Trakia Journal of Sciences, No 1, pp 81-93, 2019

Available online at:
http://www.uni-sz.bg
ISSN 1313-7050 (print)
ISSN 1313-3551 (online) **doi:10.15547/tjs.2019.01.013**

Mini Review

THE ROLE OF OXIDATIVE STRESS IN THE ETIOPATHOGENESIS OF DEPRESSION

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ABSTRACT
In recent years, the role of oxidative stress in the etiopathogenesis of depression has been increasingly discussed. The mechanisms by which stress has a negative effect on the brain are not yet fully understood. Free radicals cause rapid damage to certain cellular macromolecules that may be involved in cytotoxic effects in the central nervous system. The effectiveness of new types of supplementation therapy with antioxidants - vitamins A, E, C, Omega-3 fatty acids, Coenzyme Q10 and Zn are being studied.

Key words: Oxidative stress, depression, antioxidants

INRODUCTION

Depressive disorder is fourth in the list of most serious health problems according to the World Health Organization (WHO). It is estimated that 350 million people worldwide suffer from depression, which is around 5% of the world population, while in developed countries this percentage may reach up to 10%. The essence of the problem stems from the lack of knowledge of the etiological, neurobiological and pharmacological mechanisms of pathogenesis on cellular and molecular level. In addition, the diagnosis of the disease is made only by observation, so depressive syndromes can not yet be clearly coded and understood (1). It seems that the complex network of interconnected genetic, biological (variable levels of neurotransmitters like dopamine and serotonin), environmental and psychosocial factors predisposes to the development of depressive disorder (2, 3, 4). Although the pathogenesis of the disease is not fully understood, the role of biochemical pathways - oxidative and nitrosative stress and the pathway of tryptophan catabolites - has been reported to contribute to the development of depressive disorders.

Depression is a mental disorder characterized by a number of basic symptoms such as low mood, disturbances in the biological rhythm, psychomotor retardation, anxiety, somatic disorders as well as other non-specific symptoms (5). It has a multifactorial etiology, with biological, psychological and social factors that play an important role (6). Several hypotheses have been suggested to explain the mechanisms of development of depression. It is believed that depression is associated with disorders of serotonin, norepinephrine and dopamine neurotransmission. Moreover, many observations support the participation of the GABA system in the mechanism of depression pathogenesis (7). Patients suffering from depression have reduced GABA levels in plasma and cerebrospinal fluid (8, 9), which is an indicator that its brain synthesis is reduced. Recent evidence suggests that chronic stress by initiating changes in the hypothalamic-pituitary-adrenal axis and the immune system acts as an initiator of the above-mentioned disorder. For example, glucocorticoids and proinflammatory cytokines increase the conversion of tryptophan to kynurenine, resulting in a decrease in brain serotonin synthesis (as less tryptophan is available for

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serotonin creation) and an increase in the formation of neurotoxic metabolites, for example glutamate antagonist - quinolinic acid. It has also been shown that the activity of dopaminergic systems is reduced in response to inflammation (10). Also, some genetic factors are believed to be involved in depressive etiology (11). In addition, brain cell apoptosis appears to be also involved in the development of depression as changes in astrocyte count and morphology have been observed in patients with major depressive disorder (12-15). This may depend, at least in part, on the actions of proinflammatory cytokines, since quinolinic acid is found to contribute to increased astrocyte or neuronal apoptosis (16, 17).

