Effect of Diet on Depression: A Review of Nutritional Solutions

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ABSTRACT

Depression is a mental illness with several categories that have common symptoms such as chronic sorrow, lack of interest, lack of pleasure, mood swings between guilt and poor self-esteem, sleep disturbances, and a loss of appetite. Over 300 million individuals globally suffer from depression, and the socioeconomic cost of this debilitating disorder is expected to rise dramatically in the future decades.

Behavioral health illnesses can be prevented and treated to some extent with dietary and nutritional means. Nutritional psychiatry has produced observational and effectiveness evidence regarding the role of healthy dietary patterns in the onset and treatment of depressive symptoms. Diet is associated with depressive symptoms or depression, meaning that an increase in depressive disorders coincide with a deterioration in healthy living choices, including poor quality diets.

Healthy eating habits and adequate intake of essential nutrients via the diet can help prevent and treat depression by reducing symptoms of mental illness. In addition, because nutrition is a modifiable risk factor for depression, it is practical for the public to consider dietary changes to reduce the prevalence of depressive disorders.

This paper reviews the potential value of diet-based actions to manage depression, and ways in which dietary changes could be made to improve mental and cognitive health. Furthermore, some practical solutions for preventing and controlling depression are proposed based on health-related effects of improving dietary habits and life style.

Keywords: Depression, Prevention, Mental Health, Nutrition, Dietary Solutions

INTRODUCTION

Depression is defined as a common mental condition characterized by persistent sadness, a loss of interest and pleasure, variations between feelings of guilt and poor self-esteem, as well as sleep and/or hunger difficulties that interfere with daily functioning. These symptoms appear in many forms of depression and are classified by their strength, duration, and style of presentation (Higuera, 2021).

Depression, anxiety disorders and other mental health conditions are on the rise globally and remain a threat to public health; they are also interlinked to physical health. Some diseases can result in depression, and vice versa. In particular, major depression is a severe, life-threatening, and highly prevalent psychiatric disorder (Bartolomucci & Leopardi, 2009), which may also lead to frequent thoughts about suicide including in young adults (Ljungberg et al., 2020).

Depression may be associated with various risk and protective factors such as biological, psychological, social, environmental, physical activity, smoking, alcohol consumption, sleep quality, and particularly diet. Following the publication of data showing the link between food and mental health, the name "Nutritional Psychiatry" was established to promote and formalize this new field of study (Sarris et al., 2015; Lanuza et al., 2022).

Nutritional psychiatry has produced observational and effectiveness evidence that support the significance of good eating patterns in depression risk and symptom treatment (Marx et al., 2017; Lassale et al., 2019; Firth et al., 2019). The early research in the subject of nutritional psychiatry centered on the function of individual nutrients or single foods in the incidence of mood disorders, as well as the efficacy of separated nutrients (supplements) as therapeutic methods (Marx et al., 2019).

The associations between diet and depressive symptoms are not fully understood due to complications and diversity in the interacting biological processes (Huang et al., 2019). Hence, this review presents some solid evidence pertaining to the link between nutrition and depression, as well as novel nutraceutical treatments and management of those who suffer from such disorders, as a guide for future clinical studies and tailored nutritional interventions.

Nutrients, other dietary substances and depression

Among the various factors associated with depression, understanding the connections between depression and micronutrient deficiencies is significantly important, as deficiency in micronutrients have been related to a variety of health disorders (Wang et al., 2018). The link between depression and macronutrients has been established in several research studies, and the impacts on chronic diseases and weight management have been shown (Larsen et al., 2010; Lagiou et al., 2012). Several reports have indicated a relationship between macronutrient intake and depression, as well as association of diet with prevalence of depression (Oh et al., 2020).

Vitamins

Vitamin B1 (Thiamine) is required for carbohydrate metabolism (Mikkelsen et al., 2016) and it is very important for neuronal cell function because the nervous system is particularly susceptible to oxidative metabolisms and hence to thiamine shortage, as thiamine is the foundation for numerous coenzymes involved in neuronal cell function as well as glucose use. As a result, thiamine deficiency causes a wide range of changes in brain cell functions (Ghaleiha et al., 2016). Neuroinflammation, overexpression of pro-inflammatory cytokines, and arachidonic acid products are all connected to thiamin deficiency, which can cause emotional problems, memory defects, depression, and cognitive decline (Mikkelsen et al., 2017). The link between thiamine shortage and depression, and necessity of sufficient thiamine intake via the diet has been underlined in several studies, as low thiamin levels has commonly been reported in patients with depression

(Mikkelsen, et al., 2016). Some of the best sources of vitamin B1 are peas, beans, whole grain rice, yeast, and nuts, especially raw almonds (Nikseresht et al., 2012). In contrast, conditions that can impair thiamine levels include alcoholism and excessive coffee intake (Bowman, 2018).

The brain needs **niacin** (Vitamin B_3) to get energy and function properly. Niacin deficiency is associated with depression, and numerous research studies have shown that niacin is beneficiary for depression and anxiety symptoms, as well as in individuals with unipolar depressive disorder (Mikkelsen et al., 2016; Prakash et al., 2008; Smesny et al., 2010). An animal model also showed that niacin can help decrease the generation of pro-inflammatory cytokines by macrophages (Lipszyc et al., 2013). As a result, niacin can help decrease inflammation that is a primary cause of depression (Mikkelsen et al., 2017). Some of the best sources of vitamin B_3 are whole wheat, whole grain rice, mushrooms, green peas, potatoes, and avocado. While supplemental doses of the vitamin can have various side effects including liver toxicity, there is no danger in consuming niacin in the amounts found naturally in foods (Julson, 2018).

