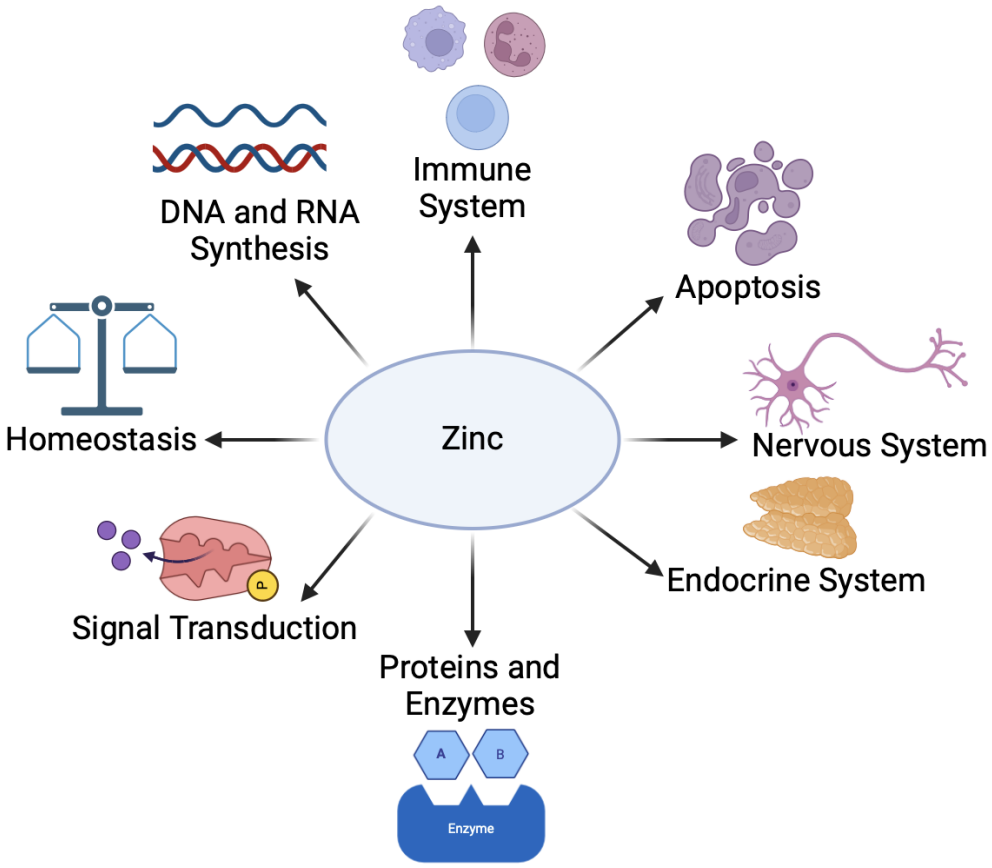


Figure 1. A chart providing the bioactive effects of zinc on the human body.

Mechanistic Insight into Zinc's Antidepressant Effects: The NMDA receptor, a key glutamate receptor, plays a significant role in depression by becoming overstimulated and causing excessive glutamate signaling in the brain. Zinc, acting as an NMDA receptor antagonist, helps inhibit this receptor, reducing glutamate signaling and alleviating depression symptoms [29]. By acting as an NMDA receptor antagonist, zinc has shown evidence to prevent many mental health disorders, including depression, anxiety, and ADHD [29-31].

Additionally, zinc supports the production and function of brain-derived neurotrophic factor (BDNF), a protein vital for neuronal growth and plasticity, which is often found at lower levels in individuals with depression. Zinc's antioxidant properties further enhance its potential to relieve depression symptoms by reducing oxidative stress in the brain [29].

Zinc is primarily found within glutamatergic neurons and modulates the NMDA receptor to inhibit excessive activity. It also has agonistic effects on AMPA receptors, enhancing glutamate signaling in a balanced way. Furthermore, zinc interacts in complex ways with 5-HT1A serotonin receptors, acting as an activator and inhibitor depending on whether it targets pre- or postsynaptic sites. These combined effects on glutamate and serotonin systems highlight zinc's multifaceted role in improving brain function and mitigating depression [4].

