

Effects of Zinc Administration on Mood and Psychotic Disorders: A Literature Review

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Abstract

Zinc is one of the macronutrients associated with emotional, cognitive, and behavioral processes. Zinc deficiency is a serum zinc concentration $< 70 \mu\text{g/dl}$. Zinc deficiency is associated with neurosensory disorders, and is also closely associated with mood disorders such as depression. Mood disorders and psychosis consist of depression, bipolar disorder, and schizophrenia. Several existing studies suggest that nutritional factors, especially the role of micronutrients such as zinc, may contribute to the pathophysiology and management of mood and psychotic disorders. To determine the effect of zinc administration on mood disorders and psychosis. This study used a systematic literature review method using three main electronic databases including Pubmed, ScienceDirect, and Researchgate. From the results of the literature search, 11 clinical articles and studies were obtained, published from 2015 to 2025. Of the eleven articles used in the literature review, nine of them showed a significant relationship between zinc and mood and psychotic disorders. There is a positive relationship between zinc supplementation, serum zinc levels, and mood disorders and psychotics.

Keywords: Depression, Micronutrient, Mood Disorder, Psychotic Disorder, Zinc

1. Introduction

In 2019, a study revealed that around 970 million individuals globally, which equates to 1 in 8 people, suffer from mental health issues like anxiety and depression. The following year, there was a notable surge of 26% and 28% in cases of anxiety and depression, respectively. Despite the availability of effective prevention and treatment options, many individuals struggling with mental health problems do not have access to the necessary services, often due to the stigma and discrimination surrounding mental illness. Around 450 million individuals globally are experiencing mental and behavioural issues. Studies suggest that one out of every four individuals will experience a mental disorder at some point in their life. The Asia Pacific region, as per the World Health Organization, has the highest incidence of depressive disorders in India (56,675,969 cases, which is about 4.5% of the population), while the lowest cases are reported in Maldives (12,739 cases, equal to around 3.7% of the population) (WHO, 2022).

Zinc has an important role in the management of mood disorders and psychosis driven by the need to deepen understanding of mechanisms, effectiveness, and therapeutic doses. Numerous research has indicated a connection between low levels of zinc and mood disorders like depression, as well as a possible correlation with psychotic disorders. A study conducted in 2017 by Gonoodi et al. demonstrated that increased zinc consumption was linked to lower levels of depressive symptoms. Similarly, a study by Afzali et al. in 2021, using a randomized controlled trial, revealed that patients with depression and anxiety experienced a notable decrease in symptoms after receiving zinc supplements



compared to those in the control group (Afzali et al., 2021). Hence, scholars are keen to delve deeper into the literature concerning the impact of zinc on mood disorders and psychotic conditions. The goal of this study is to examine and amalgamate previous research on the connection between zinc levels and mood disorders. This investigation aims to enhance the understanding of zinc's influence on mental well-being, potentially influencing future clinical approaches and aiding in the creation of tailored nutritional or pharmaceutical treatments for mood and psychotic disorders.

2. Literature Review

Depression is a multifactorial mental disorder that can be caused by genetic, neurobiological, environmental, and psychological factors. There are several pathomechanisms of depression, theories regarding neurotransmitter dysregulation, neuroendocrine dysfunction, structural and functional brain changes, neuroplasticity, and brain-derived neurotropic factor and neuroinflammation. The theory is that elevated levels of proinflammatory cytokines such as IL-1, IL-6, and TNF- α , cytokines regulate immune responses and influence mood regulation by affecting neurotransmitter synthesis (Yadav, 2023). Inflammation also activates enzymes (IDO, TDO) that divert tryptophan from serotonin (5HT) synthesis into harmful metabolites such as quinolinic acid, leading to oxidative stress and NMDA receptor overactivation (Zakaria et al., 2022).

