Nutrition and Depression

Nagihan Yılmaz1, Hatice Özyürek1, Nazlı Çetin1, Berzah Güneş1, Oytun Erbaş1,2

ABSTRACT

In the treatment of psychiatric illnesses such as depression and anxiety, pharmacological and psychotherapy approaches, such as certain antidepressants, are also usually applied. The fact that pharmacological methods have certain side effects has prompted researchers to look at alternative treatment options for depression. Nutritional oxidative stress, which has been proven by studies that can be used in the prevention and treatment of depression, can affect cognitive functions through mechanisms such as inflammation, mitochondrial dysfunction, epigenetics, intestinal microbiota, obesity, tryptophan metabolism, the hypothalamic-pituitary-adrenal axis (HPA axis) and adult hippocampal neurogenesis (AHN). This review focuses on pathways associated with depression and nutrients, nutrients, and dietary models that can affect cognitive function. Long-term and large-cohort research is required to reveal different mechanisms and to fully understand the relationship between nutrition and depression.

Keywords: Depression, diet, nutrition, obesity.


©2021 Journal of Experimental and Basic Medical Sciences. All rights reserved.

Received : July 13, 2021
Accepted : August 12, 2021
Published online : September 29, 2021

Depression is a mental disorder with a high global prevalence that has a negative impact on people’s lives. Although the exact cause of depression is unknown, certain environmental, social, biological, and psychological influences are thought to play a role in its growth. Unlike treatments such as pharmacotherapy and psychotherapy, which are often used in the treatment of depression, food should be included in the new plan.[1] The effectiveness of nutrition on depression is through nutrients and dietary models.[1,2] In the studies, fruits and vegetables, oilseeds, fish such as nutrients; fat-soluble vitamins such as A, D, E and water-soluble vitamins such as group B and C, minerals such as zinc and magnesium, omega 3 fatty acids, which are polyunsaturated fatty acids, and some phytochemicals, such as non-nutrient polyphenols, have been shown to have a positive effect on cognitive functions and mood.[3] It has also been reported that prebiotics and probiotics can affect cognitive function through the microbiota.[4] In contrast, it is thought that the western diet, which is characterized by high fat and sugar content, can negatively affect cognitive function and increase depressive symptoms.[5] Dietary models that can have a positive effect on depression include Mediterranean type nutrition, which is characterized by a high content of fruits, vegetables, dried beans, whole grains, olive oil, fish, and red wine; DASH (Dietary approaches to stop hypertension) diet, which has a high potassium content due to its high fruit and vegetable content; ketogenic diet with high fat, low protein, and low carbohydrate content; diets based on the glycemic index; it is the Zone diet with low carbohydrate and high protein content and the Paleo diet, which is characterized by the content of fruits, vegetables, oilseeds, meat.[2] The effect of nutrition on depression is explained through various pathways. These pathways: Oxidative stress, inflammation, mitochondrial dysfunction, epigenetics, intestinal microbiota, obesity, tryptophan metabolism, hypothalamic-pituitary-adrenal (HPA) axis, adult hippocampal neurogenesis (AHN).[3] This review focuses on how nutrition can affect cognitive functions

1ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Turkey
2Department of Physiology, Medical Faculty of Demiroğlu Bilim University, Istanbul, Turkey
Correspondence: Nagihan Yılmaz. Deneysel Tip Enstitüsü, 41470 Gebze-Kocaeli, Türkiye.
E-mail: yilmaznagihann@gmail.com
and depression through these aforementioned pathways.