Animal Studies of Zinc's Role in Depression: A study conducted by Mlyniec et al examines the effects of zinc supplementation, both alone and in combination with the antidepressant imipramine, on mice subjected to chronic restraint stress (CRS), which are a model for inducing depression-like behaviors. It was found that both zinc and imipramine independently alleviated depression-like behaviors in these mice. Notably, the combination of zinc and imipramine produced a more pronounced antidepressant effect than either treatment alone, suggesting a synergistic interaction [32-33].

These findings support the potential role of zinc as an adjunctive treatment in depression. The study also explored the involvement of the GPR39 zinc-sensing receptor in mediating these effects. The results indicated that the antidepressant-like effects of zinc might be associated with the activation of the GPR39-related pathway, highlighting a possible mechanism through which zinc exerts its therapeutic effects [32-33].

In another animal study, the effects of zinc supplementation on depressive-like behaviors in mice induced by chronic corticosterone administration, a model for stress-related depression, were investigated. The study found that zinc supplementation effectively reversed these behaviors. Additionally, zinc treatment normalized the expression of genes associated with glutamatergic neurotransmission and neurotrophic signaling, which were altered due to corticosterone exposure [33-34].

These findings suggest that zinc's antidepressant effects may be mediated through the modulation of glutamatergic and neurotrophic pathways, highlighting its potential as a therapeutic agent in stress-induced depression. The study underscores the importance of zinc in maintaining proper neural function and its potential role in mitigating the effects of chronic stress on mental health [33-34].

Zinc Deficiency and Depression: With its extensive role in neurobiology, zinc has been a topic of interest regarding people with MDD. On top of that, zinc has been known to target several neurotransmitters associated with depression. Many research trials have been conducted, displaying the association of lower levels of zinc with depression symptoms in patients.

A recent cross-sectional study by Dong Huang et al analyzed data from the National Health and Nutrition Examination Survey (NHANES) spanning 2011 to 2016 to explore the relationship between serum zinc concentrations and depressive symptoms in U.S. adults. Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9), with scores of 10 or higher indicating moderate to severe depression. The study found that lower serum zinc levels were significantly associated with an increased likelihood of depressive symptoms [28].

Specifically, individuals in the lowest quartile of serum zinc concentrations had higher odds of experiencing depressive symptoms compared to those in the highest quartile. This association persisted even after adjusting for potential confounders such as age, sex, race/ethnicity, education level, smoking status, alcohol consumption, body mass index, and serum concentrations of copper and selenium [28]. These findings suggest that zinc deficiency may be linked to an increased risk of depression in the general population.

The study underscores the importance of maintaining adequate zinc levels for mental health and suggests that addressing zinc deficiency could be a potential strategy for mitigating depressive symptoms. However, the study's cross-sectional nature limits the ability to establish causality [28]. Further longitudinal studies and clinical trials are needed to confirm these findings and explore the therapeutic potential of zinc supplementation in individuals with depression.

A 2020 study examined the relationship between zinc status and the prevalence of depression and anxiety among the elderly population. The researchers assessed serum zinc levels and evaluated symptoms of depression and anxiety using standardized questionnaires. They found that lower serum zinc concentrations were significantly associated with higher scores of depression and anxiety, suggesting a potential link between zinc deficiency and mental health disorders in older adults [35].

The study's findings align with previous research indicating that zinc modulates mood and cognitive function. The study suggests that zinc is involved in neurotransmitter regulation and immune function, both of which are critical in the pathophysiology of depression and anxiety [35]. The observed association between low zinc levels and increased depressive and anxiety symptoms underscores the importance of adequate zinc intake in maintaining mental health, particularly in the aging population.