Vitamin B_6 (Pyridoxine) is important in the regulation of brain functions and mood (Huang et al., 2013). It has an effect on neurotransmitters that govern sadness, pain perception, and anxiety, and deficiencies causes excessive homocysteine levels, which has been related to seizures, migraines, and depression (Hvas et al., 2004). Vitamin B_6 can influence psychotic symptoms in schizophrenia, tiredness, cognitive performance, and depression by lowering homocysteine levels in the blood (Shiloh et al., 2001). Vitamin B_6 is also necessary for the production of GABA, an inhibitory neurotransmitter present in high amounts in brain tissue and the spinal cord (Mikkelsen et al., 2016). Furthermore, plasma pyridoxal phosphate, derived from vitamin B_6, may be substantially lower in patients with depressive symptoms (Hvas et al., 2004). Depressive patients may have higher plasma homocysteine levels associated with poor vitamin B_6 and folate levels (Ebesunun et al., 2012). In contrast, diets rich in Vitamin B_6 and tryptophan can help improve serotonergic neurotransmission in depression caused by a variety of neurodegenerative illnesses (Shabbir et al., 2013). Some of the best sources of vitamin B_3 include carrots, spinach, bananas, green peas, chickpeas, sweet potatoes, and avocado (Whelan, 2017).

Folic acid (folate, vitamin B_9) works closely with vitamins B_6 and B_{12} to keep metabolic processes running smoothly. Low folate levels are linked to depression (Gilbody, et al., 2007) and can lead to problems with methylation and monoamine metabolism, which can contribute to depression. Folate is required for dopamine production in the brain, and low dopamine levels may worsen depression symptoms (Mikkelsen et al., 2016). Additionally, folate affects noradrenalin and serotonin receptors in the brain, indicating that it has antidepressant properties (Mikkelsen et al., 2017). In patients who have folate deficiency, even antidepressants may not be effective in treatment (Coppen & Bolander-Gouaille, 2005). Folate deficiency has multiple causes, including poor dietary intake, alcoholism, and weakened stomach acid such as due to routine consumption of antacids that affect folate absorption. Some of the best sources of folate are beans, citrus fruits such as lemons, sweet lemons and oranges, green leafy vegetables such as spinach, and nuts such as raw almonds. For most people, it is relatively easy to get enough folic acid through a healthy balanced diet (Cherney, 2019; Watson, 2022).

Vitamin B_{12} (Cobalamin) is a catch-all term for any molecule with a cobalt-centered corrin nucleus. B_{12}'s function is intertwined with that of folate. Vitamin B_{12} is essential for the proper

functioning of the brain and neurological system. Vitamin B_{12} deficiency causes severe depression, suicidal behavior, cognitive decline, irritability, mania, and psychosis. Indeed, up to one-third of depressive individuals have vitamin B_{12} deficiency, and sufficient levels are linked to improved treatment results (Vogiatzoglou et al., 2008). Fatigue and weakness, constipation, lack of appetite and weight loss, balance difficulties, depression, and cognitive abnormalities are all common clinical signs of vitamin B_{12} deficiency (Pawlak et al., 2014). Vitamin B_{12} deficiency has also been linked to bipolar disorder (Permoda-Osip et al., 2013) and this supports the theory that low B_{12} levels are associated to decreased production of serotonin and other monoamine neurotransmitters (Seppälä et al., 2013). Low vitamin B_{12} levels are linked to depression, and a deficit, as along with deficiencies of riboflavin and pyridoxine, is associated with major depression. Vitamin B_{12} and folate are involved in the metabolism of monoamine neurotransmitters such as norepinephrine. Noradrenergic release is inhibited in patients with major depressive disorder (Mikkelsen et al., 2016). Vitamin B_{12} is not produced by the cells in humans, animals or plants, but by some certain types of bacteria in a healthy gut, which is then absorbed and stored in the body tissues (O'Leary & Samman, 2010). Consuming natural and chemical-free raw vegetables can improve the gut microbiome, providing suitable conditions in which the "good" bacteria can produce significant quantities of vitamin B_{12} (Watanabe & Bito, 2018). Studies on Iranian villagers with traditional plant-based diets that are very low in animal products have indicated normal vitamin B_{12} levels (Halsted, 1960). Similarly, vitamin B_{12} deficiency is relatively uncommon among native Indians where their own local plant-based products are consumed, but the deficiency has been found with significant frequency among vegetarian Indian immigrants in England with similar dietary patterns, possibly because healthy Indian subjects, eating traditional farming products, may have healthier varieties of bacteria in their small intestine than those in the West (Albert, 1980). According to another study in UK, around half of the vegans with entirely plant-based diet, have had sufficient vitamin B_{12} (Gilsing et al., 2010; Sushma, 2019). This suggests that vitamin B_{12} deficiency can be prevented by maintaining a healthy gut microbiome. It is noted that taking antacids and overuse of antibiotics may significantly reduce absorption of vitamin B_{12} (Zeuschner et al., 2013; Sushma, 2019; Ramirez et al., 2020).

