New Insights into Depressive Disorder with Respect to Low-Grade Inflammation and Fish Oil Intake
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Abstract: Unipolar depression has been recognized as one of the major diseases by the World Health Organization in the 21st century. The etiology of depression is complicated and includes genetic factors, stress, aging, and special physical status (pregnancy, metabolic syndrome, and trauma). Numerous animal and human studies have demonstrated that n-3 polyunsaturated fatty acids (n-3 PUFAs) are highly correlated to cognition and depression. These nutritional antidepressants, including EPA and DHA, have a range of neurobiological activities contributing to their potential antidepressant effects. Our preclinical and clinical studies have indicated that n-3 PUFA supplementation in addition to standard antidepressant medications may provide synergistic neuroprotective and antioxidant/inflammatory effects. To translate our preliminary findings into clinical application, this paper reviews the existing evidence on the antidepressant effects of n-3 PUFAs and the potential underlying mechanisms, which include modulation of chronic low-grade inflammation and the corresponding changes in peripheral blood immune biomarkers.

Key words: depression, low-grade inflammation, n-3 polyunsaturated fatty acids, fish oil

1 Major Depressive Disorder
Unipolar depression is a common mental illness that can severely interfere with or limit one’s ability to perform major life activities. It is becoming one of the most severe social problems worldwide, particularly in developed countries. Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 defines major depressive disorders (MDDs) based on a list of signs and symptoms. Patients with MDD present with sleep and appetite disturbances and alterations in cognitive ability, psychomotor activity, and, in particular, mood.

The 2019 Global Burden of Disease study indicated that depressive disorders in all ages are fast becoming a leading cause of disability-adjusted life years, with their rank increasing from 19 in 2009 to 13 in 2019¹. The depressive disorder subset ranked 4th and 6th in age groups of 10–24 years and 25–49 years, suggesting that they might influence not only adolescents but also the productive age group¹. MDD is a major cause of suicide, which is a leading cause of death in adolescents. It is also associated with a substantial increase in susceptibility to comorbidities, such as cardiovascular disease, autoimmune disease, and cancer²-⁴.

Although various medications for depression are available, millions of individuals still suffer from depression in the world since up to 40% of depressive individuals do not adequately respond to antidepressants⁵,⁶. The National Institute of Mental Health (NIMH) has reported that 13.3% of the population aged 12–17 (approximately 3.2 million adolescents) and 7.1% or 17.3 million adults have had at least one major depressive episode in the United States.

The pathological mechanisms of depression remain unknown. The genetic etiology plays a role in approximately 35% of cases; however, environmental factors cannot be ignored⁷. Social and physical stressors, early life abuse, and female sex are major risk factors for depression. In particular, metabolic-related disease and autoimmune disease are highly associated with depression⁸. A study indicated that the immune response may be an addressable therapeutic target of depression⁹.
Treatment of depression can be roughly categorized into three modalities: medications (antidepressants and other medications that enhance the efficacy of antidepressants), psychotherapy (psychodynamic therapy, cognitive-behavioral therapy (CBT), and interpersonal psychotherapy (IPT)) \(^{10, 11}\), and somatic nonpharmacological treatments (electroconvulsive therapy (ECT) and the more moderate repetitive transcranial magnetic stimulation (rTMS)) \(^{12}\).

To date, there is a lack of clinically efficient predictors of depression and markers of the efficacy of therapies against MDD\(^{13}\). The neurotransmitter theory of depression describes that the depressive symptoms result from the impaired serotonin–kynurenine pathway, which decreases the serotonin concentration in the central nervous system (CNS) \(^{14}\). Most antidepressants, including selective serotonin reuptake inhibitors (SSRIs), are designed based on this theory and increase the serotonin concentration in the CNS. However, because of the heterogeneity of depression, over 50% of patients with depression do not respond adequately to these antidepressants, and efficient clinical biomarkers for identifying such individuals are lacking \(^{15}\). The structure and constitution of human brains are extremely complicated, which hinders the determination of the exact pathomechanisms of depression. However, a large database of characteristics of patients with depression may help in this regard \(^{16}\). Accumulating evidence indicates that patients with depression have increased inflammation. Chronic low-grade inflammation, especially in the CNS, plays a pivotal role in the pathology of depression \(^{17}\).

