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The role of nutraceuticals of natural origin in the treatment of depressive disorders

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Abstract

Introduction: Major Depressive Disorder is a prevalent mental disorder, significantly contributing to the number of disability-adjusted life years and years of healthy life lost to disability. The efficacy of currently available treatment modalities is limited by adverse effects and suboptimal treatment response, highlighting the need for additional therapeutic options. A growing body of evidence suggests that numerous nutraceuticals of natural origin may be implemented in the treatment of depression.

Aim of the study: The aim of the study was to compile and analyze current literature regarding the supplementation with polyunsaturated fatty acids, probiotics, polyphenolic antioxidants, vitamins and minerals in treatment and prevention of depression, both as an adjunct to antidepressants and as a standalone therapy.

Methods and materials: A literature search was conducted using the PubMed database and Google Scholar, focusing on recent publications, primarily from the past 10 years. Additionally, references from selected articles were included in the analysis.

Summary: Recent scientific literature suggests that all analyzed nutraceuticals may be effectively used in the treatment of depression. However, further research, particularly large-scale randomized controlled studies, is crucial to confirm the efficacy of these compounds as treatment modalities.

Keywords: Antidepressants, Depression, Natural products, Polyphenolic antioxidants, Polyunsaturated fatty acids, Probiotics, Vitamins and minerals

Introduction

Depressive disorders are a heterogenous group of mental health problems characterized by absence of a positive affect, low mood and a range of associated emotional, cognitive, physical and behavioral symptoms of diverse severity [1]. Depression (major depressive disorder, MDD) is the second most common mental disorder, with age standardized prevalence estimated for 3440,1 per 100 000 people (3097,0–3817,6; 95% UI) in 2019 globally. Depression is accountable for the largest proportion of disability-adjusted life years (DALYs) among mental disorders and positions itself as thirteenth leading cause of DALYs among all diseases. Depressive disorders are the second leading cause of years of healthy life lost to disability (YLDs) [2]. Depression is associated with the increased excess costs of illness (COI), thereby significantly increasing healthcare expenditures [3].

Pathophysiology of depression has not been fully elucidated, however a number of genetic, epigenetic, environmental and neurobiological factors have been identified as conducive to the development of the depressive disorders [4,5]. There are several theories explaining the pathophysiology of depression. The monoamine hypothesis implies a dependency between depressive disorders and deficiency of monoamines in central serotonin, dopamine and norepinephrine systems [6]. This deficiency may be explained by an increased monoamine oxidase activity, decreased transport protein function and an impairment of monoamine receptors function [7]. The inflammation theory implies a strong correlation between the concentration of peripheral proinflammatory cytokines, which cause neuroinflammation, and depressive disorders. Another theory suggests that impairment of neuroplasticity caused by diminished levels of brain-derived neurotrophic factor (BDNF), may induce depression [5]. Other theories highlight the link between the development of depression and endocrine systems abnormalities, such as hypothalamic-pituitary-adrenal axis dysfunction, defective growth hormone release and alterations in thyroid function. Lastly, genetic and environmental stress factors contribute to increased susceptibility to depression [7].

Currently, a combination of pharmacological and psychological or psychosocial interventions remains the mainstay of depression therapy. Pharmacological interventions base on implementation of antidepressants, categorized into major classes - tricyclic antidepressants.

(TCAs), tetracyclic antidepressants (TeCAs), selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (NRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), melatonin receptor agonists and noradrenaline and dopamine reuptake inhibitors (NDRIs). Treatment with antidepressants presents several limitations. Initially, 30–40% of patients do not respond to the first line of therapy, necessitating an escalation of treatment strategy. This often involves introducing additional antidepressants, switching classes of antidepressants, increasing doses, or employing pharmacological augmentation [8]. Furthermore, the therapeutic effect of antidepressants becomes evident after 2 to 4 weeks of continuous treatment [9]. Finally, the use of the antidepressants comes with a risk of numerous adverse effects, affecting up to 27% of patients [10]. Psychotherapies seem to present comparable effectiveness to pharmacotherapy; however, their scarce availability, high costs, and limited efficacy in cases of severe depression constitute significant limitations to this treatment option [5].

Given the adverse effects associated with antidepressants, the high incidence of suboptimal response, and the frequent need to modify pharmacotherapy, it is evident that introducing additional therapeutic options could improve the efficacy and safety of depression treatment. Recently, several nutraceuticals of natural origin have shown promising results in the treatment of depressive disorders, both as standalone and adjunctive therapeutics. This review aims to critically appraise the role of natural nutraceuticals in the treatment and prevention of depressive disorders in adults, with a focus on selected polyphenolic antioxidants, polyunsaturated fatty acids, probiotics, vitamins and minerals.