**INTESTINAL MICROBIOTA**

Microbiota containing approximately 100 trillion microorganisms, which can also partially affect the mechanisms involved in the pathophysiology of depression; it is significantly affected by diet, while it is also affected by stress, antibiotic use, infection, and some diseases.\(^3,6\) The effect of microbiota on brain functions and behaviors can be explained by neural pathways through the vagus nerve, metabolites such as short-chain fatty acids released by fermentation, neurotransmitters such as GABA (gamma-Aminobutyric acid), dopamine, and serotonin, the HPA axis, immune and endocrine pathways.\(^3,5,6\) Also, intestinal microbiota; plays a role in the maturation and activation of microglia cells in the brain, which have an important role in cognitive development.\(^7\)

That a Mediterranean diet may lower the risk of depression; it has been proposed that a western diet can enhance depressive symptoms.\(^7\) It is thought that the effect of certain dietary components such as fiber, polyunsaturated fatty acids, and polyphenols, which are components of the Mediterranean diet, on brain function may be due to its direct effect on the bowel microbiota.\(^3,7\) It was observed that the Mediterranean diet, which was applied for 1 year on 612 elderly individuals selected from 5 different countries, improved cognitive function by modulating microbiota components.\(^7\) Although the effect of a western diet with high fat and high sugar on the brain is not yet fully understood, it is thought that the gut microbiome affected by the diet can be effective with the brain-bowel connection.\(^3,5\)

Western-type nutrition affects cognitive functions through the microbiota through several mechanisms. One of these mechanisms is to change the microbiota in the intestine.\(^5\) A study of mice noted that the western diet resulted in a decrease in the Bacteroidetes population and an increase in the Firmicutes population. This change was associated with reduced mental flexibility.\(^8\) Similarly, an increase was observed in Bilophila sp., which can cause cognitive abnormalities by increasing inflammation and decrease in Akkermansia muciniphila filum, which increases insulin sensitivity as a result of the western diet.\(^9\) It has been reported that a high fructose diet, similar to western type nutrition, can lead to a decrease in cognitive function. It is also stated that Western-type nutrition has negative effects on intestinal permeability and ensuring the integrity of the blood-brain barrier, and this effect may be one of the reasons why western type nutrition impairs cognitive functions.\(^5\) Furthermore, it was found that the amount of circulating LPS (lipopolysaccharide) increased 3-fold at the same time as intestinal permeability in mice on a western type diet for 4 weeks.\(^5\) Increased circulating LPS levels have been linked to increased proinflammatory cytokine release in the brain and the production of neuroinflammation linked to cognitive decline, according to studies.\(^5,10\)

Another mechanism by which the Western diet can influence cognitive functions is the decrease in short-chain fatty acids including acetate, propionate, and butyrate induced by a high fat and low complex carbohydrate diet, which is caused by bacterial fermentation in the intestine. Short-chain fatty acids formed in the distal colon enter the brain and have a neuroprotective effect, although most are metabolized in the liver.\(^5\) In psychiatric patients, sodium butyrate, a short-chain fatty acid salt, enhances the release of brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF).\(^5,11\) Furthermore, butyrate may reduce systemic inflammation caused by LPS endotoxin, which is created by gram-negative bacteria in the intestine and can enter the bloodstream due to increased intestinal permeability caused by a western diet.\(^5,10\)

Some clinical trials have also focused on the effect of psychobiotics on depressed individuals, which are defined as living bacteria that positively affect mental health through the microbiota when consumed in sufficient quantities.\(^7\) Six probiotic trials for depression and one probiotic study for anxiety found important results in a systematic review of 34 studies. The most widely used bacteria in these studies is Lactobacillus species, but they have no impact on depression or anxiety.\(^4\) In contrast, a 2-week study of healthy women observed reductions in activity in the sensory regions of the brain, frontal, prefrontal, and temporal cortex, parahippocampal gypsum, and PAG (periaqueductal gray), and chronic fermented milk intake was confirmed to influence brain activity. While it has been suggested that probiotic-induced changes in brain activity are due to increased monoaminergic stimulation of multiple brain regions via the vagus nerve, further research is required to fully understand the situation.\(^12\)
Although Lactobacillus and Bifidobacterium are thought to have a positive effect on the recovery of depression and anxiety, the effect of probiotics and prebiotics on mental health is limited and varies according to their variety. Although some studies say that fermented food consumption can have a positive effect on mood, the fact that microorganisms differ in terms of their vitality and colony in the intestine causes inconsistencies in this regard.\(^3\)