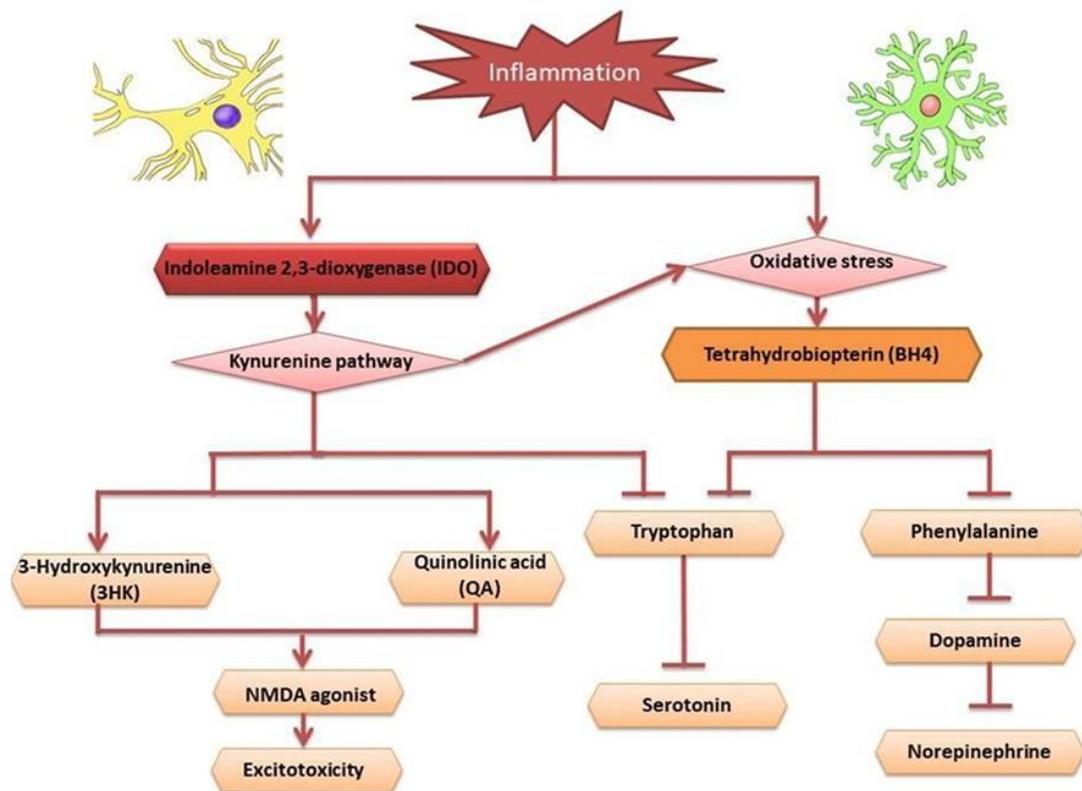


Figure 1. The mechanism of the inflammatory process in depression

3. Methods

The research design used is a literature review. Literature review is the process of tracing and examining various references, such as journals, books, and other publications, which are relevant to the research topic. The literature search in this research was taken from several electronic databases, namely: Pubmed, Google Scholar, and ScienceDirect. The keywords used were “zinc” and “mood

disorder” or “psychosis” or “depression” or “anxiety” or “schizophrenia” and used journal filters published from 2015-2025. Inclusion criteria were journals or articles with clinical data on the relationship between zinc and mood and psychotic disorders in the range of 2014-2025, using English or Indonesian. Exclusion criteria for this study were articles without clear research data, reviews, psychiatric articles/journals that did not include zinc in their discussion. The data that will be extracted include the author's name, year of publication, model used, research objectives, research subjects, research design and research results.

4. Results and Discussion

Through a structured literature search, 11 articles were obtained that met the inclusion criteria from a review of 258 clinical and research articles published between 2015-2025 shown in Table 1.