These results highlight the need for healthcare professionals to consider nutritional status when addressing mental health issues in the elderly. Regular monitoring of zinc levels and dietary assessments could be beneficial in the early identification and management of depression and anxiety [35]. Further research, including randomized controlled trials, is necessary to establish causality and to explore the therapeutic potential of zinc supplementation in alleviating depressive and anxiety symptoms among older adults.

A 2017 study published in Psychiatry Research by Li et al examined the relationship between zinc deficiency and depression among 200 adults. The researchers measured serum zinc levels and assessed depressive symptoms using the Beck Depression Inventory-II (BDI-II). They found that individuals with lower serum zinc levels had significantly higher BDI-II scores, indicating more severe depressive symptoms. This association remained significant even after adjusting for potential confounding factors such as age, gender, body mass index, and socioeconomic status [36].

The study also categorized participants into quartiles based on their serum zinc levels. Those in the lowest quartile were found to have a markedly higher risk of severe depression compared to those in the highest quartile. These findings suggest a potential dose-response relationship between zinc levels and depression severity, highlighting the importance of adequate zinc status for mental health [36].

The authors concluded that zinc deficiency is significantly associated with increased severity of depressive symptoms. They recommend considering zinc level assessments in routine evaluations of patients presenting with depression and suggest that zinc supplementation could be explored as a potential adjunctive treatment for depressive disorders. However, they also note the need for further longitudinal studies and clinical trials to establish causality and determine the efficacy of zinc supplementation in depression management [36]. A summary of the results discussed in this section, as well as different studies on zinc's correlation to lower levels of depression, can be found below in Table 3.

Table 3. Summary of discussed studies investigating the relationship between zinc deficiency and depression rates.

Participant Information	Results	Reference
4552 participants aged 20 years and over (2311 male and 2241 female)	Weighted logistic regression analysis showed that the second (Q2) quartile of zinc concentrations (odds ratio [OR] = 1.534, 95% confidence interval [CI]: 1.018 to 2.313) was significantly associated with an increased risk of depressive symptoms	[28]
297 elderly participants (144 males and 153 females)	Participants in the 3rd tertile of serum zinc concentration had a 51% lower depression chance of depression compared to the 1st tertile	[35]
A meta-analysis that included 9 studies that explored zinc deficiency and its correlation to depression	The pooled RRs with 95% CIs of depression for the highest versus lowest dietary zinc and iron intake were 0.67 (95% CI: 0.58–0.76) and 0.57 (95% CI: 0.34–0.95), respectively, indicating significant evidence that zinc deficiency is positively correlated with depression symptoms.	[36]

Potential Therapeutic Implications: After the link between zinc deficiency and depression was discovered, many researchers focused on investigating the effects of zinc supplementation with antidepressants on patients with MDD. These studies have shown significant evidence suggesting that supplementing zinc with antidepressants enhances the effects of antidepressants, decreasing depression levels in patients.

In one such study, Ranjbar et al. examined the effects of zinc supplementation combined with antidepressant therapy in patients with MDD. Participants received either 25 mg of zinc daily alongside SSRIs or a placebo with SSRIs over 12 weeks. Depression severity was assessed using the Beck Depression Inventory (BDI) at baseline, six weeks, and twelve weeks [26].

The findings indicated a significant reduction in BDI scores for the zinc-supplemented group compared to the placebo group, particularly evident at the 12-week mark. This suggests that zinc supplementation may enhance the therapeutic effects of SSRIs in treating MDD [26].

These results align with previous research, highlighting the role of zinc in modulating mood and its potential as an adjunctive treatment in depression. The study supports the consideration of zinc supplementation to improve outcomes in patients undergoing antidepressant therapy, though further research is recommended to confirm these findings and establish optimal dosing strategies [26].

A 2020 study published in General Hospital Psychiatry investigated the effects of zinc supplementation in conjunction with antidepressant therapy in patients with MDD. In this randomized, double-blind, placebo-controlled trial, participants received either zinc supplements or a placebo alongside their prescribed antidepressant medication over 12 weeks. Depressive symptoms were assessed using standardized scales at baseline, 6 weeks, and 12 weeks [31].