Dietary macro and micronutrients are needed for neurodevelopment to be sustained. EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) are omega-3 fatty acids that have a beneficial effect on both microbiota diversity and neurodevelopment. It was observed that the amount of Bifidobacterium in the intestines increased as a result of omega-3 supplementation in mice fed a high-fat diet.\(^13\) Another study reported that omega-3 fatty acids suppress HPA axis, which is associated with stress.\(^6,14\) Besides, it has been reported in some studies that nitrate processed meat products may also affect manic attacks.\(^7\)

**TRYPTOPHAN METABOLISM**

Tryptophan is an essential amino acid that plays an important role in cognitive inflammation and immune immunity. Around 1% of tryptophan's name was a large one when spraying proteins serotonin (5-hydroxychloroquine) and kynurenine. Serotonin; is a neurotransmitter, mostly found in the brain, platelets, and gastrointestinal tract, which has an important role in cognitive functions and is the target point in the treatment of depression.\(^15\)

Low tryptophan and serotonin levels were found in depressed individuals, and serotonin reuptake inhibitors were also included in the medical treatment in these individuals. Although serotonin reuptake inhibitors have fewer side effects than other antidepressants, increasing the amount of serotonin in the brain with dietary intervention is an approach that has been emphasized in many studies due to the side effects of medical treatments and the inability to be tolerated by some individuals.\(^16\)

Although it has been observed in some studies that increasing the amount of tryptophan in the diet increases the synthesis of serotonin in both humans and rats, it has not been seen in healthy individuals that reducing the amount of tryptophan in the diet increases depressive symptoms only in individuals prone to depression.\(^16\) Even though oilseeds such as walnuts, almonds, peanuts, seeds such as sesame seeds, zucchini and sunflower seeds, rice, wheat, corn, and tryptophan-rich nutrition can increase the availability of tryptophan, the carrier system used in the flow of tryptophan to the brain competes with other LNAA (long neutral amino acids) and therefore the ratio of Tryptophan: LNAA in the diet is also important. It is stated that the ways to increase the amount of serotonin in the brain may be to increase the amount of pure tryptophan in the diet or the number of carbohydrates. Besides, it is stated that nutrients such as fruits, vegetables, cereals, and oilseeds containing antioxidant properties such as polyphenols, flavonoids, vitamins cause the life of the cofactor of the enzyme that allows tryptophan to turn into serotonin, as well as the synthesis of more serotonin due to reduced destruction of tryptophan. Therefore, it is said that consuming nutrients with a high antioxidant content can increase the flow of tryptophan to the brain more than a diet with high protein content.\(^17\) Other dietary approaches that increase tryptophan flow and serotonin synthesis to the brain by increasing the plasma Tryptophan: LNAA ratio is the consumption of alpha-lactalbumin, a whey protein found in milk, and the consumption of lysozyme hydrolysis found in chicken eggs.\(^17,18\) Tryptophan in plasma: Although a 50-70% change in the LNAA ratio may be enough to increase the amount of serotonin in the brain, protein hydrolysis from eggs compared to alpha-lactalbumin has been shown in a study that increases this rate more. In individuals who were left under low and high chronic stress, it was shown that in the group given egg protein hydrolysis, tryptophan: LNAA rate was higher and depressive symptoms were lower compared to the group given casein hydrolysis.\(^17\) In the alpha-lactalbumin study on groups with a history of major depression and no history of depression (control group), it was observed that alpha-lactalbumin increased the rate of Tryptophan: LNAA but caused a slight effect on mood and post-stress cortisol release. Studies involving longer-term dietary intervention are needed, even though some studies have shown that it may be possible to reduce depressive symptoms by increasing the amount of serotonin in the brain through diet.\(^16\)

**HYPOTHALAMIC-PITUITARY-ADRENAL AXIS**

Hypothalamic-pituitary-adrenal axis of the brain is a pathway of neuroendocrine, which includes the adrenal gland, pituitary gland, regulates the
production of glucocorticoids, and is activated with stress.\cite{19-21} Long-term activation of HPA causes mood disorders, but HPA has been observed to be overactive in individuals with major depression.\cite{19,20} It is reported that increased cortisol levels as a result of stimulation of HPA, together with factors such as stress and inflammation, may adversely affect neurons in the hippocampus.\cite{20,22} A study by J. Keller and his colleagues have shown that cortisol can directly affect cognitive function.\cite{19,20}