Vitamin C (Ascorbic acid) is a water-soluble antioxidant vitamin that is required by the cells in humans and other animals (Lindblad, et al., 2013; Tveden-Nyborg & Lykkesfeldt, 2013). Vitamin C's active form (ascorbate) is known to have free radical scavenging action, interacting with free radicals such as protein thiyl radicals. Biomolecules should be protected against oxidative damage by such processes (Nauser et al., 2015). Ascorbic acid also acts as an indirect antioxidant, regenerating vitamin E and assisting in the maintenance of oxidant/antioxidant equilibrium in the plasma membrane. Ascorbic acid's neuroprotective effects have been documented in several studies, and modulation of various neurotransmitter systems, such as dopaminergic, noradrenergic, serotonergic, glutamatergic, and cholinergic systems, has been involved in ascorbic acid's activities in the central nervous system (Moritz et al., 2020). Clinical observations of scurvy patients were used to make the initial connections between ascorbic acid and depression pathogenesis. Notably, depression is known to occur before the physical signs of scurvy, suggesting that vitamin C insufficiency may be frequent among depressed people (Kocot et al., 2017). Furthermore, prolonged deficiency in vitamin C has been linked to decreased activity of the enzyme dopamine β-hydroxylase, which reduces the hydroxylation of dopamine to noradrenaline and, as a result, lowers noradrenaline levels. In rats, ascorbic acid has reduced the comorbidity of type 2 diabetes mellitus and depression (Shivavedi et al., 2019). Also, ascorbic

acid's anti-inflammatory properties may possibly contribute to its antidepressant effect. According to a meta-analysis, serum levels of ascorbic acid in depressed individuals increase following antidepressant treatment, implying that a sufficient intake of vitamin C from natural sources may reverse depression symptoms (Liu et al., 2015). Other research examined the food composition of university students and found a link between depression symptoms and low daily intake of vitamin C, when compared to healthy individuals (Prohan et al., 2014). Sufficient intake of vitamin C rich foods can be recommended as an adjuvant for the treatment of depression based on the data available in the literature (Moritz et al., 2020). Some of the best sources of vitamin C to include in the diet are citrus fruits such as on-tree ripened lemons and oranges, apples, fresh red bell peppers, turnip, and parsley (Kosheleva & Kodentsova, 2013; Chávez et al., 2015; Hill et al., 2018). It is noted that the recommended amount of vitamin C intake for the average person is between 65 to 90 milligrams (mg) a day, and natural food sources easily provide the required levels. But consuming high doses in the form of supplements such as 1000 milligrams of Ascorbic Acid, can lead to development of kidney stones (Thomas et al., 2013), which can be extremely painful and persistently annoying, worsening the severity of depression during the period (Sheng et al., 2017).

Vitamin D (Calciferol), is a fat-soluble steroid hormone necessary for calcium absorption from the stomach into the circulation (Alghamdi et al., 2020). After hydroxylation in the liver, vitamin D is transformed to its active form 25(OH) D3 (1, 25-dihydroxyvitamin D3), commonly known as calcitriol 25(OH)D, which performs a variety of activities, including preserving cellular health by regulating the equilibrium of numerous minerals, such as calcium and phosphate. The National Academy of Medicine considers serum 25(OH)D level in the range of 20-50 ng/ml as sufficient (ideal), 12-20 ng/ml as insufficient, and less than 12 ng/ml as deficient (NIH, 2022). Vitamin D deficiency (but not insufficiency) has been linked to metabolic illnesses such as obesity, diabetes, insulin resistance, and hypertension, as well as neuropsychiatric conditions including schizophrenia, Parkinson's disease, Alzheimer's disease, depression, and cognitive impairment (NIH, 2022; Hussein et al., 2022). Low levels of vitamin D in individuals with recurrent depression imply that they are a high-risk category for vitamin D deficiency that may be a major risk factor for subclinical depression symptoms, according to the findings of a micro-longitudinal observational research among healthy young people (Kaviani et al., 2020). Many tissues, including the brain, generate an active form of vitamin D, as well as vitamin D receptors and vitamin D binding proteins, which have also been found in the central nervous system (CNS), notably in regions linked with mood and depression (Caldwell et al., 2019). Vitamin D as a neurohormone has been linked to neuron cell growth and development, brain function, and mood, as well as neurotransmitter synthesis, release, and regulation (Li et al., 2014; Libuda et al., 2017). Low vitamin D levels are frequent in individuals with depression (Kaviani et al., 2020). Vitamin D metabolites have the ability to cross the blood brain barrier (BBB) (Diesel et al., 2005), and vitamin D receptors are found throughout the brain, including the hippocampus, which has been linked to depression (Menon et al., 2020). As a result, having sufficient vitamin D levels may provide extra therapeutic advantages in the treatment of depression (Sarris et al., 2016), and has shown to help with depression symptoms (Alghamdi et al., 2020), as well as lower incidence of depression (Michele et al., 2020). Most health professionals recommend getting at least 10–30 minutes of sun exposure daily, and/or consuming foods rich in active form of vitamin D. The recommended daily amount for vitamin D is 600 IU (15 mcg). Those living closer to the equator, i.e., in locations that have a latitude less than 37 degrees north of the Earth's equatorial plane, such as the Middle East, North Africa, South Asia, and Central America, may be able to meet their requirements through

sun exposure on clear sunny days of the year. But at high latitudes (such as in Scandinavian countries and Canada), very little vitamin D can be produced by the skin for at least six months of the year, and in case of deficiency, vitamin D supplements may be needed (Leary et al., 2017; Link, 2017; Pratt, 2019; Chauhan et al., 2022). Dietary sources of vitamin D include D_3 in animal products, and D_2 in mushrooms. The naturally-occurring vitamin D from D_3 are found in farm products from the animals that have sufficiently roamed outside in the sunlight, such as eggs from farm chickens, meat from farm lambs, and seafood. Mushrooms also can contain vitamin D, but only after at least 1-2 hours of direct exposure to ultraviolet sunlight in a clear day, but most commercially grown mushrooms are grown in the dark, and thereby, lack vitamin D (Burriesci, 2020; Jones, 2019; Schmid & Walther, 2013).