The findings revealed that the group receiving zinc supplementation exhibited a more significant reduction in depressive symptoms than the placebo group, particularly evident at the 12-week assessment. This suggests that zinc supplementation may enhance the efficacy of standard antidepressant treatments in individuals with MDD. The study also noted improvements in secondary outcomes, such as anxiety levels and overall functioning, in the zinc-supplemented group [31].

These results align with existing literature indicating the potential role of zinc in modulating mood and its therapeutic benefits as an adjunct to antidepressant medications. The authors recommend further research to confirm these findings and to explore the underlying mechanisms by which zinc supplementation may augment antidepressant efficacy. Additionally, they suggest investigating optimal dosing strategies and the

long-term effects of combined zinc and antidepressant therapy [31].

A 2021 systematic review and meta-analysis evaluated the efficacy of zinc supplementation combined with antidepressant therapy in patients with clinical depression. The analysis included five randomized controlled trials comparing zinc supplementation with placebo, alongside standard antidepressant treatment. The results indicated that zinc supplementation significantly reduced depressive symptoms, with a standardized mean difference of -0.36 (95% CI, -0.67 to -0.04), suggesting a modest but meaningful improvement [32].

Subgroup analyses revealed that the effect was more pronounced in studies where the mean age of participants was 40 years or older, with a standardized mean difference of -0.61 (95% CI, -1.12 to -0.09). However, analyses based on sample size did not show a significant effect in reducing depressive symptoms. These findings suggest that zinc supplementation may be particularly beneficial for middle-aged and older adults undergoing antidepressant therapy [32].

The review underscores the potential role of zinc as an adjunctive treatment for depression, highlighting its importance in brain function and mood regulation. Unlike other studies presented in this review, this study goes a step further, highlighting the age groups at which zinc supplementation would receive optimum results in depression patients. While the results are promising, the authors recommend further research to confirm these findings and to establish optimal dosing strategies for zinc supplementation in conjunction with antidepressant medications [32].

Table 4 summarizes the results discussed in this section from different studies on zinc supplementation and its role in lowering depression symptoms.

Table 4. Summary of discussed studies investigating the effect of zinc supplementation on depression symptoms.

Participant Information	Zinc Concentration	Antidepressant	Results	Reference
44 patients with significant depression, aged 18-25 years	25 mg	citalopram 20-60mg per day or fluoxetine 20-60mg per day	Mean score of the Beck test decreased significantly in the zinc supplement group at the end of week 6 ($P < 0.01$) and 12 ($P < 0.001$) compared to the baseline. The mean score of the Beck Depression Inventory reduced significantly compared to the placebo group at the end of the 12th week ($P < 0.05$)	[28]
150 elderly aged 60 years and older	30 mg	N/A	After the intervention, the mean scores of depression and anxiety in the elderly were significantly decreased in the intervention group, as compared to the control group. Moreover, after the intervention, the serum zinc level in the elderly was significantly increased in the intervention group, as compared with the control group ($P<0.05$).	[31a]
A meta-analysis that included a total of thirteen observational studies (9 cross-sectional studies and four cohort studies) that explored zinc supplementation and its effect on depression symptoms	N/A	N/A	Randomized controlled trials indicated that zinc supplementation significantly lowered depressive symptom scores of depressed patients [weighted mean difference (WMD = −4.15 points; 95% CI: −6.56, −1.75 points; $P < 0.01$)]. Cohort studies showed that the highest level of zinc intake was associated with a 28% reduced risk of depression (RR: 0.66; 95% CI: 0.50, 0.82; $I2 = 13.90$).	[37a]

Opposing Results: One thing of note is that a few studies have shown no correlation between zinc levels and the severity of depression in patients. In a survey conducted by Irmisch et al, there was no observed correlation between zinc levels and the severity of depression in treatment-resistant depression. In a specific group of depressed patients, zinc levels were only slightly lower compared to the general population, and, interestingly, self-reported depression severity (measured by the Beck Depression Inventory, BDI) showed a positive correlation with zinc levels. This suggests that higher zinc levels might paradoxically be associated with worse self-reported depression in these specific cases [34].