Although HPA regulation can be improved by decreasing the levels of the hormone cortisol, there are some suggestions that ascorbic acid can reduce cortisol levels, although there is not enough evidence yet.\cite{20,22} As a result of a study in which individuals were given high dose vitamin C supplements, increased cortisol levels decreased due to the stress factor and it was reported that it may have a protective effect against stress. Although the mechanism underlying this effect of vitamin C is not fully known, as a result of some studies, vitamin C; dopamine is said to modulate the action of agonists and antagonists, increase the amount of oxytocin with an anti-stress effect, and alter neurotransmission in the central nervous system. However, as a result of the study, it is also said that the effect of ascorbic acid reducing cortisol levels can be seen as a result of supplementation, not with dietary levels.\cite{22}

Another dietary component that can reduce cortisol levels is polyphenols, which are plant-based secondary metabolites such as fruits, vegetables, tea, cocoa, wine, and coffee. Polyphenols; contain phytochemicals such as flavonoids, phenolic acids, proanthocyanidins, resveratrol, lignans, and stilbenes.\cite{20,23} In individuals given dark chocolate containing 500 mg of flavonoids per day, cortisol and cortisol: cortisone decreased significantly at the end of the 4th week; increased positive effects on mood, decreased negative effects, but this was not statistically significant.\cite{20} The effect of polyphenols reducing cortisol levels is reportedly due to inhibiting the activity of 11 beta-hydroxysteroid dehydrogenase, which is involved in converting cortisol into cortisone, an active steroid.\cite{20,24} As a result of a study in which pomegranate juice with a high polyphenol content was consumed to individuals for 4 weeks, it was observed that urine cortisol amounts and cortisol: cortisone ratios were lower in individuals compared to the beginning, but a statistically significant difference was seen only in cortisol: cortisone ratio.\cite{24}

According to the findings, omega-3 fatty acids may be another dietary factor that can influence the HPA axis. Omega-3 fatty acids are thought to inhibit the secretion of corticotropin-release hormone (CRH), a hormone that induces HPA activation and is secreted by hypothalamic neurons. A study found that for 3 weeks, saliva cortisol levels were lower than at the beginning and reduced anxiety symptoms as a result of applying 1 gram of fish oil supplements per day to individuals who had given up alcohol.\cite{25}

In another study of rats with type-2 diabetes, it was observed that berberine supplementation reduced the amount of urine and serum corticosterone and the amount of plasma adrenocorticotropic hormone (ACTH) for 4 weeks, as well as significantly reducing the amount of orexin-A that stimulates CRH to release in the hypothalamus.\cite{26}

### ADULT HIPPOCAMPAL NEUROGENESIS

Hippocampus, which together with the amygdala forms the limbic cortex; has important roles in regulating emotions, learning, regulation of HPA, cognitive functions, and memory.\cite{27-29} Neurogenesis is the formation of mature, functional new nerve cells as a result of the proliferation, maturation, and differentiation processes of neural stem cells (NSC).\cite{27,30} Neurogenesis, which occurs during the embryonic period, is called embryonic neurogenesis, while neurogenesis, which occurs in some parts of the brain and is slower than embryonic neurogenesis, is called AHN. The subgranular region in the hippocampus, the subventricular zone (SVZ) in the lateral ventricles, and the hypothalamus are the brain regions where adult neurogenesis occurs. Neurogenesis in the hypothalamus has some effects, especially on the control of energy balance and body weigh.\cite{30}

Neural plasticity, repair of the central nervous system, repair of worn nerve cells, cognitive functions, regulation of mood, neurogenesis; intrinsic and extrinsic factors such as neurotransmitters, neurotrophins, cytokines, growth factors, hormones, DNA methylation, glucocorticoids, opioids; stress, antidepressant use, physical activity, learning, diet, aging, lack of sleep are affected by environmental factors.\cite{27,30,31} Adult hippocampal neurogenesis levels were shown to be lower in people with neurodegenerative illnesses and those who were depressed.\cite{27,31} The brain-derived neurotrophic factor (BDNF), which plays a critical role in the differentiation and survival of neurons and is created
from neural tissues, was shown to be lower in these people's hippocampus than in healthy people.\cite{27,32} It has been suggested that the cause of decreased hippocampal neurogenesis in depressed individuals may be due to increased glucocorticoid levels as a result of increased HPA axis activity due to stress. In addition, BDNF and AHN levels were found to rise in depressed people using antidepressants. Increased AHN has the ability to improve cognitive performance and alleviate depression symptoms.\cite{27}

