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Biomarker-Driven Use of Omega-3 Fatty Acids in Depression: Toward Personalized Nutritional Psychiatry

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Abstract: *Depression is a multifactorial psychiatric disorder and a leading contributor to global disability, characterized by complex interactions among neurobiological, inflammatory, genetic, and environmental factors. Despite the widespread use of conventional antidepressant therapies, considerable variability exists in treatment response, highlighting the need for more personalized therapeutic approaches. In recent years, omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have attracted significant attention as potential adjunctive interventions in depression management due to their anti-inflammatory, neuroprotective, and neuromodulatory properties.*

This paper examines the emerging role of omega-3 fatty acids within the framework of personalized nutritional psychiatry, with a particular focus on biomarker-guided treatment strategies. Current evidence suggests that omega-3 fatty acids may influence key pathophysiological mechanisms implicated in depression, including neuroinflammation, neurotransmitter dysfunction, oxidative stress, impaired neuroplasticity, and hypothalamic–pituitary–adrenal axis dysregulation. Furthermore, several biomarkers, such as C-reactive protein, pro-inflammatory cytokines, brain-derived neurotrophic factor, omega-3 index, omega-6/omega-3 ratio, cortisol levels, and genetic variants involved in fatty acid metabolism, have been investigated as potential predictors of therapeutic response to omega-3 supplementation.

The paper synthesizes findings from epidemiological studies, clinical trials, and mechanistic research to evaluate the relationship between omega-3 fatty acids and depressive disorders. Particular emphasis is placed on identifying patient subgroups that may derive the greatest benefit from omega-3 interventions and on the integration of nutritional, clinical, and molecular biomarkers into precision psychiatry models. Although existing evidence supports the therapeutic potential of omega-3 fatty acids as an adjunctive strategy in selected individuals, further large-scale and biomarker-stratified studies are required to establish standardized clinical applications.

The transition from generalized supplementation approaches to biomarker-driven nutritional interventions may lead to the development of more effective, individualized, and evidence-based strategies for managing depression.

Keywords: Depression; Major Depressive Disorder; Omega-3 Fatty Acids; Eicosapentaenoic Acid (EPA); Docosahexaenoic Acid (DHA); Biomarkers; Precision Psychiatry; Personalized Nutrition; Nutritional Psychiatry; Neuroinflammation; Neuroplasticity; Omega-3 Index; Mental Health

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I. INTRODUCTION

Depression is a leading global public-health problem, ranking among the most common psychiatric disorders and causing profound impairment in quality of life and functioning. It presents with persistent low mood, anhedonia, cognitive difficulties, disturbed sleep, fatigue, and pervasive hopelessness (World Health Organization [WHO], 2025). According to the WHO (2025), hundreds of millions of people worldwide live with depression, which remains a major contributor to disability and disease burden across age groups and is closely linked to social dysfunction, substance misuse, chronic medical comorbidities, and suicide. The disorder's etiology is multifactorial, reflecting interactions between genetic predisposition, neurobiological changes, environmental stressors, psychological processes, and lifestyle influences. Contemporary research emphasizes that depression cannot be fully explained by monoamine imbalances alone; instead, multiple biological pathways contribute to onset, symptom heterogeneity, and variable treatment response (Miller et al., 2009).

Pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and other antidepressants remains central to treatment, yet many patients experience incomplete remission, delayed benefit, or treatment resistance (Miller et al., 2009). Adverse effects—gastrointestinal symptoms, sexual dysfunction, weight gain, and withdrawal phenomena—often impede adherence and reduce overall effectiveness. Clinicians frequently observe that a considerable proportion of patients do not recover fully despite guideline-based pharmacological and psychotherapeutic care; these limitations have spurred interest in adjunctive and individualized strategies that address additional biological mechanisms. Nutritional interventions have therefore emerged as a promising complement to conventional approaches.