A similar study by Narang et al showed comparable results. After comparing zinc levels in depressed patients before treatment, after recovery, and with healthy controls, no significant differences were found between depressed and healthy individuals. However, patients who recovered from depression showed significantly higher zinc levels compared to when they were depressed [12]. This study suggests the potential role of zinc in recovery and remission from depression, even if baseline differences between healthy and depressed states aren't always clear.

Zinc Excess: Though zinc has been shown to provide many benefits for many patients, including those with MDD, its potential to induce adverse effects must also be explored and mentioned. Excess zinc, also known as zinc toxicity, has been linked to adverse symptoms like nausea, abdominal cramping, vomiting, and diarrhea. In animal models, zinc toxicity varies by administration route, with oral LD50 values for zinc salts ranging from 237–623 mg/kg and intraperitoneal LD50 values from 28–73 mg/kg. Inhalation toxicity for zinc chloride is higher, with an LD50 of 2000 mg/m^3. Acute toxicity in humans is rare but has been reported with zinc concentrations in drinks reaching up to 2500 mg/L, leading to estimated doses of 325–650 mg [38].

Chronic zinc toxicity, often from disproportionately high zinc-to-copper intakes, poses significant health risks, including copper deficiency. In humans, copper deficiency can cause adverse effects, including decreased copper-dependent enzymes such as superoxide dismutase, ceruloplasmin, and cytochrome c oxidase. The imbalances in these enzymes further affect immune abilities, cholesterol metabolism, and hematological function. Neurological symptoms, including those related to copper deficiency, have been documented with excessive zinc intake [38]. While the thresholds for these adverse effects remain unclear, these findings emphasize the critical need for proportional zinc and copper intake in dietary and supplemental regimens to prevent such outcomes. Further, these findings underscore the necessity for more studies on establishing a threshold of zinc consumption in humans.

Zinc Sources: Zinc is an essential trace element found in various foods, with animal-based sources generally providing higher bioavailability than plant-based options. Foods rich in zinc include red meat, poultry, and seafood—particularly oysters, which contain the highest zinc among all dietary sources. Dairy products such as cheese and yogurt also contribute to dietary zinc intake, albeit in lower amounts. Plant-based sources like legumes, nuts, seeds, and whole grains contain zinc, but their bioavailability is reduced due to inhibiting zinc absorption. Fortified foods and dietary supplements can serve as alternative sources to help meet daily zinc requirements, especially for individuals following plant-based diets [39].

Various factors, including dietary composition and food processing methods, influence the bioavailability of zinc in foods. Cooking, soaking, and fermenting plant-based foods can help reduce phytate levels, improving zinc absorption. Several countries have implemented zinc fortification strategies to address deficiencies, particularly in populations with limited access to animal-based foods [20]. Another area of research to improve

zinc absorption for all dietary needs is researching methods that reduce phytate levels at the highest level.

Table 5 below displays the zinc levels of common foods. This table can guide patients and consumers struggling with zinc deficiency to foods with high zinc content. For example, if someone is trying to increase their zinc consumption, they could focus on eating meats like oysters and beef rather than eggs and salmon.

Table 5. The daily value and milligrams per serving of zinc in various foods [8].

Food	Milligrams per serving (mg)	Daily Value (%)
Oysters (3 ounces)	32	291
Beef (3 ounces)	3.8	35
Breakfast Cereal (1 serving)	2.8	25
Pumpkin Seeds (1 ounce)	2.2	20
Pork (3 ounces)	1.9	17
Turkey Breast (3 ounces)	1.5	14
Cheddar Cheese (1.5 ounces)	1.5	14
Lentils (0.5 cup)	1.3	12
Greek Yogurt (6 ounces)	1.0	9
Milk (1 cup)	1.0	9
Peanuts (1 ounce)	0.8	7
Egg (1 large)	0.6	5
Salmon (3 ounces)	0.5	5
Broccoli (0.5 cup)	0.4	4
White Rice (0.5 cup)	0.3	3
Cherry Tomatoes (0.5 cup)	0.1	1
Blueberries (0.5 cup)	0.1	1

According to Table 5, pumpkin seeds are a valuable plant-based source of zinc. They deliver around 2.2 mg per ounce, constituting 20% of the daily value and thus contributes significantly to dietary zinc intake.