Studies on humans and animals suggest an interesting link between mitochondrial diseases and depression. Although depression has historically been associated with changes in monoaminergic pharmacology and hippocampal neurogenesis in adults, new data increasingly include wider forms of reduced plasticity including plasticity inside the cell. Mitochondria are the cellular power station of eukaryotic cells and regulate brain function through oxidative stress and apoptosis. Some studies have shown that mitochondrial dysfunction can play an important role in the pathophysiology of depression. Changes in mitochondrial functions such as oxidative phosphorylation and membrane polarity that increase oxidative stress and apoptosis may precede the development of depressive symptoms. However, data on the effects of antidepressant drugs are controversial: some studies have shown that they have no effect on mitochondrial function or even potentiate its dysfunction, while other studies show more favorable effects. Overall, the data show an intriguing relationship between mitochondrial function and depression, which requires further investigation. Mitochondria may be directed to the development of new antidepressant drugs, and specific forms of mitochondrial dysfunction can be identified as biomarkers for personalization of treatment and early diagnosis by differentiation between disorders with similar symptoms.

Mitochondria are the primary source of reactive oxygen species (ROS), which under normal conditions play an important role in cell signaling and homeostasis. ROS is produced by oxidative phosphorylation, but under normal physiological conditions the mitochondrias create protective factors that can neutralize harmful free radicals (18). For example, there is a mitochondrial matrix thiol system that plays an important role in antioxidant protection (19). In the electron transport chain, complexes donate electrons to oxygen-producing radicals such as superoxide and peroxidases, and high levels of these radicals and oxidative stress cause lipid damage, increase DNA breakdown, and oxidize nuclear and mitochondrial DNA (20, 21). Lower levels of ROS also play a role in normal cell function such as cell differentiation, tissue regeneration, reduction biology, and promoting adaptation to environmental changes (22). The production of highly reactive free radicals increases with premature leakage of electrons to oxygen in the electron transport chain, increasing oxidative stress. Superoxide is one of ROS's predecessors, and complexes I and III are primarily responsible for its production (22). Oxidative stress can be the cause or consequence of damage to mitochondria and mitochondrial DNA (23). Martins-de-Souza et al. (24) speculate that the decrease in ATP may be due to oxidative stress and that elevated levels of subunits in the complexes of the oxidation-phosphorylation system are compensatory. In fact, the reduction of ATP and its association with oxidative stress are associated not only with depression but also with psychotic disorders (25), autism (26), Alzheimer’s disease (27), anxiety disorders (28) and Huntington's disease (29).

Several articles report the link between oxidative stress and depression. Ben-Shachar and Karry (2008) have found an increase in oxidative damage and changes in complex I of the electron transport chain in the prefrontal cortex of depressed patients. Other researchers noted the decrease in antioxidant enzymes in depression and related cognitive deficits (30). Braughler and Hall (31) suggest that lipid peroxidation can cause mitochondrial dysfunction by damaging membranes and causing excitotoxicity that can be potentiated by increased production of reactive molecules or decreased levels of antioxidants.

Mechanisms through which environmental stress has a negative impact on the brain are still not fully understood. However, there is evidence that free radicals such as NO cause rapid damage to certain cellular macromolecules that are involved in the electron transport chain, which in turn will

reduce the production of ATP and may be involved in cytotoxic effects in the central nervous system (32, 33). Madrigal et al. (34) did not detect changes in ATP levels, which provide additional evidence that a threshold of damage in the electron transport chain may have to be reached before the mitochondria's ability to maintain homeostasis is reduced (35). Antidepressant treatment affects the level of oxidative stress in patients with depression. For example, higher total serum oxidant status and lower total serum antioxidant capacity were normalized in depressed patients after 42 days of antidepressant treatment (36). Similar findings have been reported in animal models of depression. The drug Venlafaxine increases the expression of antioxidant mitochondrial genes in the brain of mice, which reduces levels of hydrogen peroxide and peroxynitrite (37, 38).

In addition, in the presence of light chronic stress, Lamotrigine, Aripiprazole and Escitalopram normalize the activity of glutathione and glutathione peroxidase in the cortical regions (39). Mild chronic stress increases lipid peroxidation in the cortex and plasma but is also recovered from the same three drugs. A similar study revealed that Venlafaxin can reverse the chronic mild stress-induced reduction in glutathione peroxidase activity and vitamin C and increase lipid peroxidation and NO in the cortex in rats (40). Galecki et al. (41) concluded that DD is accompanied by disturbances in the balance between pro- and anti-oxidative processes; however, these disturbances did not improve in patients in remission after three months of fluoxetine therapy.