Diet, which is an environmental factor that can affect AHN, can affect AHN as a result of 4 different components such as meal frequency, meal content, meal tissue, calorie intake. As a result of some studies on mice, it was observed that calorie restriction increased AHN, while a high-fat diet reduced AHN.\cite{33,34} It is also suggested that AHN may increase with the increase of time between meals, and AHN may decrease with the softness of the food.\cite{27} Dietary components that are suggested to increase AHN as a result of some mechanisms are omega-3 fatty acids, polyphenols, vitamins A, C, D, E, B9, zinc, iron, sulforaphane.\cite{27,30,31} The effect of omega-3 fatty acids like EPA and DHA on enhancing AHN is thought to be owing to the fact that EPA and DHA can bind to retinoid X receptors, which are important in nerve cell differentiation. Depressive symptoms may be alleviated by dietary supplementation of omega-3 fatty acids, which are deficient in depressed people.\cite{27} Polyphenols, which can be found in plant-based foods including chocolate, turmeric, red wine, blackberries, green tea, and coffee, have been shown to boost AHN and lessen depression symptoms, however this impact is attributed to polyphenols' antioxidant and neuroprotective qualities.\cite{27} It has been observed that the effect of polyphenols on increasing AHN is achieved in both in vivo and in vitro conditions. As a result of the cocoa drink with high polyphenol content applied by Sathyapalan and his colleagues on people with fatigue disease for 8 weeks, significant improvement in the degree of fatigue was observed.\cite{35} As a result of a study, it was observed that AHN inhibits and depression development is stimulated in the inadequacy of zinc involved in the proliferation and differentiation of NSCs.\cite{36} According to certain mouse research, both excessive and insufficient ingestion of retinoic acid, the active form of vitamin A, decreases AHN and promotes depressed symptoms.\cite{37,38} As a result of an experiment on mice with a neurodegeneration model, it was observed that both vitamin C and vitamin D supplementation increased neurogenesis.\cite{39,40} It has been observed that eating a high-fat diet increases malondialdehyde levels, which are indicative of lipid peroxidation and have toxic effects on NSCs, corticosteroid levels that reduce AHN and reduce BDNF levels. AHN levels were also seen to decrease in rats that were given western type nutrition, which is characterized by a high-fat and high-sugar diet.\cite{34,41,42} When depressed individuals who were given the Mediterranean diet-oilseed supplements were compared to the control group at the end of three years, it was shown that BDNF levels were considerably higher in the Mediterranean diet-oilseed supplement group than in the control group.\cite{32} Furthermore, a study by Helene M. Savignac and her colleagues has shown that proliferation of the intestinal microbiota, which is shown to have an effect on brain function, can increase BDNF levels in the hippocampus.\cite{11,43}

**OXIDATIVE STRESS**

Oxidative stress, which is characterized by the production of extremely reactive oxygen species (ROS) that cannot be prevented in the body and the deterioration of cell redox balance, can also be defined as the presence of ROS that damage lipids, proteins, and DNA at high concentrations within the cell.\cite{44,45} The production of ROS, a biochemical reaction necessary for cell metabolism, occurs in mitochondria. However, activation of the immune system and inflammation also increase the production of reactive oxygen species.\cite{15} Antioxidants, defined as a substance that can significantly prevent oxidation of this reagent even at low concentrations when faced with an oxidable reagent in the body, are thought to improve blood circulation, strengthen memory, and have an effect on lowering cholesterol.\cite{15,46}

