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Omega-3 Fatty Acids in Major Depressive Disorder: Biological Mechanisms and Their Role in Treatment

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Abstract

Background: Major depressive disorder (MDD) is a common and complex psychiatric condition and a leading cause of disability worldwide. Despite extensive research, its pathophysiology is not fully understood, and current pharmacological treatments are not effective in a substantial proportion of patients. In recent years, increasing attention has been given to the potential role of nutrition in mental health, particularly dietary fatty acids. Omega-3 polyunsaturated fatty acids (PUFAs), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been widely investigated in relation to depressive disorders due to their involvement in brain structure, neurotransmission, and inflammatory regulation. Their potential antidepressant effects have been linked to anti-inflammatory and neuroprotective properties.

Aim: This review summarizes current evidence on omega-3 fatty acids and depression, focusing on biological mechanisms and clinical outcomes.

Methods: A narrative review was conducted using PubMed and Scopus. Studies on omega-3 fatty acids, depressive symptoms, mechanisms, and clinical efficacy were included.

Results and Discussion: Omega-3 PUFAs are associated with modest reductions in depressive symptoms, with more consistent effects observed for EPA-rich formulations, particularly at higher EPA proportions.

Conclusions: Omega-3 fatty acids may modulate biological pathways involved in depression and exert a modest antidepressant effect. However, evidence remains unclear, and further research is needed to clarify their clinical role.

Keywords: omega-3, PUFAs, Eicosapentaenoic acid, Docosahexaenoic acid, depression, major depressive disorder

1. Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders and a significant global health problem. According to the World Health Organization (WHO), depression affects approximately 300 million people worldwide and is expected to become the leading cause of disease burden by 2030.(1) Despite the high prevalence of depression, its exact cause has still not been fully understood. Several hypotheses have been proposed to explain the pathogenesis of depression. The oldest and most widely known is the monoamine hypothesis, which suggests that depressive symptoms are associated with reduced levels of neurotransmitters in the synaptic cleft, mainly serotonin, norepinephrine and dopamine.(2)

However, in recent years this theory has been considered too simplistic, and depression is now regarded as a much more complex and multifactorial disorder. Current evidence indicates that the development of MDD may be associated with chronic stress and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, neuroinflammation, genetic factors, brain remodeling processes and psychological factors. It has also been suggested that difficult life experiences may exceed an individual's adaptive abilities and increase the risk of developing depression.(1,3,4)The clinical presentation of MDD includes persistent low mood, anhedonia, decreased interest in daily activities, fatigue, impaired concentration, sleep disturbances and appetite changes. Patients may also experience feelings of guilt or worthlessness, psychomotor agitation or retardation, and suicidal thoughts. These symptoms significantly impair daily functioning and quality of life.(5)

Although SSRIs remain the first-line pharmacological treatment for depression, their effectiveness is not always satisfactory. Clinical improvement usually occurs after several weeks of therapy, and nearly one-third of patients do not respond adequately to antidepressant treatment. Studies have shown that approximately 30% of individuals with MDD are resistant to conventional therapies, while 10–20% of patients continue to experience significant depressive symptoms for two years or longer despite sequential treatment approaches.(6) Furthermore, antidepressant medications often fail to achieve complete remission, highlighting the need for alternative and supportive therapeutic strategies in the management of MDD. The limitations of currently available approaches have increased interest in alternative and supportive methods in the management of depression.(7)