4.1. Research Results

Table 1. Zinc-related research on mood and psychotic disorders

No	Author	Year	Country	Title	Aims	Research Subject	Results	Research Design
1.	Joe et al.	2018	USA	“Zinc in schizophrenia: A meta-analysis”	The relationship between zinc homeostasis in various psychopathologies, especially in schizophrenia	Total sample (Total sample (n = 1,266) Schizophrenia patients (n = 658) Healthy/control individuals (n = 1,008)	Individuals with schizophrenia showed significantly lower serum zinc concentrations than healthy individuals, with a mean difference of 12.81 mg/dl.	Meta-analysis
2.	Gonoodi et al.	2018	Iran	“Relationship of Dietary and Serum Zinc with Depression Score in Iranian Adolescent Girls”	Investigating the relationship between dietary patterns and serum zinc status and depressive symptoms in adolescent girls	Adolescent girls aged 12-18 years (n = 408) Subjects with no or minimal symptoms (n = 338) Subjects with moderate-severe depressive symptoms (n = 70)	Zinc consumption was inversely associated with depressive symptoms in adolescent girls, while serum zinc concentration showed no significant correlation with depression scores.	Cross-Sectional
3.	Joe, Getz, et al.	2018	USA	“Serum zinc levels in acute psychiatric patients: A case series”	Evaluation of clinically significant factors associated with low blood	Psychiatric patients (n=20) Male (n=15) Female (n=5)	Zinc insufficiency is clinically common among patients with	Case-Series

				zinc levels in patients with acute psychiatric disorders.			acute psychiatric disorders, with a close association between decreased serum zinc levels and a diagnosis of depression, as well as aggressive behavior.	
4.	Afzali et al.	2021	Iran	“A Randomized Clinical Trial of the Effect of Zinc Supplement on Depression and Anxiety in the Elderly”	Determining the effect of zinc supplementation on depression and anxiety in the elderly	Elderly aged ≥ 60 years (n = 150) Intervention (n = 75) Control (n = 75)	Zinc supplementation alleviates symptoms of depression and anxiety in the elderly.	Randomized Clinical Trial
5.	Yosae et al.	2020	Iran	“Zinc in Depression: From Development to Treatment: A Comparative/ Dose Response Meta-analysis of Observational Studies and Randomized Controlled Trials”	Effect of body zinc level and zinc supplementation on depression	Total 13 observational studies (9 cross sectional, and 4 cohort studies). Participants (n = 15,852) Depression (n = 2,243)	Zinc supplementation significantly reduced depressive symptoms in patients. Zinc has potential as an alternative to traditional antidepressant therapy, especially in individuals with mild to moderate depressive symptoms.	Meta-analysis
6.	Świądro et al.	2022	Poland	“Copper and Zinc as Potential Biomarkers of Mood Disorder and Pandemic Syndrome”	Determining blood levels of zinc and magnesium in patients with affective disorders, especially depression and bipolar disorder	Participants n=30 Patients with mood disorders (n = 15) Healthy individuals as controls (n=15)	There were higher zinc levels and lower magnesium levels in depressed patients compared to the control group, suggesting a significant relationship between	Comparative analysis

						these elements and affect.		
7.	Das et al.	2020	Germany	“The association between antioxidant intake, dietary pattern and depressive symptoms in older Australian men: the Concord Health and Ageing in Men Project”	Evaluating the association between antioxidant intakes, dietary patterns, and depressive symptoms among elderly men	Men aged ≥ 70 years (n = 1.705)	There was a significant association between low intakes of antioxidants, specifically zinc and vitamin E, and an increased risk of depressive symptoms in elderly men.	Cross-Sectional
8.	Nakamura et al.	2019	Japan	“Low Zinc, Copper, and Manganese Intake is Associated with Depression and Anxiety Symptoms in the Japanese Working Population: Findings from the Eating Habit and Well-Being Study”	Investigate the association between mineral intakes (zinc, copper, manganese, calcium, magnesium, iron) and mental disorders.	Participants with no history of depression (n = 2.089)	Low intakes of zinc, copper and manganese were found to be strongly associated with the likelihood of mental disorders.	Cross-Sectional
9.	Behrouzian et al.	2023	Iran	“Effects of zinc sulfate on schizophrenia symptoms in patients undergoing atypical antipsychotic pharmacotherapy”	Determine the effect of zinc sulfate in alleviating symptoms of schizophrenia patients undergoing atypical antipsychotic therapy.	Total (n = 88) Supplement Zinc (n = 44) Placebo (n = 44)	Zinc sulfate significantly improved schizophrenic symptoms in patients on therapy after several weeks.	Randomized Controlled Trial
10.	Kamkar et al.	2020	Iran	“Comparison of Serum Zinc Levels between Patients with Schizophrenia and Healthy Individuals”	Comparing blood zinc levels in patients with schizophrenia and healthy individuals.	(n = 110) Schizophrenia patients (n = 55) Healthy individuals (n = 55)	The study found that the mean blood zinc concentration was not significantly different between	Case-Control Study.