Nitrogen oxide and other ROSs inhibit mitochondrial 2-oxoglutarate dehydrogenase, resulting in elevated levels of glutamate, which in the end leads to glutamate excitotoxicity and cell death (42). The reelin-NO-synthase relationship should receive greater experimental attention as a number of reports indicate that changes in expression of reelin within the dentate gyrus can lead to insufficient maturation of newly formed granular neurons and reduced hippocampal plasticity and may be a key event in the pathophysiology of depression (43).

There is also an important link related to the inflammation to be considered in the context of these experiments. Many studies support the idea that inflammatory processes are involved in depression and affecting the inflammatory cytokines in order to reduce the symptoms of depression is a very active area of study (44). Studies have shown that pro-inflammatory cytokines alter the complexes of the electron transport chain and complex enzymes associated with them (45) and that they activate the pro-apoptotic proteins and the caspase cascade (46).

Changes in several components of the immune system and inflammatory markers were also observed in animals with low or zero reelin expression (47). It is reported that these animals are not only quite susceptible to the depressogenic effects of cortisol (48), but also show alterations in the grouping of specific membrane proteins in lymphocytes (49). This requires a membrane protein clustering study in lymphocytes in patients with depression and suggests the model of specific proteins in the plasma membrane of lymphocytes as a biomarker of depression and as the cause of some of the inflammatory events observed in depression (50-52). In fact, changes in the oxidative stress of lymphocytes are clearly demonstrated in depression (53, 54). Peripheral injections of the anti-inflammatory drug Etanercept (which is unable to cross the blood-brain barrier) have been shown to not only reduce the depressive behavior induced by the frequent administration of cortisol but also to normalize the neurochemical phenotype of the reelin-expressing cells in the hippocampal dental gyrus. It is speculated that both peripheral and secondary central actions can be found in the antidepressant effects of Etanercept (55). It seems clear that further research will be needed on the relationship between reelin, oxidative stress and depression, not only to determine how these factors can be an important component of the pathophysiology of depression but also to use them as possible goals in the development of new antidepressant drugs.

Nitrosative and oxidative stress are inevitably associated with the emergence of free radicals. In 1956, American specialist in gerontology, Denham Harman, described free radicals as compounds involved in processes leading to cell damage, mutagenesis, tumor development, and biological aging. Reactive Oxygen (ROS) and Nitrogen (RNS) species studies show the dual nature of the compounds. On one hand, these reactive compounds can damage

biomolecules, which can lead to tissue dysfunction. On the other hand, they represent an essential element in signal transduction pathways that activate a stress response. Concentration of radicals is crucial for their nature - at low concentrations, they are modulators; at high levels they have a toxic effect (4).

The imbalance between ROS production and neutralization is typical for patients with depression. A potential cause of DD appears to be reduced in antioxidant activity, mainly reduced levels of zinc (Zn), coenzyme Q10 (CoQ10), vitamins A, C and E, glutathione in plasma that enhance oxidation processes including lipid peroxidation and protein damage DNA (56). However, the results of the antioxidant studies are colorful. In some, patients do not differ from healthy subjects with respect to the plasma levels of vitamins A, C and E (57). On the other hand, Maes et al. (58) found that vitamin E levels in the plasma of DD patients were lower than healthy volunteers. This is confirmed by a study of serum alpha-tocopherol levels (59). Another study suggests that the severity of the disease is associated with elevated levels of vitamin C in the plasma (60). Differences in results can be due to their properties - vitamins A and E are fat-soluble and their distribution is determined by the amount of low-density lipoprotein (LDL) and triglycerides (58). In addition, some inaccuracies can arise from the differences in size of the groups studied, the impact of the environment and the severity of the disease. In addition, patients with depression are characterized by reduced glutathione peroxidase (GPx) activity, increased activity of xanthine oxidase (Ox, the enzyme responsible for the production of hydrogen peroxide and superoxide anion) and increased activity of superoxide dismutase (SOD) (61, 62). Concerning superoxide dismutase (SOD) and glutathione peroxidase (GPx), there are also some inconsistencies between studies. Some of them confirm the relationship between depression and increased SOD activity (62, 63). Some researchers have confirmed that the occurrence of depression is associated with excessive Gpx activity (64); while others did not detect a difference between study and control groups (57, 65).