In recent years, increasing attention has been paid to the role of diet in mental health. Growing evidence suggests that dietary habits may influence not only physical health, but also the development and course of psychiatric disorders, including depression.(8,9) One of the mechanisms that may explain this relationship is the gut-brain axis, which involves bidirectional communication between the central nervous system and the gastrointestinal tract through neural, endocrine and immune pathways.(10)Studies have shown that patients with MDD may present alterations in gut microbiota composition compared with healthy individuals. Disturbances in the gut microbiota composition, referred to as dysbiosis, have been associated with systemic inflammation and neuroinflammation, which are considered important factors in the pathogenesis of depression.(3)Elevated levels of pro-inflammatory cytokines and markers of chronic low-grade inflammation have been observed in patients with MDD, suggesting that inflammatory processes may contribute to the pathogenesis of the

disease. These findings have drawn attention to the possible role of diet in depression, particulary to nutritional components with anti-inflammatory properties. (11)It has been suggested that some dietary nutrients may influence inflammatory processes associated with the development of mood disorders, including depression.The Mediterranean diet has been one of the most extensively studied nutritional models and has been associated with numerous health benefits, including a lower risk of cardiovascular, neurodegenerative and metabolic diseases. The Mediterranean diet is characterized by a high intake of vegetables, fruits, legumes, whole grains, nuts and olive oil, as well as moderate consumption of fish and seafood, which are important sources of omega-3 fatty acids.(9)Among the nutrients present in this diet, omega-3 polyunsaturated fatty acids (PUFAs) have attracted particular attention because of their potential anti-inflammatory and neuroprotective properties.(8,12)

Omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are abundant in fish and seafood and constitute important structural components of neuronal cell membranes. Several studies have suggested that omega-3 fatty acids may influence neurotransmission, synaptic plasticity and brain function, while also modulating inflammatory pathways involved in the pathogenesis of depression.(13,14)Higher dietary intake of omega-3-rich foods has been associated with lower severity of depressive symptoms and stress, with EPA and DHA appearing to play a particularly important role in mood regulation. Their beneficial effects are thought to be related not only to their influence on neuronal membrane function and neurotransmitter systems, but also to their ability to reduce neuroinflammation and suppress excessive pro-inflammatory activity.(15) Therefore, omega-3 fatty acids are increasingly being considered as a promising supportive strategy in the prevention and management of depression.

In this review, we discuss the current evidence regarding the relationship between omega-3 fatty acids and depression. Particular attention is given to the potential biological mechanisms underlying their effects, including the modulation of inflammation, neurotransmission and brain function. We also examine the possible role of omega-3 supplementation as a supportive approach in the management of major depressive disorder.

2. Omega-3 Polyunsaturaded Fatty Acids

2.1 Classification of PUFAs and Sources of Omega-3 Fatty Acids

Humans obtain two major groups of polyunsaturated fatty acids (PUFAs) from the diet: omega-6 (n-6) fatty acids derived from linoleic acid (LA) and omega-3 (n-3) fatty acids

originating from α-linolenic acid (ALA). These fatty acids are critical structural components of cell membranes and plays an important role in maintaining membrane fluidity. They are classified as essential fatty acids because they cannot be synthesized by the human body and therefore must be supplied through dietary intake.(16)The difference between omega-3 and omega-6 fatty acids lies in the position of the first double bond within the carbon chain. In omega-3 fatty acids, the first double bond is located between the third and fourth carbon atoms from the methyl end, whereas in omega-6 fatty acids it is positioned between the sixth and seventh carbon atoms.(17)

Although both omega-3 and omega-6 fatty acids are essential for normal physiological function, maintaining an appropriate balance between their intake is considered important for health. Modern Western diets are typically characterized by excessive consumption of omega-6 fatty acids and relatively low intake of omega-3 fatty acids. A dietary omega-6 to omega-3 ratio ranging from approximately 4:1 to 1:1 is generally regarded as the most favorable for health. .(17,18)

Omega-3 fatty acids are naturally present in a variety of foods and include three main types: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).(19) ALA is mainly found in plant-based products such as flaxseed, chia seeds, walnuts and certain vegetable oils, whereas EPA and DHA are primarily present in oily fish and seafood, including salmon, tuna, herring and mackerel.(20)Although ALA can be converted into EPA and DHA through a series of enzymatic reactions, this process is relatively inefficient in humans. The conversion involves alternating desaturation and elongation steps mediated mainly by Δ6-desaturase and Δ5-desaturase enzymes. During this pathway, ALA is first converted into stearidonic acid and subsequently metabolized into EPA, which can be further elongated and converted into DHA. Due to the limited efficiency of this metabolic pathway, EPA and DHA obtained directly from fish and seafood are considered the main biologically active forms of omega-3 fatty acids.(13,21) Consequently, many dietary recommendations emphasize regular fish consumption as an important source of EPA and DHA. The American Heart Association recommends consuming at least two servings of fish per week, providing approximately 250 mg/day of EPA and DHA.(22)