### 2 n-3 Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) are classified into different subsets based on the carbon number and double bonds of the fatty acid chain. n-3 PUFA is one of the major fatty acid subgroups and contains eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6); these have been found to exist in substantial concentrations in marine algae and animals. Other n-3 PUFAs include α-linolenic acid (ALA, 18:3) and conjugated linolenic acid (CLNA). ALA, which is found mostly in plants, had beneficial effects on reducing liver cholesterol levels via increasing the acetyl-CoA oxidase-associated proteins and suppressing the mechanisms of PPAR-α \(^{18}\). The dietary oil extracted from *Perilla frutescens* seed upregulated the BDNF expression in prefrontal cortex (PFC) and improved the depressive-like behaviors as well \(^{19}\). Conjugated linoleic acid (CLNA), which is formed via the usage of microorganisms, has been proved that exert the anti-inflammatory properties and lipid/energy metabolism modulatory functions in some cell culture and animal studies \(^{20, 21}\). EPA is an anti-inflammatory fatty acid that can be metabolized to n-3 series eicosanoids. For example, EPA-derived prostaglandin (PGE)-3 is metabolized by cyclooxygenase 2 (COX2), and the E-series-resolvins are metabolized by 5-lipoxygenase (LOX) \(^{22}\) (Fig. 1). Over 20% of the net dry weight of the human brain is composed of lipids, mainly arachidonic acid (AA, 20:4) and DHA. Such marine-derived n-3 PUFAs are a structural constituent of membranes, specifically in the CNS. DHA is crucial for brain function, neuronal cell growth and differentiation, and neuronal signaling \(^{23}\). Fur-

![Fig. 1](image) Transformation of PUFA into lipid oxylipins. Arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), hydrolyzed and released from membrane can be converted into several different kinds of mediators via cyclooxygenase (COX) or lipoxygenase (LOX). The AA-related metabolites are pro-inflammatory whereas DHA- and EPA-derivatives are anti-inflammatory. Lower n-6/n-3 ratio can efficiently inhibit the production of n-6 metabolites and improve the inflammation status. LT: leukotriene, PG: prostaglandin, TX: thromboxane, Lx: lipoxin, RvEs: E-series resolin, RvDs: D-series resolin, NPD1: neuroprotectin D1, MaR1: maresin 1, EFOX: eletrophilic o xo-derivatives.
thermore, DHA-derived lipids play a vital role in maintaining the integrity of the blood–brain barrier (BBB), which prevents the entry of harmful materials into the brain environment\textsuperscript{29}. n-3 PUFAs, especially EPA and DHA, exerted antidepressive efficacy in many preclinical and clinical trials\textsuperscript{25–30}. Moderate intake of n-3 PUFAs (approximately 0.5–1 g/day) was significantly associated with a lower prevalence of depression\textsuperscript{31}. EPA may exert anti-inflammatory benefits in women with perinatal depression\textsuperscript{32}. The treatment efficacy of n-3 PUFA supplementation depends on the proportion and dose of EPA and DHA\textsuperscript{33}.

The mechanisms underlying the antidepressive effects of n-3 PUFAs, however, remain unclear. Several studies have indicated that DHA has no efficacy for depression (except in postnatal depression), and their findings highlight that EPA might be the main n-3 PUFA component with antidepressive activity\textsuperscript{33, 34}. Some meta-analyses have proposed that n-3 PUFA supplements with high concentrations of EPA (>50%, 60%, or 80%) have significantly greater efficacy than those with high concentrations of DHA\textsuperscript{35–37}. Furthermore, the anti-inflammatory capability of EPA, which can compete with n-6 PUFAs and lead to a decrease in the production of proinflammatory cytokines, may be its potential mechanism of action against depression.

3 CNS Inflammation

The immune system involves complex communication among various types of immune cells, including antigen-presenting cells (APCs), T-helper cells, T-regulator cells, macrophages, and monocytes. The complete immune response can be roughly divided into four steps: (1) recognition of infection or damage, (2) initiation of immune responses to infection or damage, (3) modulation of the duration and scale of immune responses to avoid self-harm, and (4) induction of memory to enhance future responses to the same infectious agent or damage\textsuperscript{38}. The immune system aims to maintain homeostasis by eliminating pathologic agents and repairing injuries, but its dysregulation leads to diseases, including psychiatric diseases such as depression\textsuperscript{7}. Thus, the role of immune dysregulation in depression is being increasingly explored.

Neurons in the CNS are sensitive and fragile, and the immune cells in the CNS quickly respond to the introduction of any harmful materials. The BBB is composed of capillary endothelial cells, astrocytes end-feet ensheathing the capillary, and pericytes embedded in the capillary basement membrane. This barrier resists the entry of pathogens; it allows the entry of some small molecules by simple diffusion and of ions and micronutrients through selective and active transport. Penetration of the BBB by pathogens or peripheral immune cells causes immune dysregulation, aberrant inflammation, and neuronal cell dysfunction. Such possible mechanisms have been shown in Fig. 2.

Damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) trigger the receptors (e.g., toll-like receptor 4 [TLR4]) on innate immune cells and activate them to immediately produce proinflammatory cytokines to attract more monocytes/macrophages. DAMPs include host molecules associated with cellular damage (e.g., heat shock protein, ATP, and HMGB1), whereas PAMPs are infectious pathogen-related substances\textsuperscript{39}. After the innate immune system responds to PAMPs or DAMPs, the adaptive immune system, which is a specific immune system and the second-line protection in mammals, is activated by specific antigens via APCs (e.g., dendritic cells). Upon antigen recognition, the T and B cells differentiate to become functional lymphocytes.

![Fig. 2](image_url) The possible mechanisms of lower grade inflammation in depressive disorders.
4 Special Immune System in the CNS

Microglia are specialized immune cells in the CNS; they are one of the neuroglial cells and are characterized by a small and thin cell body. They account for 5%–10% of total brain cells and exert macrophage functions in the CNS. Their major functions include maintaining CNS homeostasis, eliminating infection, and repairing damage. They are extremely sensitive to even the smallest of stimuli and immediately respond to any alteration in the CNS environment by transforming from the resting ramified form to the reactive form. Microglia are associated with synapse pruning and neurogenesis and are activated to their reactive form in many neurodegenerative and psychiatric diseases, thereby promoting neuroinflammation.

Normally, peripheral cells cannot cross the BBB. However, in some special conditions involving BBB disruption, infectious agents and peripheral immune cells (e.g., macrophages and T cells) can cross the BBB and enter the brain parenchyma. This results in damage to the brain tissue and may contribute to the pathology of psychiatric or neurodegenerative diseases. Activated T cells entering the CNS upregulate adhesion molecules (i.e., vascular cell adhesion molecule-1 and intercellular adhesion molecule-1), chemokines, and integrins. Although pathogenic T cells have been associated with autoimmune and psychiatric diseases, peripheral immune cells in the CNS are not always detrimental.

Cytokines have various proinflammatory or anti-inflammatory capabilities. Interleukin (IL)-6 (IL-6), IL-1β, interferon-γ (IFN-γ) are predominantly produced by immune cells, microglia, and astrocytes. In the CNS, the suitable production of cytokines by neuroglial cells is crucial to maintaining neuroplasticity and normal neuroprotective functions. However, sustained physical or physiologic stress might result in persistent cytokine production, which accounts for the chronic inflammation status in the brain. Chronic neuroinflammation status results in perturbed multiple neuronal functions, including impairment of the synthesis, reuptake, and release of neurotransmitters. One of the hypotheses implicated is that increased and persistent cytokine activity in the brain might lead to psychiatric diseases, including depression.

It also remains unclear why the same cytokines exhibit different functions in different contexts. Peripheral cytokines are the most influential factors contributing to neurobehaviors, whereas central cytokines also increase neuroinflammation. Maintenance of BBB integrity is sufficient to prevent the entry of peripheral cytokines and improve the symptoms of depression. Peripherally immune cells and cytokines can enter the CNS through the disrupted BBB directly due to its increased leakiness or by being attracted to the chemokines secreted by the local immune cells.

5 Dysregulation of Cytokines in the Brain

Several meta-analyses have concluded that patients with MDD have upregulated proinflammatory cytokine levels and acute phase proteins. Inflammation has been positively associated with depression even in younger age groups. Antidepressants also decrease the levels of inflammatory biomarkers; patients with depression who are refractory to treatment tend to have higher baseline inflammation. The peripheral blood IL-6, TNF-α, and C-reactive protein (CRP) levels are higher in patients with MDD than in healthy controls, indicating that the overactive immune system can be a therapeutic target in patients with MDD.