N-3 polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) are a group of unsaturated fatty acids characterized by the presence of two or more double bonds in a pentadiene configuration. Omega-3 (n-3) PUFAs family includes α-linolenic acid (ALA) and its metabolic products, Eicosapentaenoic acid (EPA) and clupanodonic acid (DHA). ALA is mainly found in seeds and leaves of soybeans, linseed, blackcurrant seeds and borage leaves. EPA and DHA are found in fish oils and liver of non-oily fish [11]. Omega-3 PUFAs exhibit pleiotropic influence on the function of the central nervous system, affecting mechanisms crucial for mood regulation and the development of depression [12]. Omega-3 PUFAs modulate the function of inadequately

activated microglia, thus inhibiting neuroinflammation, a driving factor for depressive disorders [13]. Increased dietary intake of omega-3 PUFAs is associated with enhanced BDNF serum level, promoting neuroplasticity [14]. Furthermore, omega-3 PUFAs modulate hypothalamic-pituitary-adrenal (HPA) axis, by enhancing its negative feedback sensitivity and down-regulating expression of proinflammatory cytokines. Hyperactivation of HPA is commonly found in patients with MDD and is associated with neuroinflammation, diminished neuroplasticity and dysfunction of serotoninergic, noradrenergic and dopaminergic neurotransmission. Lastly, n-3 PUFAs regulate the synthesis, release and reuptake of serotonin, dopamine, norepinephrine and GABA, neurotransmitters which depletion is responsible for development of depressive disorders [12,14,15].

In their 2018 observational study, Thesing et al. demonstrated an association between decreased n-3 PUFAs plasma levels and dysregulation in both the HPA axis and autonomic nervous system (ANS), as well as inflammatory markers. High evening cortisol, which is indicative of a dysfunction of the HPA axis, was significantly associated with low n-3 PUFAs plasma levels. High heart rate (HR), one of the indicators of a dysregulated ANS, was significantly associated with decreased n-3 PUFAs plasma levels. Finally, elevated inflammatory mediators – TNF-α, IL-6 and CRP – were significantly associated with low n-3 PUFAs plasma levels. Authors conclude that given the correlations between decreased omega-3 fatty acids and disrupted activity of stress systems, supplementation with n-3 PUFAs might lead to improvement of mental health due to reduction of biological stress [15].

A large prospective observational study by Matsuoka et al. conducted on a Japanese cohort showcased a correlation between increased dietary intake of n-3 fatty acids contained in fish and a decreased risk of MDD [16]. Notably, intake of EPA or DHA and the risk of MDD demonstrated a reverse J-shaped association. Possible explanations suggest that increased intake of other nutrients, possibly n-6 PUFAs, may decrease the protective influence of n-3 PUFAs on MDD. These observations corroborate the hypothesis that an elevated n-6 to n-3 fatty acids ratio may promote the development of depressive disorders due to low grade neuroinflammation and altered cell membrane integrity [17]. Similarly, a randomized controlled study by Sánchez-Villegas et al. revealed an association between moderate intake of omega-3 PUFAs and a lower prevalence of depression [18]. The results of this study support those of Matsuoka et al. confirming a non-linear association between n-3 PUFAs

intake and the prevalence of depression, however in their study Sánchez-Villegas et al. observed a U-shaped type of association.

A prospective cohort study by Mehdi et al. showcased the efficacy of omega-3 PUFAs as both a standalone treatment and an adjunctive therapy when added to three different selective serotonin reuptake inhibitors antidepressants. Severity of depressive symptoms was assessed with the Hamilton Depression Rating Scale (HDRS). Patients receiving only omega-3 fatty acid supplementation have shown a significant reduction of depressive symptoms by the end of the follow-up period. However, when combined with SSRI antidepressants, the reduction of HDRS score was significantly greater [19]. The results of the study are in line with results of a randomized control study by Gertsik et al, which support use of omega-3 fatty acids as augmentation for citalopram (SSRI). These findings highlight the potential role of n-3 PUFAs as an adjunct to antidepressants [20].