2.2 Omega-3 Fatty Acids and Human Health

Omega-3 fatty acids are associated with a wide range of health benefits and are involved in numerous physiological processes. Higher intake of omega-3 fatty acids has been linked to improved cardiovascular health, mainly due to their broad anti-inflammatory properties. EPA and DHA exert cardioprotective effects through the modulation of lipid metabolism,

antioxidant and antithrombotic actions, as well as changes in gene expression related to inflammatory pathways, including NF-κB signaling and eicosanoid synthesis(23,24).Since chronic low-grade inflammation has been implicated not only in cardiovascular diseases, but also in several psychiatric and neurodegenerative disorders, increasing attention has been paid to the role of omega-3 fatty acids in brain health and central nervous system functioning. (18,24)

Lipids constitute approximately 50–70% of the brain's dry weight, while PUFAs account for nearly 80% of membrane phospholipids. In particular, DHA is highly abundant in the brain and represents approximately 30% of the lipid fraction of the gray matter. Due to their high incorporation into neuronal membranes, omega-3 PUFAs are essential for the growth and development of the central nervous system during pregnancy, infancy and childhood. Adequate dietary intake is therefore necessary for normal brain development.(13)Rapid DHA accumulation occurs during late pregnancy and early childhood, highlighting the importance of adequate maternal omega-3 intake during these periods. Low maternal DHA levels have been associated with impaired neurodevelopment and reduced learning abilities, whereas DHA supplementation during pregnancy and lactation has been linked to improved cognitive performance, visual acuity, psychomotor development and hand-eye coordination in offspring.(25)

Omega-3 fatty acids play an important role in maintaining proper brain function in adulthood. They have been shown to support cognition, neuronal preservation and protection against neurodegeneration. They influence neurotransmission by modulating membrane fluidity and neurotransmitter release, while also affecting intracellular signaling pathways and neuronal membrane function.(26)In addition, omega-3 fatty acids interact with cellular components such as receptors, ion channels and enzymes, which may contribute to reduced neuroinflammation, enhanced synaptic plasticity and improved neuronal signaling. Furthermore, PUFAs may reduce amyloid-β accumulation and increase brain-derived neurotrophic factor (BDNF), suggesting a potential protective role against neurodegenerative processes associated with Alzheimer's disease.(27)EPA and DHA may also indirectly support brain function by improving vascular health, which can contribute to better cerebral blood flow and maintenance of blood-brain barrier integrity.(28)Deficiencies of omega-3 PUFAs, particularly DHA, have been reported in individuals with several psychiatric and neurodevelopmental disorders, including ADHD, schizophrenia, autism spectrum disorder (ASD) and depression.(29)

Overall, omega-3 fatty acids seem to play an important role in both brain development and maintaining proper nervous system function throughout life. EPA and DHA are involved in neuronal membrane structure, neurotransmission, synaptic plasticity and regulation of neuroinflammatory processes, which may influence cognitive and emotional functioning. Studies have also shown that low omega-3 levels may be associated with several psychiatric and neurodevelopmental disorders. For this reason, growing attention has been directed toward the possible role of omega-3 fatty acids in mental health, particularly in depression.