Studies have always focused on measuring IL-6, IL-1β, TNF-α or CRP levels in patients with MDD. Recently, with advancements in measurement technology, more types of cytokines and chemokines have been evaluated in association with MDD. A 2017 meta-analysis including 82 studies and 3212 patients with MDD revealed upregulation of IL-6, TNF, IL-10, sIL-2, C-C motif ligand (CCL) 2, IL-13, IL-18, IL-12, IL-1RA, and soluble TNF receptor 2 (sTNFR2), thus providing new insights into unknown potential pathways of inflammation in patients with MDD. Another meta-analysis including 69 studies focused on CNS cytokine levels by analyzing cerebrospinal fluid (CSF), positron emission tomography (PET) images, or postmortem brain tissue levels in patients with MDD compared with healthy controls. The results revealed that IL-6 and TNF-α levels were higher in the CSF of patients with MDD. The PET marker of CNS inflammation was elevated in some brain regions; however, no correlation was observed between inflammatory markers and peripheral marker levels. Postmortem data indicated that certain brain tissues had high TNF-α levels and a significantly smaller number of astrocytes, which may account for the compromised integrity of BBB, leading to increased peripheral monocyte infiltration.

Because neuroinflammation is significantly related to depression, many questions must be considered: (1) whether the adequate response to antidepressants is associated with improved inflammatory status and (2) whether conventional anti-inflammatory treatments are effective in treating depression, especially in patients with MDD with increased inflammation. Many conventional antidepressants exert some degree of anti-inflammatory effects, implying that reducing inflammation might be one of the mechanisms underlying their antidepressant efficacy. SSRIs were reported to decrease IL-6, IL-1β, and TNF-α levels, whereas some studies have stated that SNRIs increase IL-6 and TNF-α production. Another meta-analysis including 45 trials and 1517 patients with MDD demonstrated that antidepressant medication significantly decreases the peripheral levels of IL-6, IL-10, TNF-α, and CCL2, but this decrease did not correlate with treatment.
Depressive Disorder, Lower Grade Inflammation and Fish Oil

6 The Anti-inflammatory Ability of Fish Oil

Many studies have explored the depression response following treatment with immune-modulating antidepressants. Some trials have tried to treat depression using anti-inflammatory medicine, including nonsteroid anti-inflammatory drugs (NSAIDs) or cytokine inhibitors. However, the add-on therapy was not appropriate for most patients. Therefore, natural anti-inflammatory as dietary components or supplements, including polyphenols, vitamin D, and fish oil, have been discussed extensively. A large-scale trial was conducted to measure the anti-inflammatory efficacy of n-3 PUFA, especially marine fish oil. As an effective anti-inflammatory supplement, fish oil was recommended to improve the inflammatory conditions in cancer and heart disease. One randomized controlled trial (RCT) in 2017 demonstrated that daily intake of EPA and DHA (total 1.8 g of n-3 PUFA) for 30 days to newly diagnosed breast cancer patients can reduce the level of inflammation. A 2019 meta-analysis including 13 RCTs revealed that marine n-3 PUFA supplementation lowered inflammation, myocardial infarction, and CVD risks. In summary, n-3 PUFA seems to exert strong anti-inflammatory effects and may be ideal adjuvants for treating inflammation-associated diseases.

7 Possible Cellular Mechanisms Underlying the Anti-inflammatory Effects of n-3 PUFA

The mechanisms of n-3 PUFA crossing the BBB have been fully demonstrated by several articles. Three pathways dominated the entry of n-3 PUFA including simple diffusion, lipoprotein transcytosis and transport via transmembrane proteins. In situ perfusion study demonstrated that the rates of simple diffusion of EPA and DHA were no significant difference. Additional study also confirmed that diffusion of plasma non-esterified DHA is important for supplying brain. Transcytosis showed that lipoprotein receptor (e.g. LDL receptor) can bind the lipoprotein and transport them into brain via clathrin- or caveolae-dependent endocytosis. Last, some transporters on the surface of endothelium cells involved in the transporting PUFAs including FA transport protein-1 (FATP-1), FATP-4 and FA translocase/CD36. Mfsd2a was also presented in the endothelium of the brain, which is particularly important for maintaining DHA levels in brain. In addition, FAs esterified to a glycerol backbone including lysophosphatidylcholine (lysoPC) has been shown crossing the BBB easily.

Some cross-sectional studies have indicated a significant association between n-3 PUFA and depressive symptoms. The French Supplementation en Vitamines et Minéraux Antioxydants (SUVIMAX) study with a 2-year follow-up indicated that participants consuming fish containing full n-3 PUFA or taking n-3 PUFA at amounts higher than 0.1% of energy intake had a significantly lower risk of depressive disorders. Although the Nurse’s Health Study did not conclude a significant association between n-3 PUFA intake and depression occurrence over a 10-year follow-up period in 54,000 women aged 50–77 years in the United States, the findings indicated that lower linoleic acid intake decreases the depression risk, implying that the n-6/n-3 fatty acid ratio should be considered in the diet.