One way of increasing zinc concentrations in many agricultural products is by focusing on the soil in which they are grown. Soils such as sandy, peat, and calcareous types with high pH levels often lack sufficient zinc, leading to its unavailability to plants. High phosphorus levels and waterlogged conditions further reduce zinc solubility, exacerbating deficiencies. This deficiency manifests in plants through stunted growth, smaller leaves, chlorosis, and reduced grain yields, with certain crops like corn, cotton, and apple trees being particularly sensitive [40-43]. Approximately 49% of the soil worldwide is zinc-deficient, impacting agriculture and human nutrition. Low soil zinc levels correlate with reduced zinc content in staple crops like rice and wheat [44]. Addressing this issue through soil applications of soluble inorganic zinc salts, such as zinc sulfate, can enhance plant growth and increase zinc concentrations in edible plant parts, thereby improving human zinc intake [40]. However, zinc fertilizers' availability and affordability remain challenging in many regions. An area of research that could work to increase zinc concentrations worldwide is working to create affordable zinc fertilizer for countries worldwide.

Evaluation of Zinc's Role in MDD: Functional Food Product Creation and Assessment Using FFC's Guidelines: One of the central aspects of Functional Food

Science theory is creating ideal functional foods, evaluating food products to determine whether they qualify as functional foods, and identifying the necessary steps to bring them to market. Quantum and Tempus theories in functional food science provide a comprehensive framework for understanding and utilizing functional foods in personalized nutrition strategies, ultimately enhancing overall well-being [45].

According to the Functional Food Center, functional foods are: “Natural or processed foods that contain biologically-active compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms” [45-46].

The Functional Food Center has developed an updated definition of functional foods and established a classification system for functional food products. One of its latest advancements is the 17-step process for developing functional foods, which begins with defining the product’s objectives (Step 1) and identifying the specific bioactive compounds to be used (Step 2) [47].

Over the past few years, multiple food products have been assessed using FFC’s functional definition and 17-step development process [48]. These evaluations aimed to determine whether specific products and bioactive compounds meet the criteria for functional foods or if additional steps are required before they can be classified as such. Several studies have also identified missing steps necessary for future research, ensuring that newly developed functional foods have proven health effects and the ability to reduce the risk of chronic diseases [49-50]. Using this model, the Functional Food Center has successfully implemented its criteria to evaluate whether specific food products qualify as functional foods. When a product does not meet these standards, the framework provides clear guidance on the necessary steps to elevate it to a fully recognized functional food. This structured approach upholds scientific integrity and facilitates the development of evidence-based functional foods for the market [51-56].

As the article mentions, zinc has many neurobiological benefits, including anti-inflammatory and antioxidant effects. In addition, zinc's ability to act as a glutamate receptor lowers depression symptoms, allowing it to benefit the human body positively.

Step 3 involves determining the bioactive compounds' optimal and safe dosage regimen [46]. Consuming zinc in excess can cause many adverse effects, but as seen in this review, an optimal dosage has not yet been determined [38]. This highlights the importance of studies focusing on establishing a standard safe amount of zinc consumption, before it can be determined to be a functional food.

Step 4 focuses on identifying the optimal time of day for consumption to enhance the effectiveness of the bioactive compounds [46]. According to the Mayo Clinic, the best time to take zinc supplements to maximize absorption is approximately one to two hours before eating meals [57].