Vitamin E is an antioxidant vitamin that is lipid-soluble (Miyazawa et al., 2019). Vitamin E possesses antioxidant, anti-inflammatory, and anti-cancer properties in humans, as well as having direct impacts on enzyme activity and gene transcription regulation (Saremi & Arora, 2010). This vitamin is particularly crucial for CNS function, and an increasing number of studies have linked it to neurodegenerative illnesses and mental problems (Muller, 2010). Vitamin E has been shown to modulate synaptic plasticity, particularly adult neurogenesis, which is an important process for cognitive and mood regulation (Ambrogini et al., 2016). Vitamin E has an antidepressant-like impact in depressed animal models by increasing the GSH antioxidant defense system, glutathione peroxidase (GPx), and glutathione reductase (GR) activity in the hippocampus and prefrontal cortex (Farhadnejad et al., 2020). According to some research, there is a link between low vitamin E levels in the blood and severe depression (Desrumaux et al., 2018), and depressed people may have lower vitamin E and vitamin C levels in their blood than healthy people (Farhadnejad et al., 2020). A cross-sectional study of an Iranian population whose average age was 49 years found a link between dietary vitamin E and mild to moderate depression (Banikazemi et al., 2015). Previous cross-sectional studies investigations also found a link between low vitamin E serum/plasma levels and depression in adults, especially in older males aged 60 years or more (Das et al., 2021). Vitamin E may protect against brain damage, and a low dietary intake of the vitamin was linked to mood swings and depression (Banikazemi et al., 2015). According to another study, a lack of antioxidants, notably Zinc and vitamin E, is linked to an increased incidence of depressive symptoms in older males (Das et al., 2021). The amounts of vitamin E and tryptophan were also linked to mental health, implying that sufficient levels of vitamin E and tryptophan, improves mental health. As a result, the authors speculate that the interplay between vitamin E levels and inflammatory pathways may affect the elderly's quality of life (Manosso et al., 2020). The best dietary sources for vitamin E may include natural foods including nuts (such as raw almonds), seeds (particularly sunflower), fruits such as mangos, and vegetables such as turnip (Rizvi et al., 2014). The recommended daily intake of vitamin E for an average-sized adult is 15 mg that can normally be provided by a healthy balanced diet (Manosso et al., 2013).

Minerals

Magnesium ions are the most abundant divalent intracellular cation in human cells, and it plays an important part in a variety of biological activities such as oxidative phosphorylation, energy generation, glycolysis, protein, and nucleic acid synthesis. According to the 2015–2020 Dietary Guidelines for Americans, the optimal Magnesium requirement with food for women is 320 mg/day and 420 mg/day for men (Barbagallo et al., 2021). Magnesium deficiency has been linked to a variety of mental illnesses, including anxiety, depression, and psychotic behavior (Durlach et

al., 2000). In both animal and human studies, a link between magnesium shortage and depression has been shown. Mice fed a Magnesium-deficient diet had behavioral problems that were linked to depression. Similarly, cross-sectional studies have found a negative association between depressed symptoms and Magnesium intake (Wang et al., 2018). In people who suffer from depression, serum Magnesium levels have been found to be lower (Botturi et al., 2020). Magnesium rich foods may be beneficial in the treatment of depression due to association with transduction and biochemical processes linked to depression, as well as the modulatory effect of magnesium on the NMDA receptor complex's ion channel. Sufficient magnesium intakes were linked to less symptoms of depression, according to a comprehensive study (Barbagallo et al., 2021). Some of the best sources of magnesium are dates, raw almonds, whole grain rice, fresh green vegetables (spinach) and seeds such as pumpkin, sesame and sunflowers (Elliott, 2018; Razzaque, 2018).

Zinc is a crucial trace element for numerous biochemical and physiological processes in the brain (Jurowski et al., 2014; Szewczyk et al., 2011), as well as cellular metabolism (Maserejian et al., 2012). Zinc ions modulate numerous ligand- and voltage-gated ion channels in the hippocampus and cortex (Satała et al., 2016), regulating synaptic transmission or acting as neurotransmitters (Wang et al., 2018). Through processes of reduced neurogenesis (Gao et al., 2009; Pfaender et al., 2016) and Neural Plasticity (Pfaender et al., 2016), disruption of Zinc homeostasis in these areas has been linked to a variety of cognitive disturbances, behavioral, and emotional regulation (Takeda, 2000). A certain quantity of zinc is required for the correct maintenance of learning and memory function in the mature brain, and a reduction in synaptic zinc levels can lead to an increase in glutamatergic levels, which are linked to depression (Wang et al., 2018). Zinc deficiency can lower activity of brain derived neurotrophic factor (BDNF), which is one of the most important elements for optimal learning and memory function, which can lead to depression (Młyniec et al., 2015). In both animals and humans, the link between zinc and depression has been explored extensively. Studies on rodents have found a link between zinc deficiency and depressed symptoms. Researchers have also shown that animals who are more resistant to antidepressant therapy had lower serum zinc levels (Wang et al., 2018). According to a meta-analysis of studies, blood zinc concentrations in depressed people were 0.12 µg/mL lower than in healthy people (Swardfager et al., 2013). In experimental rodent studies, when adult rats were fed a zinc-deficient diet, they displayed depression-like behavior (Takeda et al., 2012). In contrast, sufficient zinc consumption was linked to a lower incidence of depressive symptoms, according to cross-sectional research (Szewczyk et al., 2011). Cross-sectional studies have found an inverse relationship between zinc intake and depression symptoms (Szewczyk et al., 2012) and increased depressed symptoms in people with a low zinc diet (Wang et al., 2018). Some of the best sources of zinc are seeds such as pumpkin, sesame and sunflowers, nuts such as raw almonds, vegetables such as green beans and potatoes, whole grain rice, whole grain wheat, lamb, and seafoods such as fish, oysters, shrimp, and mussels (Olza et al., 2017; West, 2018).