The mechanisms underlying n-3 PUFA’s preventive and therapeutic effects on depression remain unclear, and various hypotheses have been proposed. As mentioned earlier, neurotransmitter dysregulation is a well-known hypothesis, and SSRIs are the first-line medications for patients with MDD. However, chronic inflammation may also play a critical role in inducing depression. Because of the limitation and difficulty in obtaining human brain tissue samples, studies on possible molecular mechanisms have mostly involved animal models. Chronic stress is a major risk factor for depression. The chronic mild stress (CMS) animal model is an effective depression animal model. This model overcomes the limitations of single-stimuli response adaptation, and various mental stresses are administered to induce depression in rodents. It also induces a neuroinflammatory response by activating the microglia in the CNS. The neuroinflammation ensures the release of cytokines and impaired the neurotrophin system, synaptic plasticity, and neurogenesis of the hippocampus. n-3 PUFA exert their anti-inflammatory effect by inhibiting the production of n-6 series eicosanoids. Eicosanoids are biologically active lipid mediators produced from PUFAs, which modulate inflammation and regulate immune activity. The plasma fatty acid composition of patients with depression had a higher n-6/n-3 ratio or percentage of n-3 fatty acids than in healthy controls; similar results were reported in a rodent study. Whether higher plasma n-3 PUFA concentrations reduce the prevalence of depressive symptoms should be explored.

The antidepressant effect of n-3 PUFA is likely exerted by modulating inflammatory cytokine production in microglial and other neuronal cells. Some studies have indicated that n-3 PUFA treatment can influence neuronal differentiation. A study derived neuronal stem cells

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(iNSCs) from patients with MDD and treated with EPA, DHA, and stearic acid (SA) indicated that n-3 PUFAs, but not SA, facilitate astrocyte differentiation dependence on the cAMP-response element binding protein (CREB) pathway and may exert some antidepressant effects by increasing the production of neurotrophins such as brain-derived neurotrophic factor (BDNF) and glial cell–derived neurotrophic factor (GDNF). n-3 PUFAs can increase the expression of CREB and phosphorylated CREB (pCREB).

Clinical and preclinical studies have also supported the relevance of neurotrophins in depression, implying that MDD is associated with reduced BDNF or GDNF levels, which can be alleviated by n-3 PUFA supplementation.

n-3 PUFAs also substantially influence the microglia to modulate neuroinflammation by altering their morphology—reactive (inflammatory) or ramified (resolving). Understanding how n-3 PUFAs modulate microglial phenotypes and functions can aid the development of innovative therapeutics with positive effects on physiology and behavior.

In the BV-2 cell culture model, n-3 PUFAs, especially EPA, inhibited the activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome and decreased IL-1β and IL-18 levels and neurological deficit score via the GPR 40 pathway. Another BV-2 cell culture study revealed that EPA dose-dependently inhibited the expression of two inflammation-related enzymes, inducible NO synthase (iNOS) and COX2, as well as the subsequent production of NO and PGE2. n-3 PUFAs can significantly and dose-dependently reduce the expression and activity of matrix metalloproteinase 9 (MMP9) under lipopolysaccharide (LPS) stimulation in microglial cells. In vitro, 3-PUFAs inhibit the production and activity of iNOS and COX2 and the production of NO and ROS, which is correlated with the alteration of microglia from anti-inflammatory form to proinflammatory form.

Additionally, n-3 PUFAs modulate the phagocytic capacity and migration capacity of the microglia. DHA dose-dependently inhibited LPS-induced microglial migration; however, it did not exert the same function under normal physical conditions. Autophagy is essential for immune cell homeostasis; it accounts for the dampening of inflammatory processes, highlighting a new pathway to modulate the microglial inflammatory response. EPA and DHA treatment significantly activated the SIRT1 pathway and autophagy in MG6 microglial cells, which decreased the inflammatory responses of LPS stimulation. Studies have indicated that n-3 PUFAs can serve as various ligands for several nuclear receptors, including peroxisome proliferator-activated receptors (PPARs) and demonstrated that DHA and EPA activate PPARγ and lowered the presence of proinflammatory cytokines in microglial cells.