Several randomized controlled studies validate supplementation with omega-3 PUFAs in patients with depression. In their 2019 study, Yang et al. demonstrated an association between the increased plasma level of eicosapentaenoylethanolamide (EPEA) and a reduction of depressive symptoms, assessed with HDRS. EPEA is EPA-derived endogenous mediator, which modulates neuroinflammation by binding to cannabinoid receptors. Notably, it was observed that treatment with EPA alone or in combination with DHA was more effective than treatment with DHA alone. This suggests that EPA plays a key role in antidepressive properties of n-3 PUFAs [21]. A 2023 randomized control study by Lamon-Fava et al. showed a dose-dependent reduction of clinical symptoms of depression as a result of EPA supplementation in patients with a body mass index (BMI) greater than 25, depression severity score in inventory of Depressive Symptomatology-30 item (IDS-C30) greater than 25 and presence of low grade chronic inflammation. Patients were randomized into four groups, receiving placebo, 1 g, 2 g or 4 g of EPA per day. Antidepressive effect of EPA supplementation was higher in the group receiving 4 g of EPA per day than in the placebo group, with response rate of 64% and 40% in each group respectively. Remarkably, authors observed a significant correlation between the reduction in both IDS-C30 scores and plasma levels of high-sensitivity C-reactive protein, and an increase in plasma levels of 18-hydroxyeicosapentaenoic acid (18-HEPE), a mediator derived from EPA. This correlation suggests superior response to treatment with EPA in patients with greater ability to synthesize 18-HEPE from EPA [22]. A 2023 study by Chang et al. evaluated the effects of n-3 PUFAs

supplementation in patients with cardiovascular disease and comorbid MDD. Patients were randomized into a control group and a group receiving n-3 PUFAs supplementation regimen consisting of 2 g of EPA and 1 g of DHA per day. The somatic and fatigue symptoms of depression were assessed with the Neurotoxicity Rating Scale (NRS) and the Chalder Fatigue Scale. When compared to the placebo group, the n-3 PUFAs group achieved a significant reduction in fatigue scores only at week 4 of the study. However, after age stratification, younger patients (age less than 55 years old) receiving n-3 PUFAs experienced a significantly greater reduction in the NRS score at the end of the study. Authors have concluded that n-3 PUFAs may be considered as a treatment option in cardiovascular diseases comorbid depression [23].

On the contrary, there are randomized controlled studies that did not prove efficacy of supplementing n-3 PUFAs in patients with depression. A 2019 study by Tayama et al. compared the efficacy of psychoeducation combined with n-3 PUFAs supplementation in comparison to psychoeducation alone in patients with mild to moderate depression. In both groups a significant decrease of depressive symptoms, measured with Kessler Psychological Distress Scale (K6), was achieved. However, no statistically significant difference in K6 score was observed between the control group and the experimental group, suggesting that omega-3 PUFAs were not efficient as an adjunct to psychotherapy [24].

A large randomized controlled study by Okereke et al. evaluated the efficacy of n-3 PUFAs supplementation in preventing depression in the adult population. 18 353 patients were randomized into an experimental group receiving 1 g of omega-3 PUFAs (465 mg of EPA and 375 mg DHA) and vitamin D_3 (2000 IU) per day and placebo group. Notably, a statistically significant increase in the risk of developing depression was observed in the experimental group when compared to the placebo group, with adjusted hazard ratio being 1.13 (95% CI, 1.01–1.26; $p = 0.03$) [25]. Conducting further research with special emphasis on large scale RCTs is crucial to draw unequivocal conclusions regarding efficacy of n-3 PUFAs in treatment of depression.

Probiotics

A growing amount of evidence suggests a link between the disruption of the gut-brain axis and the development of MDD. Gut microbiome plays a pivotal role in the production of mediators responsible for communication between intestines and the CSN [26]. Therefore, gut dysbiosis, defined as change to the composition of resident commensal microbiota in the gut, may lead to disturbances in brain homeostasis [27,28]. Probiotics are defined as live microorganisms which when administered in adequate amounts confer a health benefit on the host. Probiotics positively affect systems crucial for the development of depression, including the HPA-axis and the immune system [28]. Probiotics exhibit anti-inflammatory effects, suppressing proinflammatory cytokines such as IL-6, IL-12, TNF-α, TNF-β, NFκB, and MCP-1m, and promoting anti-inflammatory pathways [29]. Furthermore, supplementation with probiotics may increase serum levels of BDNF, supporting neuroplasticity [30]. 178 species of probiotic organisms were identified as potentially beneficial in the treatment of depression, with *Lactobacillus spp.* and *Bifidobacterium spp.* being most frequently administered [31].