In terms of depression, zinc (Zn) is also an important microelement. Zn participates in the regulation of mental and memory functions. The researchers noticed a decrease in the number of progenitor cells and immature nerve cells in the hippocampus of rats treated with a low Zn diet (66). Additional studies involving these animals have shown that Zn deficiency leads to the appearance of depressive symptoms (67). Damage to cellular biomolecules is one of the consequences of oxidative and nitrosative stress. Some products from these processes can serve as specific tags that can be used for early and accurate diagnostics in the future. One example of such markers includes 8-oxoguanine (8-oxoG), an indicator of oxidative DNA damage whose elevated levels have been found in urine, cerebrospinal fluid, serum and peripheral blood mononuclear cells in depressed patients (68, 69). A follow-up study using peripheral blood mononuclear cells obtained from patients with depression confirms that depression is accompanied by an increased amount of oxidase-modified nucleobases (21). Another potential marker for depression may include an increased concentration of malondialdehyde (MDA), a product of polyunsaturated fatty acid peroxidation (PUFAs) caused by elevated levels of ROS and RNS (70). In addition, patients with subsequent recurrent depressive episodes have a higher MDA than those with an initial episode of this disease. Studies have shown that patients with depression are characterized by decreased levels of polyunsaturated fatty acids (PUFAs) in the erythrocyte cell membrane. Degradation of membrane lipids may be caused by the intensification of peroxidation processes (70, 71). Another product of fatty acid oxidation is 8-iso-prostaglandin F2 (8-isoPGF2), which is formed during the oxidation of arachidonic acid. 8-iso-PGF2 may be a potential biomarker in the diagnosis of depressive disorder since people with depressive disorders have elevated levels of this compound (72). Patients with depression are also characterized by abnormalities in the production pathway of reactive nitrogen species, which is manifested by elevated levels of nitric oxide (NO). NO may be highly toxic. This is due to the reaction of NO with superoxide, resulting in the formation of peroxynitrite, a compound that is highly reactive with aromatic amino acids, especially tyrosine and phenylalanine, resulting in nitrate forms of these amino acids (73). In addition, patients with depression are characterized by elevated levels of IgM class antibodies against nitrified protein substrates (predominantly nitrate form of tyrosine) that arise due to the high reactivity of peroxynitrite (72). In addition, patients after suicide attempts