3. Omega-3 Fatty Acids and Depression

3.1 Biological Mechanisms linking Omega-3 Fatty Acids and Depression

3.1.1Anti-inflammatory effects of Omega-3 Faty Acids in Depression

One of the most widely discussed mechanisms linking nutrition and depression is chronic low-grade inflammation. Numerous studies have demonstrated elevated concentrations of pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), in patients with major depressive disorder.(12,30) These inflammatory mediators can influence neurotransmitter metabolism, neuroplasticity and neurogenesis, thereby contributing to the development and persistence of depressive symptoms.Several factors may contribute to the maintenance of this pro-inflammatory state. Among them, increasing attention has been paid to disturbances in gut microbiota composition, referred to as dysbiosis. Alterations in the gut microbiota may impair intestinal barrier function, leading to increased intestinal permeability and facilitating the translocation of bacterial products into the circulation. This can trigger immune activation and promote the production of pro-inflammatory cytokines.(3) Dietary habits are considered one of the key factors influencing both gut microbiota composition and inflammatory status. In particular, the typical Western diet, characterized by a high intake of processed foods and an excessive omega-6 to omega-3 ratio, has been associated with increased inflammatory activity and may contribute to the development of dysbiosis.(10)Sustained inflammatory signaling can further be amplified by the release of damage-associated molecular patterns (DAMPs), such as high mobility group box 1 (HMGB1) and S100β proteins, from stressed or damaged cells. These endogenous danger signals activate immune cells, including microglia, through pattern-recognition receptors such as toll-like receptors (TLR2 and TLR4) and the receptor for advanced glycation end products (RAGE). Activation of these receptors promotes intracellular signaling cascades involving PI3K-AKT-mTOR, MAPK and NF-κB, ultimately

leading to increased transcription of pro-inflammatory cytokines, including IL-1β, IL-6 and TNF-α. Chronic activation of these pathways contributes to neuroinflammation, impaired neurogenesis and neuronal dysfunction, processes that have been implicated in the pathophysiology of depression.(12)

In contrast, omega-3 fatty acids, particularly EPA and DHA, may counteract several of the inflammatory mechanisms implicated in depression. EPA and DHA can modulate inflammatory signaling pathways, reduce the production of pro-inflammatory cytokines and inhibit the activation of transcription factors such as NF-κB. (12)Furthermore, these fatty acids serve as precursors of specialized pro-resolving mediators (SPMs), including resolvins, protectins and maresins, which actively promote the resolution of inflammation rather than merely suppressing it.(30) Experimental studies suggest that EPA may exert stronger anti-inflammatory effects, whereas DHA appears to play a more prominent role in neuroprotection and the maintenance of neurogenesis under inflammatory conditions.(31)Clinical findings support these biological observations. Although omega-3 supplementation does not appear to produce uniform antidepressant effects across all patients with major depressive disorder, EPA has shown particularly promising results in individuals presenting with elevated inflammatory markers. Greater reductions in depressive symptoms have been reported among patients with higher baseline levels of inflammation, including increased concentrations of hs-CRP, IL-6 and other inflammatory biomarkers.(32)

3.1.2 Modulation of HPA axis activity by Omega-3 Fatty Acids

The hypothalamic-pituitary-adrenal (HPA) axis constitutes one of the major biological systems involved in the stress response. Under physiological conditions, activation of the HPA axis leads to the release of glucocorticoids, which help maintain homeostasis during stressful situations. (3)However, chronic stress may result in sustained cortisol secretion and dysregulation of HPA-axis activity. Prolonged exposure to elevated glucocorticoid levels has been associated with neurotoxic effects, including reduced neuroplasticity, impaired neurogenesis and hippocampal atrophy, all of which have been implicated in the pathophysiology of depression.(9) Interestingly, lower plasma concentrations of omega-3 fatty acids have been linked to markers of HPA-axis dysregulation, particularly elevated evening cortisol levels. It has been suggested that omega-3 fatty acids may improve the sensitivity of glucocorticoid receptors and enhance the negative feedback regulation of the HPA axis. Furthermore, by reducing the production of pro-inflammatory cytokines, omega-3

fatty acids may indirectly counteract inflammation-induced impairment of glucocorticoid receptor function, thereby limiting HPA-axis hyperactivity. (33,34)