Nutritional psychiatry, an interdisciplinary field, studies how diet and nutritional status influence mental health. Accumulating evidence links dietary patterns to brain structure and function through effects on neurotransmission, neuroinflammation, oxidative stress, and neuroplasticity (Lopresti et al., 2013). Among nutritional factors, omega-3 polyunsaturated fatty acids (PUFAs) have gained particular attention given their roles in neuronal membrane composition, synaptic signaling, and immune modulation. Epidemiological data associate low dietary omega-3 intake with higher prevalence of depressive symptoms, implicating these nutrients in mental-health maintenance and prevention (Hibbeln, 1998). The field is moving beyond simple supplementation toward personalized dietary strategies tailored to individual biological characteristics, aligning with precision medicine principles.

Omega-3 fatty acids—principally alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)—are essential nutrients that humans must obtain from diet or supplements (Spector & Kim, 2015). DHA is a major structural lipid in neuronal membranes, supporting membrane fluidity, signal transduction, and synaptic function, while EPA is notable for anti-inflammatory and immunomodulatory actions. Both fatty acids influence processes relevant to depression, including neurotransmitter dynamics, neurogenesis, neuroprotection, and regulation of inflammatory pathways (Calder, 2006). Over two decades of observational studies, randomized trials, and meta-analyses have probed omega-3s' antidepressant potential; although results are mixed, evidence suggests EPA-rich formulations may benefit specific patient subgroups, particularly as adjuncts to standard antidepressant therapy (Su et al., 2014).

A major treatment challenge is interindividual variability in therapeutic response. Emerging data indicate depression comprises biological subtypes with distinct inflammatory, metabolic, neuroendocrine, and genetic signatures (Rosenblat et al., 2014). Biomarkers could therefore identify patients most likely to respond to targeted interventions. Candidate markers for omega-3 responsiveness include C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), brain-derived neurotrophic factor (BDNF), cortisol, the omega-3 index, omega-6/omega-3 ratio, and polymorphisms in fatty-acid metabolism genes such as FADS1 and FADS2 (Malau et al., 2024; Simopoulos, 2010). Integrating nutritional biomarkers with clinical and molecular data under the personalized nutritional psychiatry framework may optimize omega-3–based strategies by matching treatment to biological profiles. This review examines the evidence on biomarker-guided omega-3 therapy in depression and its potential to advance individualized, evidence-based care.

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1. Biology of Omega-3 Fatty Acids

Omega-3 fatty acids are essential polyunsaturated fatty acids defined by a double bond at the third carbon from the methyl end. Humans cannot introduce double bonds beyond the ninth carbon and therefore must obtain omega-3s through diet (Spector & Kim, 2015). The three principal biologically relevant omega-3s are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA is the plant-derived precursor (flaxseed, chia, walnuts, soybean oil), but its conversion to EPA and DHA in humans is inefficient (Arterburn et al., 2006), so direct dietary EPA and DHA from marine sources are often necessary for adequate physiological levels.

Table 1: Classification of Major Omega-3 Fatty Acids

Fatty Acid	Chemical Name	Carbon Structure	Primary Sources	Major Biological Functions
ALA	Alpha-Linolenic Acid	18:3n-3	Flaxseed, chia seeds, walnuts, soybean oil	Precursor for EPA and DHA synthesis
EPA	Eicosapentaenoic Acid	20:5n-3	Fatty fish, fish oil	Anti-inflammatory and immunomodulatory functions
DHA	Docosahexaenoic Acid	22:6n-3	Fish oil, algae oil, seafood	Brain structure, neuronal function, vision