had higher serum NO levels than patients without such attempts. Analisys using neurons originating from the suprachiasmatic nucleus of patients who have committed suicide confirms the increased expression of nitric oxide synthase. In addition, studies have shown that patients with recurrent depression have significantly elevated NO levels in the blood serum (72). Another problem in MDD is microvasvular dysfunction, which can be triggered by oxidative stress-induced reductions in NO-dependent dilation, as well as alterations in vascular smooth muscle function. This may lead to the development of new strategies targeting vascular oxidative stress for improving NO-mediated endothelial function and reducing cardiovascular risk in MDD (74). Interestingly, Talarowska et al. did not detect significant differences in the expression of nitric oxide synthase between patients with a single depressive episode and a group suffering from the recurrent form of the disease (75). Nevertheless, studies have shown that the decrease in the activity of mechanisms for protection against ROS and RNS, both in peripheral blood cells and in nerve cells, may be accompanied by the development of a depressive disorder (76). This suggests that peripheral factors involved in oxidative and nitrosative stress can penetrate the blood-brain barrier. ROS and RNS may be neurotoxic for the brain (75). One of the meta-analyzes confirms that elevated levels of ROS in depression may cause neuronal degradation in the hippocampus (77). In addition, the blood-brain barrier permeability tests suggest that it is over-permeable in depression - protein components (for example tryptophan catabolites - TRYCAT) can easily penetrate the brain (78). Some studies examine the relationship between vitamin C and depression. (79) summarize the involvement of vitamin C in psychiatric disorders by presenting available data on its pharmacological effects in animal models as well as in clinical studies. Vitamin C, especially its reduced form, draws attention to its numerous functions in various tissues and organs, including the central nervous system (CNS). Vitamin C protects the neuron from oxidative stress, relieves inflammation, regulates neurotransmission, impacts neuronal development, and controls epigenetic function. All of these processes are closely related to psychopathology. Over the last few decades, scientists have discovered that vitamin C deficiency can lead to motor deficiency, cognitive impairment and abnormal behavior, while vitamin C supplementation has a potential preventive and therapeutic effect on mental illnesses such as major depressive disorder, schizophrenia, anxiety disorders and Alzheimer's disease. Although several studies support the possible role of vitamin C against mental disorders, the development of more research is essential to speeding up knowledge and exploring the mechanism in this area.

Based on several studies (7, 9, 80-82), there is proof that vitamin C exerts an antidepressant effect by modulating the monoamine system (83) (for example, Vit C has been shown to activate serotonin receptor 1A (5-HT1A)), this activation is a mechanism of action of many antidepressants, anxiolytic and antipsychotic drugs). Another mechanism is by modulation of GABA-systems (by activation of GABA-A receptors and possible inhibition of GABA-B receptors) (9). It also inhibits N-methyl-d-aspartate (NMDA) receptors and the pathway of L-arginine-nitric oxide (NO) -cyclic guanosine 3,5-monophosphate (cGMP). Blocking of NMDA receptors is associated with reduced levels of NO and cGMP, and the reduction in NO levels within the hippocampus indicates that it induces antidepressant-like effects (84). Vitamin C blocks potassium channels (K +) - it has been found that its application results in an antidepressant effect in the tail suspension test by inhibiting potassium channels (84). Since potassium channels belong to the physiological purposes of NO and cGMP in the brain, their inhibition plays an important role in the treatment of depression. In addition, vitamin C activates phosphatidylinositol-3-kinase (PI3K) and inhibits the activity of glycogen synthase kinase 3 beta (GSK-3β) (85, 84). Vitamin C induces the expression of heme-oxygenase 1. This is a candidate-depressive biomarker that can be a factor in the relationship between inflammation, oxidative stress and biological as well as functional changes in brain activity in depression. Reduced expression of heme-oxygenase 1 is associated with depressive symptoms (82, 86). Since depression is well known to be associated with altered anti- and pro-oxidant profiles, vitamin C can play anti-depressant function with its antioxidant properties (87, 84).

Available data from the literature suggest that vitamin C deficiency is very common in patients with depressive disorder. Gariballa (88) in a randomized, double-blind, placebo-

controlled study observed that low vitamin C status is associated with increased symptoms of depression after acute illness in elderly people. The parameters were measured in the beginning as well as after 6 weeks and 6 months. Patients with vitamin C deficiency significantly increase the symptoms of depression compared to those with higher concentrations at start as well as at week 6. Significantly lower serum vitamin C levels in patients with depression versus healthy controls are also shown by Bajpai et al. (89) and by Gautam et al. (90). Something more, the addition of Vit C (1000 mg/day) to food along with vitamins A and E for a period of 6 weeks resulted in a significant reduction in depressive symptoms (90). In addition, a case study of 60 male university students has shown that patients with depression have a significantly lower intake of vitamin C (91). Similarly, in another controlled-case study involving 116 girls identified as having depressive symptoms, depression was negatively related to the intake of vitamin C (92). Rubio-López et al. (93), in turn, examined the relationship between dietary intake and depressive symptoms in 710 valencian students aged 6-9 years and also noted that vitamin C nutrition was significantly lower in children with depressive symptoms. In conclusion, the increase in inadequate vitamin C intake is significantly higher in people with depressive symptoms.