3.1.3 Omega-3 Fatty Acids and Oxidative Stress in Depression

Oxidative stress has been increasingly implicated in the pathophysiology of variety of mental disorders, including depression. (35)Excessive production of reactive oxygen species in the brain may contribute to neurotoxicity and neurodegenerative processes, including impaired neuroplasticity, reduced neurogenesis, and increased neuronal apoptosis.(34)The brain is particularly susceptible to oxidative damage due to its high oxygen demand, abundance of polyunsaturated fatty acids, and relatively limited antioxidant capacity. Chronic psychological stress may further exacerbate oxidative imbalance, leading to excessive production of reactive oxygen species and damage to lipids, proteins, and cellular structures.Consistent with this, patients with depressive disorders have been reported to exhibit altered oxidative stress markers and reduced activity of endogenous antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GPx). Notably, successful antidepressant treatment has been associated with a reduction in oxidative stress markers, suggesting that oxidative imbalance may contribute to depressive pathology.(9,35) Omega-3 polyunsaturated fatty acids (PUFAs) may counteract these processes by strengthening antioxidant defenses. Both experimental and clinical studies have demonstrated that omega-3 supplementation increases the activity of antioxidant enzymes such as SOD, catalase, and GPx, while reducing lipid peroxidation, protein carbonylation, malondialdehyde concentrations, and myeloperoxidase activity.(34) Furthermore, omega-3 PUFAs may attenuate oxidative stress indirectly through their anti-inflammatory properties and the generation of bioactive DHA-derived metabolites that enhance antioxidant pathways. Collectively, these mechanisms may contribute to the antidepressant effects of omega-3 PUFAs observed in clinical studies, where supplementation has been associated with significant improvements in depressive symptoms compared with placebo and, in some trials, efficacy comparable to that of fluoxetine.(35)

3.1.4 Omega-3 Fatty Acids and Neuroplasticity and Neurotransmission

In depression, neurobiological alterations are frequently observed in brain regions involved in mood regulation, including the prefrontal cortex, hippocampus, amygdala. These changes are closely linked to disrupted neuroplasticity, which may manifest as reduced neurogenesis, decreased dendritic spine density, loss of synaptic connections, impaired synaptic remodeling, and dendritic atrophy. In parallel, abnormalities in neurotransmission are also evident, affecting key systems such as serotonergic, dopaminergic, noradrenergic, glutamatergic, and

GABAergic signaling, which collectively contribute to mood dysregulation and cognitive symptoms of depression. PUFAs may help counteract these dysfunctions through multiple mechanisms. They have been shown to promote neuroplasticity by enhancing the proliferation and differentiation of neural stem and progenitor cells, supporting the survival of newly formed neurons, and increasing dendritic spine formation and synaptic remodeling. (34)Omega-3 PUFAs also influence the expression of proteins involved in synaptic structure and plasticity, including brain-derived neurotrophic factor (BDNF), a key regulator of neuronal survival and synaptic adaptation. Reduced peripheral BDNF levels have been consistently observed in individuals with major depressive disorder, supporting its involvement in the pathophysiology of depression, while increased BDNF signaling is thought to contribute to the therapeutic effects of antidepressant treatments. (9)This may occur through modulation of monoaminergic neurotransmission via changes in cell membrane properties and interaction with the endocannabinoid system, ultimately leading to an upregulation of BDNF expression through pathways that do not depend on cyclic adenosine monophosphate (cAMP) signaling.(10,36)In addition, PUFAs modulate neurotransmitter systems by affecting the synthesis, release, and uptake of serotonin, dopamine, norepinephrine, glutamate, and GABA. (34)