ALA undergoes elongation and desaturation reactions—mediated by enzymes such as Δ6- and Δ5-desaturases encoded by FADS genes—to form EPA and ultimately DHA, though conversion yields are generally low (Arterburn et al., 2006; Simopoulos, 2010). EPA, abundant in oily fish and fish oils, exerts notable anti-inflammatory and immunomodulatory effects. It competes with omega-6 arachidonic acid for cyclooxygenase and lipoxygenase enzymes, thereby reducing pro-inflammatory eicosanoid production and promoting synthesis of specialized pro-resolving mediators such as resolvins and protectins (Calder, 2006). Because chronic low-grade inflammation is implicated in depression, EPA's ability to modulate inflammatory pathways underpins its therapeutic interest in psychiatric disorders. DHA is the predominant omega-3 in the brain and retina and is integral to neuronal membrane phospholipids. It maintains membrane fluidity, supports synaptic transmission and signal transduction, and influences neurodevelopment, cognition, vision, and neuroprotection (Innis, 2007; Bazinet & Layé, 2014). DHA affects neurotransmission, neuronal survival, and neuroplasticity—functions directly relevant to mood regulation and psychiatric and neurodegenerative conditions.

Dietary sources reflect these functional differences: plant foods predominantly supply ALA, while marine sources and algal oils provide preformed EPA and DHA (Salmon, sardines, mackerel, tuna, algal oil). After intestinal absorption, omega-3s are packaged into chylomicrons and transported systemically; tissue incorporation and conversion are affected by enzymatic steps and genetic variability. Polymorphisms in FADS1 and FADS2 substantially influence conversion efficiency, contributing to interpersonal variability in omega-3 status and likely affecting therapeutic responses to supplementation (Simopoulos, 2010).

The brain's high lipid content—approximately 20% of dry weight—makes it particularly dependent on polyunsaturated fatty acids, with DHA as a major structural constituent (Innis, 2007). Omega-3s serve several physiological roles in neural tissue: maintaining membrane fluidity, regulating synaptic transmission and neurotransmitter release, supporting neurogenesis and neuronal survival, modulating inflammatory responses, and enhancing cognitive function and emotional regulation. Whereas DHA primarily supports membrane and neuronal functions, EPA's effects are more pronounced on inflammatory and immune pathways (Bazinet & Layé, 2014).

Interactions between omega-3 and omega-6 fatty acids are crucial. Both families compete for the same metabolic enzymes, and modern Western diets typically feature an elevated omega-6/omega-3 ratio—often >15:1—compared with evolutionary ratios near 1:1–4:1 (Simopoulos, 2002). High omega-6 intake favors arachidonic-acid–derived pro-inflammatory mediator production, contributing to chronic systemic inflammation that can impair neurotransmission, neuroplasticity, and thus increase risk for depressive symptoms (Miller et al., 2009). Restoring a more balanced omega-

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6/omega-3 ratio and increasing EPA/DHA availability can reduce inflammatory signaling and support neuronal function. Biomarkers such as the omega-3 index and omega-6/omega-3 ratio may therefore inform nutritional status and predict responsiveness to omega-3–based interventions in depression (Harris & von Schacky, 2004).

2. Pathophysiology of Depression: Biomarker Perspectives

Omega-3 fatty acids are essential PUFAs defined by a double bond at the third carbon from the methyl end, and humans must obtain them from the diet because we cannot introduce double bonds beyond the ninth carbon (Spector & Kim, 2015). The three principal omega-3s are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA, abundant in plant sources such as flaxseed, chia, walnuts, and soybean oil, is a metabolic precursor to long-chain EPA and DHA, but human conversion is inefficient, so dietary EPA and DHA from marine or algal sources are often required to achieve sufficient physiological levels (Arterburn et al., 2006).

Table 2: Neurotransmitters Implicated in Depression

Neurotransmitter	Primary Function	Depression-Related Effects of Dysregulation
Serotonin (5-HT)	Mood regulation, sleep, appetite	Sadness, anxiety, sleep disturbances
Norepinephrine (NE)	Attention, arousal, stress adaptation	Fatigue, poor concentration
Dopamine (DA)	Reward processing, motivation	Anhedonia, loss of motivation
Glutamate	Excitatory neurotransmission	Cognitive dysfunction, neurotoxicity
GABA	Inhibitory neurotransmission	Anxiety, emotional instability

Following ingestion, omega-3s are absorbed in the small intestine, packaged into chylomicrons, and distributed systemically. ALA undergoes stepwise elongation and desaturation—mediated by Δ6- and Δ5-desaturases encoded by the FADS gene family—to form EPA and ultimately DHA, but conversion yields are generally low and influenced by genetic polymorphisms in FADS1 and FADS2, which contribute to interindividual variability in omega-3 status and response to supplementation (Arterburn et al., 2006; Simopoulos, 2010). Marine foods (salmon, sardines, mackerel, tuna) and algal oil supply preformed EPA and DHA, which bypass conversion limitations.