Step 5 focuses on identifying the precise mechanisms of action and biological pathways through which the bioactive compounds exert their effects [46]. Zinc, functioning as an NMDA receptor antagonist, helps regulate this signaling, alleviating symptoms of depression, anxiety, and ADHD. Additionally, zinc supports BDNF production for neuronal growth and reduces oxidative stress, further enhancing its antidepressant effect [4, 29-31].

Step 6 identifies and confirms the most relevant biomarkers [46]. To assess whether zinc effectively lowers depression symptoms, biomarkers that reflect changes in brain activity, inflammation, or neuroplasticity can be measured. Some key biomarkers to track include measuring serum zinc levels [27-28, 35-37], evaluating BDNF levels [31], assessing oxidative stress through markers like malondialdehyde [29], and quantifying changes in glutamate signaling [29-30, 31]. Though many

biomarkers are established for evaluating zinc's role in reducing depression symptoms, many of these methods are long and tedious, so more insight into more efficient biomarkers would help establish zinc as a functional food.

Step 7 involves choosing an appropriate food medium to deliver the bioactive compounds to the human body [46]. As seen in Table 5, many food sources are available to deliver zinc to the body. the most effective foods include oysters, beef, breakfast cereal, pumpkin seeds, pork, and turkey breasts [8].

Step 8 includes preclinical studies to assess the efficacy and safety of the bioactive compound, while Step 9 involves clinical trials to optimize dosage, timing, and evaluate its effects in humans [46]. As cited in this review, many clinical trials and studies have been conducted to learn more about zinc and its impact on depression patients with depression. However, more research can be done to get a clearer image of this goal, specifically in optimizing dosage, the safety of the bioactive effects in humans, and timing. Step 10 focuses on developing consumer-friendly labeling that provides clear instructions on consumption methods, benefits, and recommended dosages [46].

In Step 11, the research findings on the functional food product will be shared with the scientific community through publications in peer-reviewed journals, ideally in open-access platforms [46]. By citing many peer-reviewed articles that have been published on zinc and its ability to lower depression symptoms, this step is adequately met. Similarly, step 12 emphasizes raising public awareness and educating consumers about the functional food product, ensuring they are well-informed and to make educated choices [46]. This has not been done to the best extent because the idea that zinc can benefit patients with MDD is a relatively new concept in the scientific community, which is still being investigated and evaluated before public use. This shows the need for more research in this area to confirm certain aspects of zinc for patients with MDD.

Step 13 submits the required information to the relevant government authorities for review and approval. The scientific evidence requirements may vary by country. Step 14 signifies the successful completion of the functional food product's development [46].

Future Directions on Investigation of Zinc's Role in Reducing Symptoms in Patients with MDD: The current understanding of zinc's involvement in MDD suggests a promising avenue for future research. While studies have indicated lower serum zinc levels in individuals with MDD, and some clinical trials have shown benefits of zinc supplementation as an adjunct to antidepressant therapy, several key areas warrant further investigation to solidify its role and optimize its potential clinical application.

Future research related to MDD should focus on identifying plant and food-based sources of zinc and investigating the mineral's role in alleviating symptoms in affected patients. Future studies should also consider the potential of dietary interventions, such as the incorporation of zinc-rich foods like pumpkin seeds, given their significant contribution to dietary zinc intake (around 2.2 mg per ounce, constituting 20% of the daily value, according to the NIH Office of Dietary Supplements).

1. Elucidating the Precise Mechanisms of Action:
    a. Neurobiological Pathways: Future research should aim to more precisely define the neurobiological mechanisms through which zinc exerts its antidepressant effects. This includes in-depth studies on its interaction with neurotransmitter systems (e.g., glutamatergic, serotonergic, dopaminergic), neurotrophic factors like BDNF, and its role in neurogenesis and synaptic plasticity. For instance, investigating how zinc modulates NMDA receptor activity and its downstream

effects on neuronal signaling pathways could be crucial.

b. Inflammatory and Immune Modulation: Given the link between inflammation and depression, further research should explore zinc's immunomodulatory properties in the context of MDD. Understanding how zinc influences cytokine production and immune cell function in depressed patients could reveal critical therapeutic targets.

c. Genetic and Epigenetic Factors: Future studies could investigate the interplay between genetic predispositions, zinc metabolism, and the development and severity of MDD. Examining potential gene-environment interactions related to zinc and depression could lead to more personalized interventions. Epigenetic studies could also explore how zinc levels might influence gene expression related to mood regulation.