Recent scientific literature supports the use of probiotics as a treatment option in depressive disorders. A 2023 meta-analysis conducted by Zhang et al. showed antidepressant effects of probiotics. In comparison to placebo, probiotics were significantly superior in ameliorating symptoms of mild to moderate depression. Authors have concluded that probiotics might become a novel therapeutic option in cases of less severe depression [32]. These conclusions are in line with a meta-analysis by Nikolova et al. which supports the use of probiotics as adjunctive therapy to antidepressants. It is noteworthy that probiotics did not demonstrate efficacy as monotherapy, however only a limited number of trials regarding their efficacy were included in the analysis [33]. On the contrary, a meta-analysis by Zhao et al. suggests that probiotics may demonstrate efficacy when used either as adjunctive therapy or as monotherapy of MDD. Authors compared the therapeutic potential of 22 interventions including probiotics and antidepressants. Probiotics were found to be noninferior to all analyzed antidepressants and superior to brexpiprazole, cariprazine, desvenlafaxine,

venlafaxine and vortioxetine as an add-on therapy. The tolerability of probiotic intervention was comparable to that of antidepressants [34].

Furthermore, there are recent randomized controlled trials supporting the use of probiotics in patients with depressive disorders. A single center randomized controlled study by Nikolova et al. investigated the efficacy, safety and tolerability of multistrain probiotics as adjuvant treatment to SSRI antidepressants. 50 patients with moderate depression were randomly assigned to intervention group receiving 8 billion colony-forming units of multistrain probiotic per day and to placebo group. After 8 weeks of intervention, depressive symptoms assessed with HDRS and Inventory of Depressive Symptomatology (IDS), improved in both groups. However, the reduction in IDS scores at week 8 and HDRS scores at week 4 were greater in patients receiving probiotics in comparison to the placebo group. As only minor and transient adverse effects were observed in the probiotic group, the intervention was considered safe and well-tolerable. These results suggest that probiotics may constitute an efficient and well-tolerable adjuvant to antidepressants [35].

The results of a clinical trial by Schaub et al. extends the work of Nikolova et al. on use of probiotics as an add-on to antidepressants. In their randomized controlled study authors have evaluated the efficacy of short term, high dose probiotic supplementation as an adjuvant to the mainstay therapy of MDD. Patients diagnosed with ongoing depressive episodes, who received treatment with various antidepressants were included in the study. 60 participants were randomized into an experimental group, receiving supplements consisting of 8 strains of probiotics, and a placebo group. Depressive symptoms were assessed with the HDRS scale. In both groups a decrease in depressive symptoms was observed. However, the experimental group achieved a greater decrease in the HDRS scores compared to the placebo group from the baseline to the post-intervention assessment. The difference in reduction of the HDRS score between the groups remained statistically significant to the follow-up assessment [36]. These results suggest that probiotics work synergistically with a variety of antidepressants and their adjunctive properties are not limited to the SSRI antidepressant group. Supplementation with probiotics may also be effective in the treatment of depressive disorders without concomitant use of antidepressants. A single center, randomized controlled, crossover trial by Ullah et al. investigated effects of supplement containing *Lactobacillus helveticus*, *Bifidobacterium longum* and S-adenosyl-L-methionine in patients with subthreshold and mild to moderate depression. 65 patients were randomized into two experimental groups (group A

and B) after the run-in period. Group A initially received supplementation and after the wash-out period received placebo. Group B was initially treated with placebo and after the wash-out period was treated with supplement. Depressive symptoms were assessed with the HDRS and the Patient Health Questionnaire-9 (PHQ-9). At the end of the crossover clinical trial, patients receiving supplements achieved greater reduction in HDRS scores and PHQ-9 scores than patients receiving placebo. During the follow-up period, patients from group A showed higher HDRS and PHQ-9 scores than patients from group B, suggesting a lasting effect of supplementation with probiotics on depressive symptoms [37].

Polyphenolic antioxidants

Polyphenols encompass a wide variety of compounds that are plentiful in plants, including fruits, vegetables, and beverages such as tea and wine. The presence of polyphenols in the human diets has garnered attention due to their potential health benefits, including their role in combating oxidative stress, and in modulating signaling pathways that influence gene expression [38].