There are endogenous antioxidants produced in the body and exogenous antioxidants taken from the outside to prevent the formation of ROS and to prevent damage caused by these substances. Enzymatic endogenous antioxidants produced in the body are superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR); the antioxidants produced non-enzymatic in the body are glutathione, coenzyme Q 10, melatonin, selenium, uric acid, α-lipoic acid, bilirubin, transferrin, albumin, ceruloplasmin.\cite{47} Vitamin E (α-Tocopherol), vitamin A (β-carotene), vitamin C (Ascorbic acid), Folic acid (vitamin B9) are also exogenous antioxidants taken from the outside.\cite{44,47} Fruits, vegetables, cereals, and
hard nuts are foods with high antioxidant value. The most discussed compounds are vitamins, flavonoids, and polyphenols. \[47\]

Several chronic disorders and mental illnesses are linked to oxidative and nitrosative stress. \[1\] Oxidative and nitrosative stress; low levels of zinc, coenzyme Q10, vitamin E, and glutathione, increased lipid peroxidation, and damage to proteins, mitochondria, and DNA is characterized by secondary autoimmune responses and low antioxidant defenses for nitrile proteins and oxidative specific epitopes modified as a result of redox. \[48\] Glutathione, the primary endogenous free radical cleaner, is reduced, increasing susceptibility to oxidative stress. \[49\]

In a meta-analysis study, it was observed that antioxidant levels including serum paraoxonase, uric acid, albumin, high-density lipoprotein, cholesterol, and zinc levels were lower and serum uric acid, albumin, and vitamin C levels increased with the use of antidepressant drugs. \[50\] In another study, oxidative damage to nucleic acids was examined using the immunohistochemical method with a monoclonal antibody that recognizes both 8-hydroxyguanosine (8-OHG) in RNA and 8-hydroxy-2'-deoxyguanosine (8-OHdG) in DNA and schizophrenia, oxidative damage to nucleic acids has been observed to increase in some parts of the brain in patients with major depressive disorder and bipolar disorder. It was recorded that there was high damage in schizophrenia patients, moderate damage in those with bipolar disorder, and lower damage in patients with major depression. As a result of the information obtained as a result of the study, it was determined that there is a positive relationship between the high oxidative damage in RNA and the severity of mental illness. \[51\]

Oxidative stress has been recognized as the most effective of environmental factors that negatively affect neurogenesis as a result of inhibiting various stages of neurogenesis, which are involved in events such as cognitive functions and mood regulation and appear to decrease in depressed individuals. \[52,53\] Many diets have been shown to have a positive effect in preventing cellular damage and improving cognitive function, thereby reducing oxidative stress and neuroinflammation. \[54\]

Mediterranean diet; is a type of diet that includes various fruits, vegetables, olive oil, whole grains, dried beans, but also contains nutrients and antioxidants (vitamins C and E) components that have a positive effect on brain function. \[55\] It is also thought that the DASH diet model, which is considered an antioxidant-rich diet due to its high vegetable and fruit content, has a positive effect on mood. \[2,47,56\] The Zone diet, a type of diet characterized by low-carb, high-protein foods, is also thought to affect mood due to its antioxidant activity. \[2,44,57\] Besides, as a result of a study examining the effect of physical activity on depression, it was determined that oxidative stress and inflammation markers found increased in individuals with depression showed improvement with physical activity. \[51,58,59\]

**INFLAMMATION**

It is thought that neuropsychiatric disorders and inflammation are directly proportional to each other, inflammation reactions will increase with depression and thus inflammation can cause depression and neuropsychiatric disorders to increase. \[59\] The main inflammation markers are C-reactive protein (CRP) and interleukin-6 (IL-6). \[60\] Some nutrients and nutrients are thought to reduce inflammation. \[61\] In a study, it was observed that inflammatory marker levels increased with western-style nutrition, vegetables and fruits were abundant, and inflammatory marker levels of individuals who adopted a type of nutrition including whole grains, legumes, and also fish decreased. \[60\] Another research found that males who eat a western diet have higher CRP levels, while those who eat a Mediterranean diet have lower inflammatory values. \[62\]