						patients with schizophrenia and healthy individuals. A significant negative correlation was found between blood zinc concentration and age in schizophrenia patients.	
11.	Baj et al. 2020	Poland	“Beyond the Mind—Serum Trace Element Levels in Schizophrenic Patients: A Systematic Review”	Evaluating blood concentrations of trace elements in patients diagnosed with schizophrenia	((n = 4901) Schizophrenia patients (n = 2,191) Controls (n = 2,710)	The findings indicate that there are no consistent blood levels of trace elements in patients with schizophrenia, so it cannot be used as a definitive diagnostic or prognostic marker.	Systematic-Review

4.2. Discussion

The research conducted by Joe and colleagues (2018) delved into the impact of zinc balance in schizophrenia, indicating a possible link to the condition as a result of irregular zinc transporter functions. An analysis combining data from 10 different studies found that individuals with schizophrenia had notably lower levels of serum zinc compared to those without the disorder, with an average variance of 12.81 mg/dl. The drop in zinc concentrations was particularly significant in individuals who were admitted to hospitals and those who were recently diagnosed and had not started any treatment. These results imply an imbalance in zinc levels, although the exact connection between decreased zinc levels and symptoms of psychosis remains ambiguous.

A study conducted by Gonoodi et al. (2018) examined how dietary and serum zinc levels in Iranian adolescent girls related to their depression scores. The results emphasised a notable link between lower dietary zinc intake and more severe depressive symptoms. Interestingly, the study revealed that higher dietary zinc intake was linked to lower depression scores, while serum zinc levels did not show a significant correlation with depression scores.

Joe et al. (2018) conducted research to identify important factors linked to low blood zinc levels in individuals with acute psychiatric conditions. The study involved 20 participants, 15 of whom were male and 5 were female. The findings revealed a high prevalence of zinc deficiency in patients with acute psychiatric disorders, showing a strong correlation between low serum zinc levels and the presence of both depression and aggressive behaviour.

The Parallel Randomized Clinical Trial study by Afzali et al. (2021) investigated the impact of zinc supplementation on depression and anxiety in the elderly, highlighting its significance as a mental

health intervention. A randomised clinical trial included 150 elderly participants, with one group given 30 mg of zinc every day for 70 days. The findings revealed a notable enhancement in depression and anxiety levels in the group that received the intervention compared to the control group. This research suggests zinc supplementation as a fresh approach to address these mental health issues in older individuals, as shown by the considerable decrease in depression and anxiety levels in the intervention group when compared to the control group.

A study conducted by Joe et al. (2018) in 2018 analysed the connection between serum zinc levels and depression. The results indicated that a higher intake of zinc led to a 28% decrease in the likelihood of experiencing depression. The study also found that taking zinc supplements had a significant impact on reducing symptoms of depression, particularly when used on its own, resulting in an average drop of -4.15 points in depression scores. These results propose that zinc could be a cost-efficient substitute for traditional antidepressant treatment.