Resveratrol

Resveratrol is a phytoalexin that can be found in certain fruits that are part of the human diet, such as grape skins, berries, blackberries, and peanuts. However, the main source of resveratrol in the Mediterranean diet is red wine [39]. The small molecular structure of resveratrol allows it to passively cross cell membranes or bind to hormonal receptors and enzymes. Additionally as a member of the polyphenol group it has demonstrated antioxidant properties [39]. Resveratrol exists in two isomeric forms, trans-(E) and cis-(Z), which can isomerize when exposed to ultraviolet light. The 4-hydroxystilbene structure in resveratrol acts as an antioxidant, effectively scavenging free radicals. Initial studies highlighted its antioxidant properties, showing it could inhibit copper-catalyzed LDL oxidation and lipid peroxidation in liver microsomes. Later research found that resveratrol could reduce the release of inflammatory mediators linked to cardiovascular disease, helping to explain the 'French paradox' where certain European populations have low cardiovascular disease rates despite high-fat diets. A significant 1997 study demonstrated resveratrol's chemopreventive

effects on skin cancer [40], later supported by findings that it can prevent various malignant neoplasms. Additionally, resveratrol was found to have neuroprotective effects. These benefits are largely mediated by cyclooxygenases, NF-κB, and AP-1, key players in inflammation and carcinogenesis. Although rare, some early studies suggested resveratrol might increase atherosclerosis and DNA damage when administered in diets [41].

In the systematic review conducted by Moore et al. regarding the impact of resveratrol on depression in animal models, it was found that resveratrol increases sucrose consumption by animals, suggesting a counteraction to the decrease in reward-seeking behaviors typically seen in depression. Additionally, a reduction in immobility time was observed in relevant tests following administration of resveratrol in the doses ranging from 15 to 80 mg/kg/day. Furthermore, the recent study has reported that resveratrol exhibits antidepressant effects in rodents at a level similar to traditional antidepressant drugs such as fluoxetine, desipramine, and ketamine [42].

Green tea

Reports indicate that consuming green tea, a beverage with a long-standing history, might assist in alleviating depression. Catechins, found in teas have been shown to increase levels of noradrenaline and dopamine in the blood [43], which play a crucial role in combating depression [6]. Additionally, theanine, a prominent amino acid found in green tea, has demonstrated anti-stress effects [44,45]. Given that stress is an acknowledged risk factor of depression [46], theanine may exhibit antidepressive properties.

In the systematic review and meta-analysis conducted by Akinori Yaegashi et al., the results indicated that high consumption of green tea is inversely associated with symptoms severity of depression, measured using appropriate depression scales (the 15-item and 30-item Geriatric Depression Scale [GDS], the Center for Epidemiological Studies Depression Scale [CES-D], the Patient Health Questionnaire-9 [PHQ-9], the Japanese version of the Hospital Anxiety and Depression Scale [HADS]), with an odds ratio of 0.66 (95% CI: 0.58-0.74) [47].

In the experimental study conducted by Kimura et al., which utilized a double-blind trial design, researchers assessed the effects of l-theanine on stress responses. Subjective evaluation of stress intensity, heart rate (HR) frequency, heart rate variability (HRV) and

salivary immunoglobulin A (s-IgA) levels were measured. Twelve participants were allocated to four groups: one where they consumed l-theanine (at a dose of 200 mg) at the beginning of the experimental procedure, another where they consumed l-theanine midway, and two control groups where they either received a placebo or did not receive anything. The findings suggested that l-theanine consumption led to a decrease in HR frequency and a reduction in s-IgA response during an acute stress-related task, compared to the placebo group where a placebo was administered [45].

Vitamins and minerals

Zinc

Zinc is a vital micronutrient that is essential in cell growth, apoptosis, and several metabolic pathways. It also plays a role in regulating endocrine, immune, and neuronal functions, which are associated with the pathophysiology of depression [48]. In the hippocampus and cortex, zinc ions cause increased expression of hippocampal and cortical BDNF, and also serve as antagonists of the N-methyl-D-aspartate (NMDA) receptor [49]. The normal zinc concentration for adults ranges from 11 to 18 μmol/l (70–120 μg/dl), and from 11 to 24 μmol/l (70–160 μg/dl) in children [50].

There are scientific studies demonstrating that serum zinc levels correlate with the frequency of depression occurrence. In a meta-analysis by Swardfager et al., which included 17 studies examining peripheral blood zinc levels in a total of 1643 individuals with depression and 804 individuals in the control group, it has been discovered that zinc levels were lower by approximately 1.85 μmol/l in individuals with depression compared to those in the control group (95% confidence interval [CI]: -2.51 to -1.19 μmol/l, $Z = 5.45$, $p < 0.00001$). Furthermore, in the studies where depression symptoms were quantitatively assessed, greater depression severity was linked to a more significant relative zinc deficiency ($B = –1.503$, $t = –2.82$, $p = 0.026$) [48].