3.2 Clinical evidence on Omega-3 supplementation in Depression

Clinical evidence supports a potential role of omega-3 polyunsaturated fatty acids (PUFAs) in reducing depressive symptoms.(37–41) Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, escitalopram, and sertraline, remain the first-line pharmacological treatment for depression due to their balance between efficacy and safety compared with other antidepressants. In parallel, omega-3 supplementation has been investigated as a complementary strategy.(40) In a 12-week intervention study involving patients with major depressive disorder (MDD), omega-3 PUFA monotherapy significantly reduced depressive symptoms. Interestingly, the therapeutic benefits were not observed immediately but became apparent after approximately four weeks of treatment, suggesting that the antidepressant effects of omega-3 PUFAs may require sustained supplementation before clinically meaningful improvements emerge.(41)

Another line of evidence comes from a meta-analysis, which indicates that efficacy of PUFAs supplementation in depressed patients is strongly ormulation-dependent. The most consistent benefits are observed in EPA-rich preparations. This is particularly evident when eicosapentaenoic acid (EPA) constitutes at least 50–80% of total omega-3 content or in EPA-

dominant interventions (≥60%). In contrast, DHA-dominant or low-EPA formulations show weaker or inconsistent effects.(39)

A further systematic review and meta-analysis supports these findings, reporting that antideppressant effects are most evident at EPA proportions ≥60% of total EPA + DHA. Effective doses typically range between 1 and 2 g/day, while higher doses (≥2 g/day) do not appear to provide additional benefit.These findings point to distinct biological roles of EPA and DHA. EPA is likely to exert antidepressant effects through anti-inflammatory pathways, including the production of less pro-inflammatory eicosanoids that counteract arachidonic acid–derived inflammatory processes implicated in depression. Differences in efficacy may also relate to neurobiological effects, as EPA appears to enhance neurogenesis, particularly cellular proliferation, potentially via modulation of the endocannabinoid system, whereas DHA does not demonstrate the same effect.(37)

Emerging evidence further suggests that inter-individual variability in response may depend not only on baseline omega-3 levels, but also on the capacity to convert EPA and DHA into specialized pro-resolving lipid mediators involved in the resolution of inflammation, which may partly explain differences in clinical outcomes.(38)

Similar conclusions are supported by epidemiological evidence linking dietary omega-3 intake with depression risk. The Ryukyus Child Health Study reported an inverse association between fish consumption and depressive symptoms during pregnancy, with lower seafood intake-and consequently reduced omega-3 exposure-associated with higher rates of depression.(40)

4. Conclusions

The findings summarized in this review suggest that omega-3 polyunsaturated fatty acids are involved in several interrelated biological systems relevant to the pathophysiology of depression. Rather than acting through a single mechanism, their potential effects appear to reflect a broader regulatory influence on inflammatory, neuroendocrine, oxidative, and neuroplastic processes. Among these mechanisms, modulation of inflammation appears particularly important. EPA and DHA may contribute to the resolution of inflammatory activity through the production of bioactive lipid mediators and the regulation of pro-inflammatory signaling pathways. This is especially relevant given the growing evidence implicating chronic low-grade inflammation in a subgroup of patients with MDD. In this context, EPA seems to demonstrate more consistent biological and clinical effects than DHA,

which may be more closely related to structural functions within neuronal membranes.Beyond inflammation, omega-3 fatty acids may also influence hypothalamic–pituitary–adrenal axis regulation, oxidative balance, and neuroplasticity, including effects on BDNF signaling and synaptic remodeling. These pathways are closely interconnected, suggesting that omega-3 PUFAs may act as modulatory factors rather than direct antidepressant agents. Clinical evidence supports a modest but consistent association between omega-3 supplementation and improvement in depressive symptoms, particularly in EPA-rich formulations. However, heterogeneity across studies remains substantial, likely reflecting differences in baseline inflammatory status, metabolic processing of fatty acids, and individual capacity to generate specialized pro-resolving lipid mediators.Taken together, omega-3 fatty acids should be considered as biologically relevant modulators of systems implicated in depression, with EPA emerging as the most promising component. Future research should focus on identifying clinical and biological predictors of response, as well as clarifying which patient subgroups may benefit most from supplementation.

DISCLOSURES

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