Many studies have reported a close relationship between microglial function and n-3 PUFAs. A CMS study demonstrated that EPA and DHA can improve aberrant corticos-terone and IL-1β levels as well as hippocampal noradrenaline and 5-hydroxytryptamine concentrations. The researchers also reported that n-3 PUFAs can ameliorate microglial and astrocyte functions suppressed by CMS stimuli and improve depressive symptoms of rodent animals. Notably, studies on models of brain development have indicated that n-3 PUFA supplementation reduces microglial activation or cause phenotype alteration. In a mouse study, lower dietary consumption of n-3 PUFAs during the perinatal period led to increased microglia-mediated phagocytosis of synaptic elements in the developing hippocampus, altered neuronal morphology, and impaired the cognitive performance of the offspring through 12/15-LOX/12-HETE signaling. Impairment of DHA synthesis of mice alters synaptic plasticity, BDNF expression, learning, and memory formation and results in brain inflammation, including higher levels of TNF-α, IL-1β, and iNOS. Overall, n-3 PUFAs are crucial for CNS development and reduce CNS inflammation by modulating various neuronal glial cells.

8 EPA or DHA?

n-3 PUFAs play a potent role in shaping the brain struc-
ture and maintaining homeostasis. Extensive research has been conducted to determine which n-3 PUFA, especially EPA or DHA in marine fish oil, is more efficacious in improving depressive symptoms. Notably, the fatty acid profile analysis of rodent brain tissues revealed that lipids extracted from the brain contain a part of DHA, whereas the levels of EPA are extremely scarce. In the whole brain, DHA concentrations are approximately 250 times higher than EPA concentrations, but in the microglia, EPA concentrations are at least two-fold higher than DHA concentrations. EPA may not cross the BBB, but EPA-only supplementation still has anti-inflammatory capability (Fig. 3).

Although the EPA concentration is considerably lower than the DHA concentration in brain tissue, EPA is more neuroactive than DHA with respect to inhibition of neuro-inflammation. A meta-analysis revealed that EPA might be more effective than DHA in treating depression. An RCT demonstrated that EPA, but not DHA, can significantly reduce IFN-α-induced depression-like behaviors. A rodent study also reported that EPA but not DHA lowered IL-6 and TNF-α levels and improved the suppressive expression of astrocyte markers and TrkB-BDNF signaling. By contrast, a cell culture study suggested that EPA and DHA have equal potency and efficacy and that they both increased the expression of GFAP and BDNF but not SA.

A similar result revealed DHA and EPA both dose-dependently inhibited LPS-induced microglial migration by regulating the ligand of PPARγ receptors to ameliorate inflammation.

9 Future Work

The relationship among n-3 PUFAs, depression, and neuroinflammation has been extensively examined in recent years, especially with the advancements in measurement technology. A wide variety of possible mechanisms of n-3 PUFAs in the CNS have been unveiled gradually, including shaping the brain structure, maintaining neuronal function, and modulating the immune response. Neuroinflammation, as the main reason for most psychiatric diseases, was relieved through the intake of n-3 PUFAs. However, some paradox still exists in the application of n-3 PUFAs for depressive symptoms even if hundreds of experiments are conducted to explore the clinical use of n-3 PUFA. Given that some meta-analyses have indicated that n-3 PUFAs are not effective for treating depression, the patients’ dietary habits and n-6/n-3 ratio may be critical factors. However, the most valuable problem might be the exact utilization of n-3 PUFAs in the CNS. Updated detection technology is lacking for measuring inflammation conditions and the entry/usage of one factor in people. However, the novel manufacturing approaches of n-3 PUFA supplements have increasingly attempted to increase the entry and utilization of n-3 PUFAs into the CNS (Fig. 4). For example, condensed fish oil (with a higher percentage of n-3 PUFAs) and lysophosphatidylcholine-EPA/DHA (LPC-EPA/DHA) form products were investigated in preclinical or clinical studies. These findings should inform the scope of future clinical trials on the efficacy of n-3 PUFAs. Finally, consolidated analysis could be completed being combined with the results via using the state-of-the-art detection technology—multiomics analysis, such as transcriptomic, proteomic, metabolomic, and microbiome. In this context, the whole picture of anti-inflammatory ability of fish oil in CNS could be disclosed in the future.

Contributions

The author’s responsibilities were as follows: Te-Hsuan Tung, Ngan Thi Kim Nguyen and Shih-Yi Huang conducted the conception of topic. Te-Hsuan Tung and Shih-Yi Huang collected the related articles. Ngan Thi Kim Nguyen, and Shih-Yi Huang assisted with the editing of the manuscript. Te-Hsuan Tung and Shih-Yi Huang prepared the initial draft and finalized the manuscript. All authors approved the final version of the manuscript.

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Conflict of Interest

No potential conflicts of interest were reported by the authors.

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