Selenium is a trace element that is required for the correct functioning of numerous selenoproteins in the brain and nervous system that are involved in antioxidant defenses. The recommended average daily dose of selenium is 55 µg/day, with optimum serum levels between 70 and 90 µg/L (Wang et al., 2018). Recent research has looked into a link between selenium levels and depression because of its neuromodulatory involvement in brain function (Gao et al., 2012; Pasco et al., 2012). Selenium deficiency was linked to decreasing concentrations of BDNF in rodent research. It is

possible that BDNF concentrations might influence the association between selenium deficiency and depression because it is a neurotrophic factor that has been extensively linked to the pathophysiology of major depressive disorder (Wang et al., 2018). Selenium is required for the correct production and metabolism of thyroid hormones, and thyroid function is linked to neuropsychiatric symptoms such as mood disorders, cognitive impairment, and other psychiatric symptoms (Młyniec et al., 2015). Selenium deficiency and the resulting dysregulation of thyroid function may contribute to the onset of depression. Selenium has been reported to have potent modulatory effects on the dopaminergic, serotonergic, and noradrenergic systems, all of which are implicated in the physiopathology of depression and other mental disorders (Wang et al., 2018). In an intervention trial with mice, treatment with a multi-target selenium-based compound decreased depression symptoms in female mice, indicating that selenium may have an antidepressant effect (Brüning et al., 2011). Poor dietary selenium consumption was linked to a greater risk of developing major depressive disorder, according to data from a case-control study on women aged 20–89 years (Pasco et al., 2012). A cross sectional study that found depressed symptomatology was shown to be enhanced below and above serum selenium levels of 82 and 85 µg/L, with depressive symptomatology being lowest at 85 µg/L (Conner et al., 2015). Some of the best sources of selenium are sunflower seeds, whole grain rice mushrooms, fish, boiled egg, bananas, and spinach (Olsen, 2019).

Iron is a necessary nutrient for humans and serves as a cofactor for numerous enzymes as well as a key component of oxygen transporters in the body (Bao et al., 2012). It has a cofactor function in many processes including the production of tyrosine and tryptophan, which are precursors to the neurotransmitters serotonin, dopamine, and norepinephrine (Richardson et al., 2015). Iron is required for energy generation, DNA synthesis, neurotransmitter synthesis, myelination of neurons (Dusek et al., 2012), and the maintenance of serotonin levels in the brain (Toxqui et al., 2010). Iron and zinc are necessary for cellular function regulation and neuromodulation (Bibi et al., 2020). Many clinical investigations have recently suggested that iron pathology is linked to glutamatergic system dysfunction, as well as malfunctions in the processes and metabolism of cytoarchitectural and glutamate maladaptive alterations in many brain regions that enable cognitive–emotive behaviors (Bibi et al., 2020). In adults, iron deficiency has been linked to depression (Li et al., 2018). In women of reproductive age who are sensitive to depletion of nutritional components, especially iron, a link between inadequate nutrition and depression has been postulated (Bibi et al., 2020). There was a link between serum ferritin, blood hemoglobin, and depression (Pamuk et al., 2016). Iron deficiency anemia also leads to the development of tiredness, anxiety, depression, social, and attention-deficit problems in children (Li et al., 2017). One study indicated that anxiety and depression are more common in children with iron deficiency anemia than in the general population. Anemic patient, particularly one with iron deficiency anemia, exhibits depression-like symptoms in terms of social behavior, gestures, and mood (Noorazar et al., 2015). Overall, it appears that the rise in neurotransmitter concentration is predominantly caused by blood hemoglobin content, with iron-dependent enzymes playing a significant role (Bibi et al., 2020). Not only is iron deficiency potentially connected to the genesis and presentation of depression in the general population, but an iron-rich diet may also help to alleviate depression symptoms (Dama et al., 2018) and lower incidence of depression (Kim et al., 2015; Miki et al., 2015; Li et al., 2018). Some of the best foods rich in iron include date fruits, pistachio, almonds, whole grain bread, red grape, pomegranate, spinach, pumpkin seeds, and red kidney beans (Khan, 2018). Some food sources of iron, also contain some vitamin C that promotes iron absorption, such as raw spinach

that contains 0.8 mg of iron and 8.4 mg vitamin C per cup (Skolmowska et al., 2022; Ware, 2022). Furthermore, adding vitamin C rich sources such as fresh lemon juice to our meal can help improve iron absorption from the foods, as can avoiding coffee and black tea at meal times (Hills, 2019; Fan, 2016; Skolmowska et al., 2022).