A randomized, placebo-controlled, double-blind study was conducted in 5 public schools in a low-income community in the city of Guatemala, which constitutes a population at risk of zinc deficiency, to assess the impact of zinc supplementation on mental health [51]. Prior to the study, the presence of any known serious organic diseases in children that may affect zinc

levels, such as sickle cell anemia, cystic fibrosis, kidney or liver diseases, severe burns, or enteropathic skin inflammation [52], was excluded. 674 children were randomly assigned to two groups: one group received zinc supplementation (10 mg of zinc oxide [ZnO] daily for 5 days a week), while the other group was given a placebo (10 mg of glucose). After six months, no significant differences in mental health outcomes have been observed between the group receiving zinc supplementation and the placebo group. What is interesting, an independent milk program unrelated to the study has been implemented during the period of the study. Subsequently, an increase in serum zinc levels in both groups has been observed that was associated with a reduction in internalizing symptoms, such as depression and anxiety [51].

Furthermore, a correlation has been established between zinc deficiency and depressive symptoms among women, but not among men. Women who consumed low levels of zinc, either through their diet or supplementation, were more likely to experience depressive symptoms [53].

Magnesium

Magnesium is a crucial macromineral in the human diet that acts as a cofactor for over 300 enzymatic reactions. It takes part in regulating muscle contraction (including the heart), blood pressure, insulin metabolism, and the synthesis of DNA, RNA, and proteins [54]. In the nervous system, magnesium is essential for optimal nerve transmission and neuromuscular coordination and provides protection against excitotoxicity, which is excessive excitation leading to cell death. A key neurological function of magnesium involves its interaction with the NMDA receptor, where it blocks the calcium channel as a calcium antagonist. This blockade must be removed for glutamatergic excitatory signaling to occur [55]. Low magnesium levels can potentially enhance glutamatergic neurotransmission, creating a supportive environment for excitotoxicity, which may result in oxidative stress and neuronal cell death [56].

A meta-analysis was conducted, covering a total of 17 epidemiological studies retrieved from 12 articles. Out of these studies, 11 investigated the correlation between dietary magnesium intake and the risk of depression. Six of the studies identified a statistically significant correlation between dietary magnesium intake and depression risk, whereas the remaining

five studies did not find any association (the combined relative risk (RR) of depression for those with the highest magnesium intake compared to the lowest was 0.81 (95% CI: 0.70–0.92). Regarding dose–response analysis, data from six studies indicated a nonlinear relationship between dietary magnesium intake and depression risk (p for nonlinearity = 0.0038), with the most substantial risk reduction observed at an intake level of 320 mg/day [57].

A study conducted by Tarleton and Littenberg [58] examined the relationship between depression (as indicated by a PHQ-9 score ≥5) and low magnesium intake (<184 mg/day) among 8894 adults in the USA. It revealed a significant association between low magnesium intake and depression, with an odds ratio (OR) of 1.21 (95% CI, 1.02–1.42) and a risk ratio (RR) of 1.16 (95% CI, 1.06 –1.30). Upon further analysis, low magnesium intake appeared to be linked to depression in individuals under 65 years old (RR, 1.22 [95% CI, 1.06–1.40]), while it seemed to have a protective effect in older individuals (RR, 0.75 [95% CI, 0.56–0.98]).

Selenium

Selenium is a trace element in the human diet that ensures proper functioning of selenoproteins. Two main selenoproteins are glutathione peroxidase and thioredoxin reductase, which are important antioxidants that reduce hydrogen peroxide to water and reduce harmful lipid hydroperoxides to alcohol. Selenium inhibits NF-κB activation by modulating the expression of selenoprotein genes and suppressing the production of C-reactive protein - a marker of inflammation [59]. The recommended daily intake of selenium is 55 µg/day. The optimal level of selenium in the blood is considered to be in the range of 70 µg/l to 90 µg/l [49].

The anti-inflammatory effect of selenium might have an impact on depression, given the proposed inflammatory etiology of MDD [59]. Additionally, selenium plays an important role in thyroid metabolism as it is a component of iodothyronine deiodinases (DIO). Thyroid disorders are known to be linked with mental health conditions, such as depression [60].