The efficacy of Vit C as an adjuvant in the treatment of pediatric severe depressive disorder in a double-blind, placebo-controlled pilot study was evaluated by Amr et al. (94). Patients (n = 12) treated for 6 months with Fluoxetine (10-20 mg/day) and Vitamin C (1000 mg/day) showed a significant reduction in depressive symptoms compared to the fluoxetine + placebo group. No serious side effects have been identified. Zhang et al. (95) in a double-blind clinical study observed the effect of Vit C (500 mg twice daily) on the mood in emergency hospitalized non-depressive patients. The applied therapy increases vitamin C concentrations in plasma and mononuclear leukocyte and is associated with a 34% reduction in affective disorder (95). Similarly, Wang et al. (96) found that short-term treatment with vitamin C (500 mg twice daily) is associated with 71% reduction in affective disorder and 51% reduction in psychological stress in emergency hospitalized patients with high levels of hypovitaminosis C. Khajehnasiri et al. in a randomized, double-blind, placebo-controlled study involving 136 depressed male workers observed that the use of vitamin C (250 mg twice daily for 2 months) alone and in combination with omega-3 fatty acids significantly decreased the points on the BECK Depression Inventory Scale, except that the omega-3 fatty acid supplement itself is more effective (97). Furthermore, the addition of vitamin C and omega-3 fatty acids separately (not in combination) significantly reduces serum levels of malondialdehyde (MDA). Fritz et al. (98) conducted a systematic review of human and observational studies assessing the efficiency of interventional Vit C as a contentious adjunctive cancer therapy and reported that it could improve quality of life, physical function, as well as prevent some side effects of chemotherapy, including fatigue, nausea, insomnia, constipation and depression.

Tryptophan is a major aromatic exogenous amino acid. Approximately 30% of the total volume of tryptophan delivered to the body is used for protein synthesis. The residue of tryptophan degrades through the kynurenine pathway and undergoes a non-protein transition to serotonin and melatonin. The metabolism of tryptophan can be divided according to the place where it occurs. In the periphery, tryptophan undergoes three types of transformation: rupture of the indole ring leading to the generation of kynurenine, hydroxylation leading to serotonin formation, and decarboxylation resulting in the formation of tryptamine. In the central nervous system, tryptophan is a substrate for the production of melatonin (the hormone responsible for maintaining a normal circadian rhythm) and serotonin (a neurotransmitter responsible for emotions) (2).

Antioxidants that simultaneously modulate oxidative and nitrosative stresses are important in the treatment of depressive disorder. Ebselen (an organic compound containing selenium) that mimics the effect of glutathione peroxidase and simultaneously inhibits indolamine 2,3-dioxigenase (IDO) is one of these examples. Studies in mice indicate that Ebselen influences the behavior of experimental animals (improves behavioral test results), showing the potential of organic selenium as a therapeutic agent for affective disorders (99). On the other hand, a study on macrophages derived from human monocytes confirms that Ebselen inhibits the cellular activity of IDO at the post-translational level.

Ebselen acts by binding cysteine residues to the enzyme, resulting in a conformational change of the protein and prevents the formation of bonds in the substrate at the binding site (100).