In a study conducted by researchers in 2022, the focus was on examining copper and zinc as possible indicators of mood disorders like depression and bipolar disorder. Blood samples from both patients with these disorders and from healthy individuals were evaluated using a sophisticated method known as triple-quadrupole inductively coupled plasma mass spectrometry (TQ ICP-MS). The findings revealed that the patients had lower levels of copper and higher levels of zinc compared to the control group, suggesting a noteworthy association between trace elements and mood disorders (Świądro et al., 2021).

Das et al. (2021)'s cross-sectional study explored the links between antioxidant consumption, eating habits, and feelings of depression in older men. The research revealed that not consuming enough antioxidants, in particular zinc and vitamin E, was linked to a higher likelihood of experiencing notable depressive symptoms. The prevalence of depressive symptoms was 12.8% at the start of the study and increased to 13.2% after three years. This study suggests the need for clinical trials to explore this antioxidant-rich dietary intervention to reduce depressive symptoms.

In a cross-sectional study conducted by Nakamura et al. (2019), the link between mineral consumption (such as zinc, copper, manganese, calcium, magnesium, iron) and mental health conditions, namely depression and anxiety, was explored within a group of Japanese employees. The research revealed a notable correlation between inadequate mineral intake and an increased likelihood of experiencing mental disorders, with the lowest 25% displaying a prevalence rate of 6.9%. The odds of experiencing symptoms of depression and anxiety were three times higher in individuals with low levels of zinc and copper intake compared to those with higher levels of intake.

The RCT study by Behrouzian et al. (2023) investigated the effects of zinc sulfate in alleviating symptoms of schizophrenia patients undergoing atypical antipsychotic therapy. Conducted as a double-blind intervention in 2020, the study involved 88 participants who were divided into experimental and control groups. The results showed significant improvements in positive, negative, and psychopathological symptoms in the experimental group after two, four, and six weeks of treatment. The research findings suggest that zinc sulfate can effectively alleviate various symptoms of schizophrenia. The reported side effects were minimal, which indicates a good safety profile.

Kamkar et al. (2020) conducted a case-control study to examine the levels of zinc in the blood of individuals with schizophrenia compared to those without the condition. They selected 55 patients and 55 controls, ensuring they were similar in terms of age and gender. The study results revealed no noticeable difference in the zinc levels between the two groups ($P=0.93$). Interestingly, they did find a significant link between age and zinc levels in individuals with schizophrenia, indicating a negative correlation ($r=-0.298$, $P=0.027$). Furthermore, the researchers observed that men in both groups had notably higher levels of zinc in their blood compared to women ($P<0.05$).

Baj et al. (2020) carried out a thorough examination to assess the levels of trace elements in the blood of individuals with schizophrenia, reviewing 33 studies spanning from 1950 to 2020. The research highlighted changes in trace elements like iron, zinc, copper, and aluminum, which could impact the development and intensity of psychotic symptoms. Despite these findings, the review ultimately determined that there is insufficient reliable proof to suggest that these trace elements can be relied upon as definitive indicators or predictors for schizophrenia.

The recommended daily zinc intake for adults is between 10-15 mg/day, while pregnant women should aim for 20 mg/day. Red meat and seafood are rich sources of zinc, with white meat and meat from young animals containing less zinc. Zinc is the second most plentiful mineral in the body after iron, and it plays a crucial role in immune function, as well as in protein synthesis, wound healing, DNA synthesis, and cell division. In addition, zinc is involved in regulating inflammation, promoting neurogenesis, enhancing neuroplasticity, and controlling the overactivity of the glutamate system in the central nervous system. Imbalances in zinc levels have been linked to reduced immune response, growth issues, and problems with the gastrointestinal system. Zinc deficiency is linked to neurological symptoms that may cause changes in behaviour, memory problems, reduced cognitive abilities and feelings of sadness. Various mental health issues like mood swings, anxiety, PTSD, panic attacks, eating problems, ADHD and autism are commonly associated with zinc insufficiency (Petrilli et al., 2017).