In the intervention study conducted on mice by Brüning et al., it was shown that the administration of m-trifluoromethylphenyl diselenide (m-CF_3–PhSe)$_2$, a selenium-containing

compound, at doses of 50 and 100 mg/kg, resulted in a reduction of depressive symptoms, as assessed by the immobility time in the forced swim test (FST) in female mice. Additionally, it was found that administration of $(m–CF_3–PhSe)_2$ counteracts the antidepressant effect induced by prior administration of 5-HT receptor antagonists (ritanserin at a dose of 4 mg/kg or ondansetron at a dose of 1 mg/kg) and an opioid antagonist (naloxone at a dose of 1 mg/kg). The obtained results suggest that $(m\text{-}CF_3–PhSe)_2$ might exhibit antidepressant effects, likely influenced by interaction with serotoninergic and opioid systems [61].

In a nested case-control study conducted by Pasco et al., women aged 20 years or older were selected from a randomly chosen cohort that was prospectively observed as part of the Geelong Osteoporosis Study. Cases were individuals with incident MDD identified using the SCID-I/NP structured clinical interview, while controls had no such history. Dietary selenium intake was measured at the start of the study using a food frequency questionnaire, along with anthropometric and lifestyle measurements. Eighteen cases of *de novo* MDD and 298 controls were identified. Low dietary selenium intake (<8.9 μg/MJ/day) was linked to an increased likelihood of developing MDD (OR = 2.74; 95% CI 0.95–7.89). After adjusting for age and socio-economic status (SES), low selenium intake was associated with a nearly threefold increase in the risk of developing *de novo* MDD (OR 2.95; 95% CI 1.00–8.72). Smoking, alcohol consumption, and physical activity did not affect this association. These findings suggest that reduced dietary selenium intake is linked to a higher likelihood of developing *de novo* MDD [59].

Vitamin D3

Vitamin D3 has been shown to play a role in serotonin production [62], thereby suggesting a link between the presence of vitamin D3 and the occurrence of depression. It has been found that vitamin D improves serotonergic neurotransmission in a depression model by regulating serotonin metabolism. The signaling of 1,25-dihydroxyvitamin D3, an active form of vitamin D, through the vitamin D receptor (VDR) induces the expression of the tryptophan hydroxylase 2 (TPH2) gene that encodes the enzyme TPH2 responsible for the rate-limiting step in serotonin synthesis in the central nervous system [63]. Additionally, it affects the expression of the serotonin reuptake transporter (SERT) and the levels of monoamine oxidase A (MAO-A), the enzyme responsible for the catabolism of serotonin [64]. Additionally,

Vitamin D acts by reducing the elevated levels of calcium ions (Ca^{2+}) in neurons, which may contribute to the reduction of depressive symptoms [62].

There are reports showcasing a reduction in depression symptoms in individuals who received vitamin D supplementation. A study conducted by Alghamdi et al. assessed the impact of vitamin D supplementation in the treatment of MDD. Participants were divided into two groups: one received oral vitamin D supplementation for 3 months along with standard care, and the other received only standard care. The severity of MDD symptoms was assessed using the Beck Depression Inventory (BDI) scale and serum serotonin and vitamin D level measurements were obtained. A noteworthy finding was that women with moderate, severe and extreme depression achieved significantly lower BDI scores, whereas only males with severe depression demonstrated statistically significant improvement in BDI scores. Serum serotonin levels were significantly higher following vitamin D supplementation, compared to baseline values, in both men and women. These findings suggest that vitamin D supplementation may alleviate symptoms of MDD, particularly in women, through a serotonin-dependent mechanism [65].

Vitamin B6

Vitamin B6 is a cofactor for various enzymes that affect neurotransmitters in the brain, such as norepinephrine and serotonin, which play a major role in mood regulation [66]. Studies have shown that patients with depression have lower levels of pyridoxal phosphate, an active form of vitamin B6 [67]. Vitamin B6 functions as a cofactor in the tryptophan-serotonin pathway, so its deficiencies may lead to depression. Therefore, vitamin B6 may be important in the context of mental health and well-being.

A cross-sectional study by Kafeshani et al. with 3362 adult participants has been conducted. The aim of this study was to examine how vitamin B6 intake, assessed using a validated 106-item semi-quantitative food frequency questionnaire (DFQ) in Willett's format, impacts the occurrence of depression and anxiety states. The average intake of vitamin B6 was significantly lower in individuals with depression (1.86 ± 0.72 mg/day vs. 1.99 ± 0.74 mg/day; $p = 0.001$) compared to healthy participants. Moreover, lower vitamin B6 intake was associated with a higher risk of depression (OR = 1.41; 95% CI: 1.19–2.31; $p < 0.001$) in the overall population, particularly among women [67].