EPA and DHA have distinct but complementary biological roles. EPA is noted for anti-inflammatory and immunomodulatory effects: it competes with omega-6 arachidonic acid for cyclooxygenase and lipoxygenase enzymes, reducing production of pro-inflammatory eicosanoids and promoting specialized pro-resolving mediators such as resolvins and protectins (Calder, 2006). Because chronic low-grade inflammation is implicated in depression, EPA's capacity to modulate inflammatory pathways underlies its therapeutic interest in psychiatric disorders. DHA is the predominant omega-3 in the brain and retina and a major constituent of neuronal membrane phospholipids; it preserves membrane fluidity, supports synaptic transmission and signal transduction, and influences neurodevelopment, cognition, vision, and neuroprotection (Innis, 2007; Bazinet & Layé, 2014). DHA affects neurotransmission, neuronal survival, and neuroplasticity—mechanisms directly relevant to mood regulation and neuropsychiatric conditions.

Table 3: Major Inflammatory Biomarkers in Depression

Biomarker	Biological Role	Clinical Relevance
C-Reactive Protein (CRP)	Acute-phase inflammatory marker	Associated with depression severity
IL-6	Pro-inflammatory cytokine	Linked to neuroinflammation
TNF-α	Immune activation mediator	Influences neurotransmitter metabolism
IL-1β	Neuroimmune signaling	Associated with mood disturbances

The brain's high lipid content—approximately 20% of dry weight—makes it particularly dependent on polyunsaturated fatty acids, with DHA playing a central structural and functional role (Innis, 2007). Omega-3s contribute to multiple neural processes: maintaining membrane fluidity, regulating neurotransmitter release and synaptic function, supporting

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neurogenesis and neuronal survival, modulating neuroinflammation, and enhancing cognitive and emotional regulation. Whereas DHA primarily supports membrane-related and neurodevelopmental functions, EPA exerts more pronounced effects on inflammatory and immune pathways within the central nervous system (Bazinet & Layé, 2014).

Interactions between omega-3 and omega-6 fatty acids are physiologically important because both families compete for the same metabolic enzymes. Modern Western diets typically have an elevated omega-6/omega-3 ratio—often greater than 15:1—contrasting with evolutionary diets closer to 1:1–4:1 (Simopoulos, 2002). A high omega-6/omega-3 ratio favors arachidonic-acid–derived pro-inflammatory mediator production, contributing to chronic systemic inflammation that can impair neurotransmission and neuroplasticity and increase risk for depressive symptoms (Miller et al., 2009). Restoring a more balanced omega-6/omega-3 ratio and increasing EPA/DHA availability can reduce inflammatory signaling and support neuronal function. Biomarkers such as the omega-3 index and the omega-6/omega-3 ratio may therefore help assess nutritional status and predict responsiveness to omega-3–based interventions in depression (Harris & von Schacky, 2004).

3. Mechanistic Basis of Omega-3 Action in Depression

Omega-3 polyunsaturated fatty acids (PUFAs) may alleviate depressive symptoms through multiple, interrelated biological mechanisms that extend beyond monoaminergic modulation, supporting biomarker-guided interventions in precision psychiatry (Bazinet & Layé, 2014; Su et al., 2018). A principal pathway is anti-inflammatory activity: EPA and DHA compete with arachidonic acid for COX and LOX enzymes, reducing pro-inflammatory eicosanoids and promoting specialized pro-resolving mediators (resolvins, protectins, maresins). They also suppress NF-κB activation, lowering cytokine expression (IL-6, TNF-α) and CRP, thereby decreasing neuroinflammation which otherwise disrupts neurotransmission, neuroplasticity, and HPA-axis function (Calder, 2015; Novak et al., 2003; Miller et al., 2009).