Copper is an important trace metal because it is a cofactor for several enzymes involved in biochemical processes including cholesterol, glucose, iron metabolism, cellular respiration, and hormone production (Grubman & White, 2014). Copper concentration and spatial distribution in the brain are unbalanced (Davies et al., 2014) and may fluctuate over time, including during development, aging, and neurodegenerative conditions (Ramos et al., 2014). Copper is essential for the development and operation of the central nervous system and both deficiency and excess can have a significant impact on brain functioning (Scheiber et al., 2014). Copper levels are crucial in oxidative stress processes and have an impact on the catalytic and structural characteristics of several antioxidant enzymes, which might be one of the major causes of depression (Młyniec et al., 2015). The concentration of copper in patients with depression tends to be lower than in those without depression (Ni et al., 2018). Copper consumption was linked to a lower incidence of depression, according to research in Korean teenage females (Kim et al., 2015). The abnormal changes in blood copper levels in individuals with depression, as well as the link between copper and depression etiology, point to its potential as a biomarker and offer a research route for screening and combining useful biomarkers for depression diagnosis and therapy (Ni et al., 2018). Potatoes, nuts, seeds, and whole-grain products are some of the best sources of copper (Pierson et al., 2019).

Amino Acids

N-acetyl cysteine (NAC) lowers inflammatory cytokines, controls glutamate, stimulates neurogenesis, and lowers apoptosis, all of which contribute to depression's neurobiology. As a result, it has numerous possible antidepressant effects (Berk et al., 2013; Michele et al., 2020). Hence, dietary changes towards sufficient intake of proteins, particularly from plant-based sources such as beans and peas, but also from seafood, may help reduce depression (Shen et al., 2021).

S-adenosylmethionine (SAMe) is one of the most important molecules that methionine (a sulfur-containing amino acid) can be converted into. In healthy people, SAMe is found in safe low levels in almost every tissue and fluid in the body and appears to have a number of potential mechanisms of action, such as improving cell signaling pathways (Lande, 2020; Anjum et al., 2018). However, SAMe in higher than normal levels can make it to be a potentially toxic compound, and abnormal levels in the body have been reported in liver diseases and depression (Hopp & Shurtleff, 2017; Tinsley, 2018). SAMe is not significantly found in foods, but its precursor, methionine, is plentiful in many protein-rich foods. Although methionine has important roles in the body and is the most variable metabolite found in human plasma, diets that are low in this amino acid are beneficiary for health. Even some cancer cells are dependent on dietary methionine to grow. In these cases, limiting dietary intake of methionine, such as by consuming less animal proteins, could further improve health (Tinsley, 2018; Gao et al., 2019).

Researchers have found that **homocysteine**, an amino acid with significant impact on depression, can be lowered by saffron, therefore, saffron can be considered as a natural antidepressant (Jelodar

et al., 2018). Saffron can be used as a flavoring in food preparations or consumed in the form of tea.

Omega-3 Fatty Acids

Changes in membrane lipids may play a role in the pathophysiology of depression, making lipid-based therapies a viable option (Müller et al., 2015). In the CNS, omega-3 fatty acids have both long-term and short-term effects. Their long-term consequences include an impact on brain structure development, maintenance, and function. The physiology of neuronal signal transduction is affected by omega-3 fatty acids' short-term impacts (Bazinet & Layé, 2014). Animal studies show that omega-3 fatty acids may have an effect on numerous neurobiological mediators thought to be involved in the pathophysiology of MDD (Müller et al., 2015).

Preclinical studies have shown that a diet lacking in omega-3 fatty acids causes depressive-like symptoms and aberrant social behavior in rodents (Bondi et al., 2014). Mice raised on an omega-3 fatty acid-deficient diet, for example, exhibited lower amounts of polyunsaturated fatty acids like docosahexaenoic acid in the brain and higher levels of omega-6 fatty acids, as well as a variety of depressive symptoms in behavioral tests (Lafourcade et al., 2011). Omega-3 fatty acids have also been found to prevent and decrease depression-like behaviors in rat models. However, it's important to remember that most animal models of major depressive illness have significant flaws, especially when it comes to depression subtypes, TRD, and recurrent depression (Lange et al., 2021).

The evidence for using omega-3 fatty acids in the prevention and treatment of depression in humans is based on observational data, including a correlational link between lower prevalence of MDD and higher intake of Omega-3 rich foods such as fish (Ross, 2016). Another study looked at the link between depression and dietary omega-3 fatty acid intake, and found that consumption of Omega-3 rich foods was linked with a substantially lower risk of depression (Grosso et al., 2016). In addition, older individuals in France who eat fish on a regular basis (at least weekly) had less depression symptoms than persons in a control group (Barberger-Gateau et al., 2005). Furthermore, depressed people have lower omega-3 fatty acid levels and a higher omega-6 to omega-3 polyunsaturated fatty acid ratio in their blood and brain (Parletta et al., 2016). A meta-analysis found that omega-3 fatty acids have an overall positive impact on depression symptoms (Liao et al., 2019).

The richest omega-3 sources are certain seafood. Also, regularly consuming sufficient amounts of some plant foods, such as walnut and olive oil that chronic consumption is safe, may provide our daily needs for omega-3 (Wardhana et al., 2011; Sánchez-Villegas et al., 2018; Petrović-Oggiano et al., 2020). In contrast, high dose Omega 3 supplements not only may not be a sustained solution for depression, but they were even found to cause some side effects such as eructation, dyspepsia, diarrhea, vomiting, nausea, and arthralgia, as well as increased risk of aggressive prostate cancer, which all may contribute to worsening depression (Reinberg, 2013; Krupa at al., 2022).