As noted above, depression is associated with low CoQ10 levels. Mehrpooya et. al. (101) suggest that among patients with bipolar disorder, adjuvant CoQ10, probably due to its antioxidant and anti-inflammatory properties, may improve the symptoms of depression for a period of 8 weeks. Additional studies have shown that patients with treatment-resistant depression have significantly lower plasma levels of CoQ10 compared to patients without resistant depression. Therefore, this parameter can be used to distinguish between resistant depression and classical depression (71). Another experiment showed that patients with resistant depression were characterized by low serum Zn^{2+} concentrations (102). Patients who do not respond to SSRIs, tricyclic antidepressants and electroshock have significantly reduced Zn^{2+} levels in blood plasma (103, 104). Treatment with SSRI supplemented with zinc may reduce the severity of the disease according to the Bek depression inventory compared to the placebo group (105, 106). Sawada and Yokoi pointed to the potential use of zinc as an additive to prevent depressive symptoms. However, research in this area is unclear (107). Nguyen et al. (108) do not confirm the hypothesis of the healing properties of zinc. In the frontal cortex, Cu/Zn-SOD concentrations are increased in patients with DD compared to matched controls 109. This finding was of specific interest since Cu/Zn-SOD is located only partly in neurons, but mainly in glial cells, which are more vulnerable to oxidative damage (110, 111). In contrast to Cu/Zn-SOD, Mn-SOD (Manganese-superoxide dismutase) is a mitochondrial enzyme, which can be found mainly in neurons and only in much smaller amounts in glial cells (112). In DD, glial cells have repeatedly been described as altered, especially in the frontal cortex (113, 114).

Depression is also associated with low levels of vitamin A. Studies in rats show that SSRI treatment helps optimize the level of vitamin A in the brain (39). After 24 weeks of treatment, patients with SSRIs showed normal levels of vitamin A in the plasma. Adjusting the level of vitamin A in the serum of treated patients may be helpful in monitoring the effectiveness of SSRI treatment (57). Studies have shown that diet is important for the prevention and treatment of depression. The results of epidemiological studies have shown that a diet rich in omega-3 fatty acids (mainly of fish origin) can prevent the development of depression (115). Omega-3 acids affect the metabolism of neurotransmitters and modulate the effects of signal transduction pathways in cells (116). Maes et al. (117) found a change in fatty acid composition in the serum of patients with depressive disorder. Depressive patients are characterized by low levels not only of polyunsaturated fatty acids but also of omega-3 and omega-6 fatty acids (117). Furthermore, Nemets et al. (118) confirmed enhanced efficacy of antidepressant therapy when supplemented with ethyl ester of eicosapentaenoic acid (acid from the omega-3 group). Patients given an additional ethyl ester of eicosapentaenoic acid (E-EPA) were characterized by a lower mean score on the Hamilton scale than those in the placebo group (treated with antidepressants and placebo) (118). Another compound that can effectively modulate the treatment of depression is N-acetylcysteine. It is a precursor to glutathione (the major antioxidant) and is particularly important for maintaining the normal level of glutathione in the brain. In addition, it has been demonstrated that N-acetylcysteine modulates neurogenesis and prolongs survival of neurons (119). Studies have shown that treatment with the addition of N-acetylcysteine reduces the severity of depressive symptoms compared to classical treatment. Patients undergoing assisted therapy show improvement in quality and life satisfaction (120). Depression is a serious mental disorder that affects an increasing number of people. In addition, depressive disorder is a disease that may vary depending on the patient. That is why the right diagnosis, as well as appropriate and effective therapy, are so difficult. The level of knowledge regarding the mechanisms of DD development is still insufficient. Previous studies have confirmed the involvement of certain processes in the development of symptoms of depression and resistance to traditional pharmacotherapy. These include oxidative and nitrosative stress and tryptophan catabolite pathways. Knowing the molecular mechanisms of depression can lead to the development of effective biomarkers in the future. Regulating specific processes can also enable the development of new, effective and personalized treatment options. Therefore, it is

essential to continue the study to confirm the links between biochemical pathways - oxidative and nitrosative stress and tryptophan catabolites - and depressive disorders.

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