Omega-3s modulate neurotransmitter systems by altering membrane composition and receptor function, influencing synthesis, release, and signaling of serotonin, dopamine, norepinephrine, glutamate, and GABA (Hibbeln et al., 1998; Bazinet & Layé, 2014). DHA-rich membranes enhance receptor–ligand interactions and synaptic efficiency; concurrently, anti-inflammatory effects protect tryptophan availability from kynurenine-pathway diversion, supporting serotonin synthesis and mood regulation (Miller et al., 2009). These actions can improve motivation, reward processing, attention, and excitatory/inhibitory balance relevant to depressive phenotypes.

Omega-3s also promote neuroplasticity and BDNF expression. Reduced BDNF and impaired neurogenesis are hallmark features of depression, and experimental data indicate EPA/DHA increase BDNF, foster neuronal survival, dendritic complexity, and synaptic remodeling—particularly in hippocampal and prefrontal circuits—thereby restoring networks tied to mood and cognition (Duman & Monteggia, 2006; He et al., 2009). EPA's inflammation-lowering effects indirectly support neuroplastic processes while DHA directly contributes structural substrates for synaptogenesis.

Membrane incorporation of DHA alters lipid-raft organization and membrane fluidity, enhancing ion-channel function, receptor dynamics, and intracellular signaling pathways essential for efficient neurotransmission (Salem et al., 2001; Bazinet & Layé, 2014). Such membrane-level effects help explain links between omega-3 status and cognitive as well as affective function.

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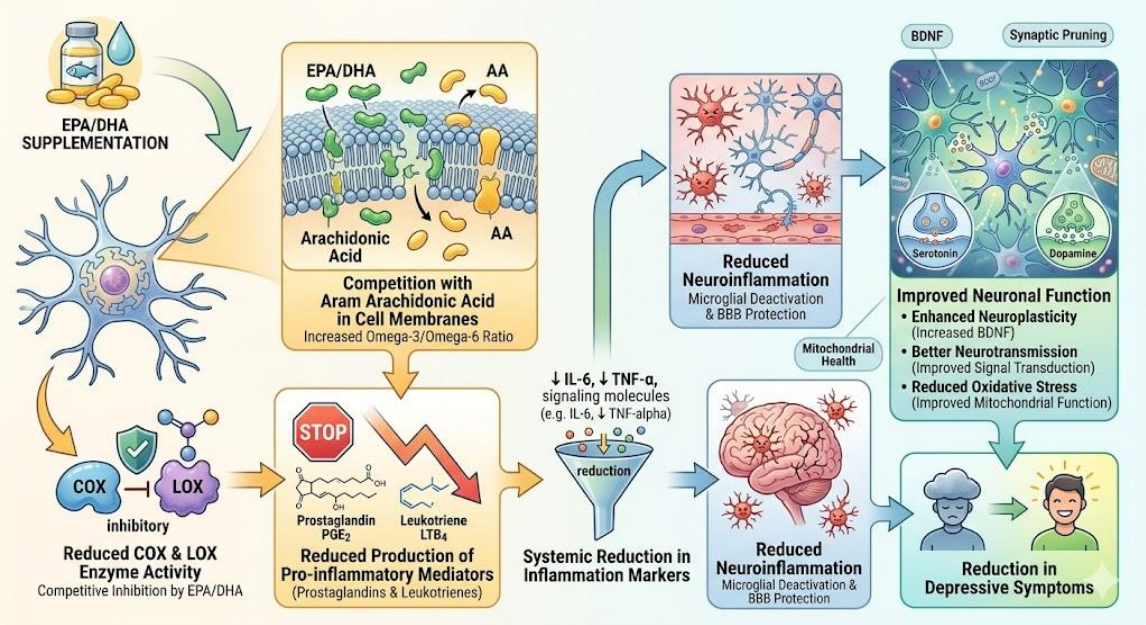

Figure 1: Anti-inflammatory mechanism of omega-3 fatty acids in depression.