Carotenoids

Carotenoids are a diverse collection of colorful liposoluble pigments found naturally in plants, fungus, bacteria, and algae, as well as in a variety of foods such as fruits, vegetables, and fish

(Milani et al., 2017). 40 carotenoids are present in a typical human diet, but only about around 20 are found in human blood and tissues. Among these carotenoids, β-carotene, α-carotene, lycopene, lutein, and cryptoxanthin are the most significant dietary pigments (Milani et al., 2017). These pigments have been linked to a variety of health benefits, including effects on the neurological system that contribute to neuronal differentiation, neuronal patterning, and motor axon development, due to their powerful anti-inflammatory and antioxidant properties (Ahmed et al., 2021). Inflammation mediates the link between plasma carotenoids and depression. Carotenoid deficiency has been linked to an increased risk of depression, as a result of inflammation or dysregulation of the HPA axis (Milaneschi et al., 2012). Depressed individuals have significantly low levels of antioxidants, especially carotenoids, according to case control studies, and dietary treatment with carotenoids has resulted in a significant decrease in depression (Gautam et al., 2012). Increasing intakes of β-carotene to achieve sufficiency may significantly increase the levels of serotonin and BDNF in individuals suffering from depression (Kim et al., 2015). These findings suggest that sufficient carotenoid levels might help people feel less depressed (Kim et al., 2016) and contribute to treatment of people with depression and anxiety who had low levels of antioxidants in their blood (Gautam et al., 2012). In university students from the United Kingdom, a higher consumption of fruits and vegetables, which are the major source of dietary carotenoids, was found to be inversely associated to various mental health issues (Boozari et al., 2021). Additional data from several groups suggests that carotenoid rich foods is inversely linked with depression risk in both adults and the elderly (Ge et al., 2020; Li & Li, 2019; Milaneschi et al., 2012). Some fruits and vegetables that are rich in dietary carotenoids include red bell peppers, carrots, mangoes, oranges, and spinach (Tan & Norhaizan, 2019).

Polyphenols

Polyphenols are natural chemicals that may be found in a wide range of foods (Pathak et al., 2013). The main groups of polyphenols include phenolic acids, flavonoids, and the less frequent stilbenes and lignans. The majority of polyphenols are digested by colonic bacteria rather than being absorbed via the intestinal barrier (Bayes et al., 2020). Polyphenols preserve mental health by upregulating the body's natural defensive mechanisms, decreasing oxidative damage, and stabilizing free radicals (Gomez-Pinilla & Nguyen, 2012). Polyphenols have been shown in animal tests to decrease depression-like behavior in rodents (Pathak et al., 2013). Polyphenols have also been shown to have neuroprotective effects, regulating particular cellular signaling pathways involved in cognitive functions (Gomez-Pinilla & Nguyen, 2012). Polyphenols' anti-inflammatory characteristics, which include suppression of pro-inflammatory cytokines, free radical scavenging, and antioxidant activity, as well as neuroprotective capabilities, are another proposed explanation for how they benefit mental health (Dias et al., 2012). Metabolic routes and metabolites of polyphenols may potentially be one of the features responsible for their therapeutic benefits, according to research (Bayes et al., 2020). Polyphenols are found in plant-based foods, notably apples, citrus fruit, grapes, whole-grains, nuts and olive oil, and numerous dark colored vegetables, which are common in the Mediterranean diet (Grosso, 2018; Schwingshackl et al., 2020). According to the findings of a meta-analysis, the Mediterranean diet reduces the incidence of depression (Lassale et al., 2019) and improves overall health due to the anti-inflammatory and oxidative stress protective effects of the diet (Lassale et al., 2019; Psaltopoulou et al., 2013).

Probiotics

Probiotics are living microorganisms that colonize the gastrointestinal system, and provide health advantages to the host when consumed in sufficient numbers (Wallace & Milev, 2021; Gawlik-Kotelnicka et al., 2021). Probiotics have been studied in both animal and human research, with promising findings such as reduction of depression- and anxiety-like behavior, meaning that it can act like natural antidepressant in patients with depressed and anxiety symptoms (Gambaro et al., 2020; Wallace & Milev, 2021). Probiotics impacted mice's behavior and reduced symptoms of depression and anxiety (Reininghaus et al., 2020; Peirce & Alviña, 2019). Healthy diets, particularly sufficient intake of fresh vegetables and fruits as a habit, normally can lead to metabolic activity of the human gut microbiota, and natural availability of probiotics in the gut, which in turn can impact health (Conlon et al., 2014; Rinninella et al., 2019). Probiotics can also be acquired via naturally fermented foods such as plain yogurt (Li et al., 2009; Ho & Prasad, 2013).

Dietary components that may worsen depression

In some cross-sectional and prospective studies, dietary patterns such as the Mediterranean diet rich in plant-based foods have been linked to a lower incidence of depression (Lassale et al., 2019). In contrast, eating too few calories, or, excessively consuming animal proteins, may cause metabolic syndrome by slowing down the metabolism, a factor that may be associated with depression (Petre, 2017; Cai et al., 2021).

Consumption of nutrient-rich plant-based foods has significantly decreased in the last few decades because of increased consumption of ultra-processed foods, which involve the removal of key nutrients. Hence it is best for the patients suffering from depression to increase consumption of naturally produced unprocessed foods, in particularly those that can be eaten raw, and minimize consumption of processed fast foods (Razzaque, 2018; Campbell, 2018).

Dietary habits that include plant-based raw foods, such as the traditional African Mediterranean diets, can gradually improve the mood by naturally enhancing the functions related to nervous system and brain, sustainably leading to reduced depression symptoms and anxiety-induced behaviors (Jacka et al., 2017). In addition, if alcohol, addictive substances, refined foods, fast foods, diets containing high levels of trans-fatty acids, sugar-sweetened beverages, and smoking are avoided, depression can be resolved more effectively (Johnson, 2019; Moludi et al., 2020).