The link between vitamin B6 levels and depression is further supported by an experimental study conducted by Mesripour et al. that investigated the impact of vitamin B6 on dexamethasone (DEX)-induced depression in mice. Male mice were divided into groups of six. Depression was assessed by measuring immobility time in the forced swim test (FST), sucrose preference and locomotor test. It has been demonstrated that administering vitamin B6 (100 mg/kg for 7 days) significantly reduces immobility time in the FST to 85 ± 3.7 seconds compared to control animals (164 ± 6 seconds), confirming its antidepressant effect. Additionally, premedication with vitamin B6 for 7 consecutive days before administering DEX prevented the DEX-induced increase in immobility time in the FST (with a dose of 250 mcg/kg DEX, immobility time was 51.6 ± 2.5 seconds with vitamin B6 premedication compared to 188.3 ± 5 seconds without premedication). There were no differences in locomotor activity observed among the different groups of animals. Furthermore, the addition of vitamin B6 (100 mg/kg) to DEX therapy (15 mcg/ kg) for 7 consecutive days increases sucrose preference compared to therapy without vitamin B6 (66% ± 2 vs. 50% ± 3). The above results confirm that vitamin B6 prevented DEX-induced depression [68].

Folic Acid

Folic acid (FA), also known as folate, is a vital vitamin necessary for health throughout life because it plays a role in the synthesis of nucleotides, amino acids, neurotransmitters, and some vitamins. It undergoes metabolism in the body, converting into S-adenosylmethionine. Both S-adenosylmethionine and folic acid are involved in the synthesis of neurotransmitters, such as serotonin, dopamine, epinephrine, and monoamines [69].

In an observational study conducted by Pan et al., 12 patients with treatment-resistant depression (defined as having undergone at least three therapies with drugs at the maximum dose and for an appropriate duration) and diagnosed with cerebral folate deficiency (CFD) (<40 nmol/l) were treated with folinic acid (a 5-formyl derivative of tetrahydrofolate) (1–2 mg/kg per day) for a minimum of 6 weeks (ranging from 6 to 79 weeks) while continuing their existing treatment. During the observation period, ten out of twelve patients showed a reduction in depression symptom scores assessed by the BDI and the Suicidal Ideation Questionnaire (SIQ). One patient was lost to follow-up, and another did not adhere to the folinic acid treatment. The mean score on the SIQ decreased from 38.0 points (SD=23.13) at

the beginning of the study to 23.1 points (SD=17.09) during the observation period, although the change was not statistically significant (Z=1.24, p=0.107). The mean score on the BDI scale decreased from 30.6 points (SD=7.3) at the beginning of the study to 19.6 points (SD=11.04) during the observation period (Z=2.0, p=0.022) [70].

Conclusions

Depression is a highly prevalent mental disorder and a leading cause of DALYs among all psychiatric disorders. There are several classes of antidepressant medications available, such as MAOI, TCA, SSRI and SNRI, but they have numerous side effects. SSRIs are most frequently prescribed due to their effectiveness and fewer side effects. However, only half of patients achieve complete remission, and the side effects of SSRIs, such as gastrointestinal problems, weight gain, sleep disturbances, and sexual dysfunction, can significantly impact the quality of life of these patients [71]. Therefore, it is necessary to search for alternative therapies with fewer side effects. Our study highlights the significance of nutrients in treating depression.

The nutritional status of an individual, diet quality, and intake of vitamins and minerals have been identified as contributing factors to mental well-being. In recent years, numerous discoveries have been made regarding the treatment of MDD with natural nutraceuticals, offering a promising future for patients and healthcare providers. Several studies have demonstrated the potential of n-3 PUFAs in alleviating depressive symptoms, especially when used as an adjunct to antidepressants. Current research indicates a relationship between anti-inflammatory properties of n-3 PUFAs and their antidepressant effects. Additionally, there is increasing evidence supporting the use of probiotics in patients with depressive disorders. Probiotics proved to be an effective adjunct to multiple antidepressants. However, evidence regarding the efficacy of probiotics as a standalone therapy of depression is limited, warranting further research. Numerous reports suggest that the bioactive components of tea and wine may reduce symptoms of depression by increasing serum levels of noradrenaline and dopamine. Additionally, adequate blood levels of B vitamins, folic acid, and minerals such as zinc, selenium, and magnesium, which are involved in the synthesis process of neurotransmitters, are associated with the prevention of depression, and supplementation of these components may help combat its symptoms. However, further large-scale randomized

and placebo-controlled studies are necessary to confirm the potential of these compounds in the treatment of MDD.

Disclosure

Supplementary materials

Not applicable.

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The data presented in this study are available upon request from the correspondent author.

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