Various studies have looked into how zinc's ability to treat depression works, with a focus on its impact on N-Methyl-D-Aside receptors, also known as zinc channel proteins. These receptors are present on nerve cells and play a role in regulating synaptic plasticity. Studies have found that zinc reduces the activity of NMDA receptors and boosts the presence of serotonergic 5-HT_{1A} receptors. Additionally, zinc has been shown to have antidepressant effects by interacting with NMDA receptors and the l-arginine-nitric oxide (NO) pathway (Gonoodi et al., 2018).

Zinc plays a crucial role in the activity of DNA and RNA polymerases. Zinc fingers enable interactions between DNA-proteins and proteins-proteins that play a key role in the binding of transcription factors and receptors for DNA steroid hormones, thereby affecting gene expression. Around 10% of human proteins depend on zinc for their functioning, and it also regulates numerous other proteins, influencing various cellular processes such as signal transmission, gene expression, and programmed cell death. The brain's limbic system contains the highest concentrations of zinc, which is released from vesicles within the zinc-enriched neuronal network called the glutamatergic zinc-enriched neuronal network (ZEN) that is found in the hippocampus. Zinc also acts as a blocker of NMDA. PCP, ketamine, and other widely recognized NMDA blockers have the ability to cause psychotic symptoms in healthy people. This occurs by interfering with GABAergic interneurons that communicate with the prefrontal cortex, ultimately heightening brain activity in those specific areas according to research (Joe et al., 2018).

Mood disorders and psychoses, which include conditions such as depression, bipolar disorder and schizophrenia represent a burden on individuals globally. Depression is a worldwide disease, affecting more than 350 million people and accounting for 4.4% of the world's population. Depression has several variations from regular attitude changes and short-term emotional changes to difficulty carrying out daily activities. Severe depression increases the risk of suicide. Every year about 800,000 people die by suicide. Suicide is the second leading cause of death in adolescents aged 15-29 years. Bipolar disorder is a neurological disease consisting of cycles of depression and manic episodes, affecting as many as 1 in 25 people. At least 25 out of 50 % of bipolar disorder patients have attempted suicide (Butola et al., 2020). Zinc deficiency is associated with impaired serotonergic function, increased inflammatory response, and oxidative stress. Research by Ranjbar et al. (2013), demonstrated the potential antidepressant effects of zinc supplementation, as monotherapy and also as adjunctive

therapy to conventional therapies such as selective serotonin reuptake inhibitors (SSRIs). Zinc supplementation is associated with increased response rates and more improvement in depressive symptoms compared to placebo in clinical trials (Ranjbar et al., 2013).

Schizophrenia is a syndrome; consisting of multiple indications and symptoms with an unknown primary etiology. Schizophrenia is characterized by psychotic manifestations and neurodevelopmental changes affecting as many as 21 million individuals worldwide. In severe cases, schizophrenia with visual and audiotic psychotics develops in late puberty and young adulthood (Butola et al., 2020). Schizophrenia and other psychotic disorders are complex conditions characterized by disturbances in dopamine signaling, neuroinflammation, and oxidative stress. The role of zinc in modulating glutamatergic and dopaminergic neurotransmission shows the relevance of zinc to psychosis disorders. Research has also found changes in serum zinc levels in schizophrenia patients. A 2020 study by Kamkar found that zinc supplementation can alleviate negative symptoms and cognitive deficits. In addition, zinc's antioxidant and anti-inflammatory properties can reduce some of the neurobiological disorders found in psychosis disorders (Butola et al., 2020; Kamkar et al., 2020).

5. Conclusion

The review of academic sources suggests a link between increasing zinc intake, serum zinc levels, and mental health conditions such as mood and psychotic disorders. Despite the results showing a positive effect of zinc administration in patients with mood and psychotic disorders, there are still significant gaps in the understanding of the therapeutic potential of zinc. Variability in study design, dosage, and patient population may complicate the interpretation of study results. It is hoped that new research will focus on longitudinal studies to assess the long-term efficacy and safety of zinc supplements in varied patient populations, as well as elucidate the precise molecular processes of how zinc affects the central nervous system.

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