Antioxidant and neuroprotective actions further contribute: omega-3s mitigate oxidative stress and protect mitochondria, partly through DHA-derived neuroprotectin D1, which inhibits apoptosis and inflammatory signaling while preventing oxidative damage (Bazan, 2007; Maes et al., 2011). Improved neuronal energy metabolism and reduced oxidative injury support resilience of neural circuits compromised in depression.

Emerging evidence also implicates the gut–brain axis. Omega-3 intake can modulate gut microbiota composition, reduce intestinal inflammation, and enhance barrier integrity, lowering systemic inflammatory signaling and altering microbial metabolites that influence central neurotransmission and immune responses (Cryan et al., 2019; Costantini et al., 2017). These peripheral changes may translate to reduced neuroinflammation and improved mood via neural, endocrine, and immune communication pathways.

Collectively, these mechanisms map onto measurable biomarkers—CRP, IL-6, TNF-α, BDNF, cortisol, the omega-3 index, and microbiome-derived metabolites—making biomarker profiling a plausible strategy to identify responders to omega-3 therapy. By targeting inflammation, neurotransmitter preservation, neurogenesis, membrane stability, oxidative protection, and gut microbial balance, omega-3s offer a multimodal intervention that could be tailored to patients' biological profiles. This mechanistic convergence underpins the rationale for incorporating biomarker-driven omega-3 supplementation into personalized nutritional psychiatry for depression.

4. Biomarkers Relevant to Omega-3 Response in Depression

Omega-3 polyunsaturated fatty acids (PUFAs) exert antidepressant-relevant effects via multiple, interrelated biological pathways that extend beyond classical monoaminergic mechanisms, providing a strong rationale for biomarker-guided interventions in precision psychiatry (Bazinet & Layé, 2014; Su et al., 2018). A primary mechanism is anti-inflammatory activity: EPA and DHA compete with arachidonic acid for cyclooxygenase and lipoxygenase enzymes, lowering production of pro-inflammatory eicosanoids and promoting specialized pro-resolving mediators such as resolvins, protectins, and maresins. Omega-3s also inhibit nuclear factor-kappa B (NF-κB) signaling, which reduces expression of inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), and lowers C-reactive protein (CRP). Because chronic neuroinflammation disrupts neurotransmission, neuroplasticity, and

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hypothalamic–pituitary–adrenal (HPA) axis regulation, these anti-inflammatory effects are central to their potential antidepressant action (Calder, 2015; Novak et al., 2003; Miller et al., 2009).

Beyond inflammation, omega-3s modulate neurotransmitter systems by altering membrane composition, receptor function, neurotransmitter synthesis, and intracellular signaling (Hibbeln et al., 1998; Bazinet & Layé, 2014). DHA-enriched neuronal membranes increase fluidity, facilitating receptor–ligand interactions and efficient synaptic transmission. In parallel, reducing peripheral and central inflammation helps preserve tryptophan availability by limiting kynurenine-pathway activation, thereby supporting serotonin synthesis. Together, these effects can enhance serotonergic, dopaminergic, and noradrenergic signaling—improving mood, motivation, reward processing, attention, and excitatory/inhibitory balance that are often disturbed in depression (Miller et al., 2009).

Omega-3s also promote neuroplasticity and elevate brain-derived neurotrophic factor (BDNF). Depressive states are associated with reduced neurogenesis and lower BDNF; experimental studies indicate EPA and DHA increase BDNF expression, foster neuronal survival, encourage dendritic complexity, and enhance synaptic remodeling—especially in hippocampal and prefrontal circuits implicated in mood regulation. While DHA supplies structural substrates required for synaptogenesis, EPA may potentiate neuroplasticity indirectly by dampening inflammatory constraints on neuronal repair (Duman & Monteggia, 2006; He et al., 2009).