It is thought that the interaction between the brain and inflammation may play a role in the formation of depression. \[63\] It was determined that inflammation was greater than it should be in individuals with severe mental illness and that pro-inflammatory food intake was high and anti-inflammatory food intake was low. \[64\] In a meta-analysis study, it was determined that anti-inflammatory agents contributed to the recovery in patients with depressive disorders. \[65\] It is also reported that polyphenols contained in cocoa, blueberries, and curcumin, which have strong anti-inflammatory properties, can have a positive effect on neuropsychiatric patients. \[66\] The effect of omega-3 polyunsaturated fatty acids, especially long-chain EPA and DHA, on depression was evaluated in a meta-analysis study and as a result of this study, it was concluded that omega-3 polyunsaturated fatty acids have a positive effect in improving depression. \[66\] It is reported that
Nutrition and Depression

Phytochemicals contained in cereals, which are a rich food source, can also protect against oxidative stress caused by inflammation.[67,68]

**MITOCHONDRIAL DYSFUNCTION**

While oxidative phosphorylation in mitochondria provides the majority of the body's energy, mitochondria also regulate neurotransmitter signaling in dendrites and synapses. The number of mitochondria in the brain is directly proportional to the amount of energy required by the brain. Damage to the electron transport system (ETS) in the mitochondria, which is effective in generating energy, is thought to have a significant impact on the development of psychiatric disorders. As a result of biochemical changes, it is thought that neuropsychiatric disorders (bipolar disease, depression, schizophrenia) have developed with damage to the ETS.[69] During the formation of energy in the mitochondria, electrons can escape and superoxides can be formed with the escape of electrons. These superoxides can cause a decrease in molecular oxygen concentration. Therefore, it is reported that mitochondria are an endogenous ROS center.[70] Chronic stress causes oxidative damage to mitochondrial functions and lipids in cell membranes and alters the composition of lipids in the brain.[71] The main distinguishing symptom of mitochondrial dysfunction is thought to be lack of energy, mental or physical fatigue, fatigue that can be defined as reduced endurance.[72] Coenzyme Q10, an endogenously derived antioxidant, was found to be at lower levels in exhausted populations, according to research on fatigue.[47,72] They reported that the studies were insufficient and that more work was required.[72]

Omega-3 fatty acids, antioxidants, group B vitamins, zinc, and magnesium have all been shown to improve neurocognitive function and enhance mitochondrial function.[71] Lipid accumulation and mitochondrial dysfunction were observed as a result of consuming a high-fat diet for an extended period. Abnormal mitochondrial formation is associated with a high-fat diet; Free radical production is also associated with inflammation and insulin resistance.[73,74] Although it is claimed that the low-carb ketogenic diet, characterized by high fat, low carbohydrate, and low protein content, targets the opposite of mitochondrial dysfunction with the transition from aerobic energy production to glycolytic energy production in depression, not enough work has been done yet.[75,76]

**EPIGENETICS**

As a result of various factors, the occurrence of hereditary changes in gene expression without any changes in the sequencing of DNA, also referred to as genetic code, is called epigenetics.[77] Epigenetic modifications that can be passed on to new generations and are essential for normal cell development and differentiation; DNA methylation, histone modification, chromatin folding, the regulatory effects of mRNA.[78,79] Epigenetic modifications that regulate processes such as stress response, immune functions and neurodevelopment are affected by endogenous and exogenous factors, but it is also said that it may be possible to reprogram them through nutrition and lifestyle.[78,80]

Nutri-epigenetics, which covers the effect of nutrition, which is one of the environmental factors affecting epigenetic processes, through epigenetic modifications, is a new and promising area that has emerged in the last few years, but it is also said that nutrition can prevent diseases along with this pathway.[81] It is thought that both overeating and nutrient restriction can lead to epigenetic changes in genes that are effective in metabolic processes and behaviors.[3]

There is also evidence linking epigenetic changes to neurodegenerative diseases such as Parkinson's and Alzheimer's disease. Epigenetic processes such as DNA methylation and histone acetylation, which have significant effects on memory and learning functions, have been shown to decrease Alzheimer's, a neurodegenerative disease. For this reason, it is said that dietary components, which are methyl group donors, can be used to prevent and treat Alzheimer's disease by increasing DNA methylation.[81]