Reducing animal protein, and consuming sufficient amounts of fruit, vegetables, and plant-based proteins can help improve mood and reduce depression. Proteins from plants are often lower in methionine than animal proteins, hence plant-based diets could better improve the overall health and increase lifespan (Tinsley, 2018; Gao et al., 2019). In general, diets high in animal proteins may worsen depression, as such proteins are metabolized primarily by microbial fermentation in the intestine, which production of protein fermentation products and metabolites can affect the gut microbiota. The protein fermentation generally forms toxic products, including hydrogen sulfide, amines, and ammonia. Hence, high-protein diets increase the risk of intestinal diseases by producing toxic metabolites in the colon (Cai et al., 2021). In this case, if animal products are consumed excessively, due to increased risk of inflammatory bowel diseases (Wu et al., 2022), the gut microbiota is negatively affected (Alam et al., 2020). The gut microbiota is responsible of regulating availability of tryptophan, and thus the concentration of serotonin (Terry & Margolis,

2016; Carlessi et al., 2021), which have a significant impact on brain serotonin accessibility and depression-like behavior (Lukić et al., 2019; Albenberg & Wu, 2014).

High glycemic-load meals (such as cakes, cookies, sweet treats, fried potatoes, chips) have negative impacts on depression symptoms in non-depressed adults, compared to low glycemic-load meals (such as vegetables, fruits, nuts). Overall, a high glycemic-load diet may cause overall mood changes, increased tiredness, and depressed symptoms (Breymeyer et al., 2016).

Increased sugar consumption from sugar sweetened drinks and foods has been linked to an increased risk of depression according to prospective cohort studies (Knüppel et al., 2017; Sanchez-Villegas et al., 2018; Guo et al., 2014). A meta-analysis also found a nonlinear dose-response connection between increased sugar-sweetened beverage intake and increased risk of depression (Hu, et al., 2019). A prospective analysis of the Women's Health Initiative cohort found that higher intake of added sugars was linked to an increased risk of incident depression after three years of follow-up (Gangwisch et al., 2015). It should be noted that, as pointed out above, much of the research relating diet to depression could be finding reverse causation. For example, chocolate addiction (which is often consumed with high levels of sugar) is more common in people with untreated chronic depression but this does not inform us which is cause and which is result (Woznicki, 2010).

A diet high in acidogenic (acid-forming) foods (See Bahrami & Greiner, 2021.) may increase the risk of depression, anxiety, stress, and obesity. The researchers found that a high dietary acid load was associated with a higher incidence of psychological disorders. Hence, reducing high dietary acid, such as by sufficient consumption of foods that have alkalizing properties (As explained in Bahrami & Greiner 2021), these are not alkaline foods, can be effective in reducing depression and other mental disorders (Mozaffari et al., 2020). Some foods that form acidic metabolic waste (strong acidifiers) and increase acidity of the blood more significantly include red meats from pork, commercial dairy products, soft drinks, chocolate, coffee, high-fructose corn syrup, table sugar, frying oil, sour plums, peanuts, and fried potatoes (Bahrami and Greiner, 2021; Corriher, 2009). In comparison, plant-based foods result in significantly less acid load (Ronco et al., 2021), and could perhaps be beneficial in treating the depressed patients. Foods that form alkaline metabolic waste include raw almonds, date fruits, olive oil, figs, grapes, lemons, apples, pomegranates, fresh ginger, garlic, onion, carrot, and celery (Bahrami & Greiner, 2021; Bridgeford, 2015). However, bicarbonate supplements and alkaline drinks are not very effective over the long-term (Bahrami & Greiner, 2021).

Hypoxia, poor oxygenation of body tissues including the brain, negatively affects a person's mood and causes depression. Even mild hypoxia may decrease serotonin synthesis, reducing appetite and motivation, and disrupting sleep patterns. Chronic hypoxia in patients with respiratory or cardiac dysfunction could similarly precipitate depression (Kanekar et al., 2015). Healthy dietary habits, as well as aerobic exercise can help improve mood by reducing hypoxia (Kang et al., 2020).

There are now consistent and convincing threads of evidence that support the importance of food and dietary habits as predictors of depression and other prevalent mental maladies. Diet is a very important component of mental health with significant effects on development of depression (Tello, 2020). Some of the diet-related factors that are associated with depression may include

micronutrients deficiency (Ljungberg et al., 2020), metabolic syndrome (Moradi et al., 2021; Cai et al., 2021), and unhealthy diet (Lanuza et al., 2021).

CONCLUSIONS

The existing evidence confirms that nutrient deficiency and unhealthy diets can cause emotional problems, memory defects, depression, and cognitive decline. Healthy dietary patterns can also have a role as an adjunctive treatment for mental disorders; hence, dietary solutions can be considered as novel nutraceutical treatments and management approaches for those who suffer from depression and other mental disorders.

There are a variety of lifestyle and diet modifications that have appropriate potential clinical applications to better manage depression, alongside pharmacotherapies and psychological techniques. Indeed, the time has come for a more integrative approach to treat depression, with acknowledgment of the potential applicability of lifestyle changes and diet modifications. The integrated approach may then allow people live happier, feel less stressed, achieve higher levels of life satisfaction, and face less depression.

In addition to individual solutions, depression should be looked at as a social problem, which requires utilization of healthy diets, not just in individuals, but also in the majority of societies via public training and education, as well as the use of public policy mechanisms such as taxation of harmful foods and subsidization of unprocessed foods.

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