2. Optimizing Clinical Application and Dietary Interventions:

a. Dosage and Formulation of Supplements: Clinical trials are needed to determine the optimal dosage, form (e.g., zinc sulfate, zinc gluconate), and duration of zinc supplementation for patients with MDD. Factors such as bioavailability and tolerability should be carefully considered.

b. Investigating Dietary Zinc Sources: Future research could explore the impact of incorporating zinc-rich foods, such as pumpkin seeds, into MDD. Studies could investigate whether increasing dietary zinc intake through food sources alone or in combination with supplementation can influence depression symptoms.

c. Identifying Responders: Research should identify potential biomarkers or patient characteristics that predict a positive response to zinc supplementation or dietary interventions. This could involve examining baseline zinc levels, genetic profiles, or specific symptom clusters within MDD.

d. Combination Therapies: Further investigation into the synergistic effects of zinc supplementation or dietary zinc interventions with different classes of antidepressants or other therapeutic interventions (e.g., psychotherapy, exercise) is warranted. Understanding how zinc can enhance the efficacy of existing treatments could significantly improve patient outcomes.

3. Addressing Methodological Considerations:

a. Rigorous Clinical Trial Design: Future clinical trials should employ robust methodologies, including larger sample sizes, double-blinding, and placebo controls. Standardized outcome measures for depression severity and zinc levels should be used across studies to allow for meaningful comparisons and meta-analyses.

By addressing these future research directions, including the potential of dietary zinc sources like pumpkin seeds, we can better understand zinc's role in MDD and potentially develop more effective and personalized treatment and preventative strategies for this debilitating condition.

Scientific Innovation and Practical Implications: This review distinguishes itself by providing a comprehensive examination of zinc's potential as a supplemental therapy for MDD, a topic that, despite its clinical relevance, has received comparatively limited scholarly attention. Unlike existing literature that often focuses solely on pharmaceutical interventions, this work integrates insights from diverse perspectives, including the limitations of conventional antidepressants, the

feasibility of agricultural modifications to address zinc deficiency, and the potential risks associated with excessive zinc intake. By synthesizing these varied aspects, this review offers a holistic understanding of zinc's role in depression management. Furthermore, it uniquely applies the Functional Food Center's 17-step process to assess zinc's viability as a functional food, identifying key areas requiring further research and standardization before widespread clinical application. This systematic evaluation, particularly concerning optimal dosage, timing, and biomarker validation, positions this review as a pivotal resource for advancing zinc-based therapeutic strategies in mental health.

CONCLUSION

Zinc has shown promise in addressing depression, particularly in elderly patients, where low zinc levels are strongly associated with depressive symptoms. Some studies suggest that supplementing zinc alongside antidepressants can improve outcomes, but more research is needed to optimize this combination therapy and understand its mechanisms. Expanding research to include multiple age groups and exploring the effects of combining zinc with other functional foods, such as magnesium and flavonoids, could provide innovative strategies for managing depression. However, caution is warranted, as excessive zinc consumption may lead to adverse effects, including abdominal cramping and chemical imbalances, underscoring the need for clear guidelines on safe dosages before clinical application. Overall, zinc holds potential not only in managing depression but also in supporting patients with anxiety, Alzheimer's, and other neurological disorders, making it a promising area for future investigation.

Abbreviations: MDD: Major Depressive Disorder, NMDA: N-methyl-D-aspartate, SSRIs: Selective Serotonin Reuptake Inhibitors, 5-HT: serotonin, NE: norepinephrine, AEs: adverse effects, HPA: hypothalamic-pituitary-adrenal, BDNF: Brain-Derived Neurotrophic Factor

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