Especially prenatal and postnatal nutrition can cause epigenetic changes in the offspring, leading to metabolic disorders in later years.[77,78] As a result of a study of rats fed a western diet during pre-mating-pregnancy and lactation processes, maternal obesity, increased adipose tissue and puberty entry rate, decreased muscle mass and locomotive activity, and hyperphages were observed in the offspring.[77] As a result of a study conducted by Barker and his colleagues, it was found that prenatal and postnatal nutrition, toxins, stress exposure may affect DNA methylation, the most common epigenetic modification in the mammalian genome, and this effect may be associated with difficulties
in internalization and externalization in childhood and adolescent periods.\textsuperscript{[78,79]} It has been determined by some studies that only early-life nutritional conditions such as breastfeeding and maternal obesity can affect neuron development through epigenetic modifications.\textsuperscript{[3]}

As a result of some studies, polyphenols, secondary plant metabolites, are reported to regulate abnormal gene expression by altering the activity of histon deacetylase and DNA methyltransferase enzymes.\textsuperscript{[78]} In addition, metionin, betain, group B vitamins, and omega-3 fatty acids have been shown to affect epigenetic processes through a number of pathways.\textsuperscript{[80,81]}

Antioxidant compounds such as flavonoids and non-natural polyphenols and organosulfide compounds, which have the advantage of being able to cross the blood-brain barrier, have been shown to have a protective effect on neurons in both \textit{in vitro} and \textit{in vivo} neurodegenerative models.\textsuperscript{[81]}

**OBESITY**

Depression, a mental disorder, is associated with genetic, environmental, and psychological factors. It has been stated that obesity and chronic systemic inflammation are seen in individuals who consume high-fat diets. Deficiencies in some brain functions (memory, learning, and execution) were observed in obese individuals compared to normal-weight individuals. While some epidemiological studies have shown a higher risk of depression and anxiety in obese individuals, some studies do the opposite. Western-type nutrition is thought to be among the main causes of obesity and can also cause dysfunction in the intestinal microbiota. It has been observed that obesity complications increase as a result of dysfunction in the intestines.\textsuperscript{[82]} In research, the relationship between obesity and mood disorders was investigated, and it was reported that neurotransmitters like serotonin and dopamine were also necessary to control mood in people who ate high-fat diets.\textsuperscript{[83]} The presence of cytokines linked to increased inflammation in mood disorders and obesity indicates a connection between the two conditions’ causes.\textsuperscript{[84,85]}

**Conclusion**

According to the information mentioned above, it can be said that nutrition is a factor that can be used in the prevention and improvement of depression. Nutrient and non-nutrient components such as omega 3 fatty acids, zinc, magnesium, iron, tryptophan, polyphenols, alpha-lactalbumin, methionine, which is a methyl group donor, vitamins of group A, C, D, E, and group B; functional nutrients such as fruits, vegetables, whole grains, oilseeds, chocolate; The use of dietary models such as Mediterranean diet, DASH diet, ketogenic diet, zone, and the paleo diet are nutritional approaches that are effective in improving cognitive functions and treating depression. In this review, the effect of nutrition on cognitive functions and depression is focused, but it is explained through which pathways this effect can be achieved. It’s also been stated that vitamin C’s effectiveness on cortisol levels is only seen when it’s taken as a supplement. It should also be taken into account whether the nutritional components used can provide the effect on cognitive functions with the amount taken on a normal diet or when taken as supplements, and the reliable upper limit level of these components should be determined. To fully reveal the mechanisms involved in the relationship between nutrition and depression, which are tried to be clarified in the light of the information obtained as a result of systematic compilation, meta-analysis, and clinical studies, more studies are required on individuals with a larger population, longer-term dietary treatments, and clinically ill patients.

**Declaration of conflicting interests**

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

**Funding**

The authors received no financial support for the research and/or authorship of this article.

**REFERENCES**


67. Volman JJ, Ramakers JD, Plat J. Dietary modulation of immune function by beta-glucans. Physiol Behav 2008;94:276-84.