At the membrane level, DHA incorporation reorganizes lipid rafts and modulates ion channels, receptor dynamics, and intracellular signaling cascades, thereby optimizing neuronal responsiveness and signal transduction (Salem et al., 2001; Bazinet & Layé, 2014). These membrane effects underpin links between omega-3 status and cognitive as well as affective performance.

Antioxidant and neuroprotective properties further support resilience of neural circuits. Omega-3s reduce oxidative stress and improve mitochondrial function, with DHA-derived neuroprotectin D1 demonstrating antiapoptotic and antiinflammatory actions that protect neurons from oxidative injury (Bazan, 2007; Maes et al., 2011). Enhanced energy metabolism and reduced oxidative damage help restore neuronal function compromised in depression.

Finally, omega-3s influence the gut–brain axis. They can modulate gut microbial composition, reduce intestinal inflammation, and strengthen barrier integrity, thereby decreasing systemic inflammatory signaling and altering microbial metabolites that affect central neurotransmission and immune responses. These peripheral shifts may translate into reduced neuroinflammation and improved mood through neural, endocrine, and immune pathways (Cryan et al., 2019; Costantini et al., 2017).

Collectively, these mechanisms correspond to measurable biomarkers—CRP, IL-6, TNF-α, BDNF, cortisol, the omega-3 index, and microbiome-derived metabolites—supporting biomarker profiling to identify likely responders. By targeting inflammation, neurotransmitter preservation, neurogenesis, membrane stabilization, oxidative protection, and gut microbial balance, omega-3s provide a multimodal, biologically plausible approach suitable for personalization within nutritional psychiatry.

5. Clinical Evidence for Omega-3 Fatty Acids in Depression

Omega-3 polyunsaturated fatty acids (PUFAs) may improve depressive symptoms through multiple, interconnected biological mechanisms that extend beyond classic monoaminergic targets, supporting their use in biomarker-guided precision psychiatry (Bazinet & Layé, 2014; Su et al., 2018). A key mechanism is anti-inflammatory action: EPA and DHA compete with arachidonic acid for cyclooxygenase and lipoxygenase enzymes, reducing pro-inflammatory eicosanoids and promoting specialized pro-resolving mediators (resolvins, protectins, maresins). They also inhibit nuclear factor-kappa B (NF-κB) signaling, lowering expression of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) and reducing C-reactive protein (CRP). Because chronic neuroinflammation disrupts neurotransmission, neuroplasticity, and HPA-axis regulation, these anti-inflammatory effects are central to omega-3s' potential antidepressant benefits (Calder, 2015; Novak et al., 2003; Miller et al., 2009).

Omega-3s modulate neurotransmitter systems by changing membrane composition and receptor function, affecting synthesis, release, and signal transduction of serotonin, dopamine, norepinephrine, glutamate, and GABA (Hibbeln et

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al., 1998; Bazinet & Layé, 2014). DHA-enriched membranes increase fluidity and improve receptor–ligand interactions and synaptic efficiency. Concurrently, lowering inflammation limits kynurenine-pathway activation, preserving tryptophan availability for serotonin synthesis and supporting mood regulation. These combined effects can enhance serotonergic, dopaminergic, and noradrenergic signaling, improving mood, motivation, reward processing, attention, and excitatory/inhibitory balance often impaired in depression (Miller et al., 2009).

Omega-3s promote neuroplasticity and upregulate brain-derived neurotrophic factor (BDNF). Depression is characterized by reduced neurogenesis and low BDNF; experimental evidence shows EPA and DHA increase BDNF expression, support neuronal survival, enhance dendritic complexity, and facilitate synaptic remodeling—especially in hippocampal and prefrontal regions implicated in mood regulation. DHA provides structural substrates for synaptogenesis, while EPA may indirectly boost plasticity by reducing inflammatory constraints on neuronal repair (Duman & Monteggia, 2006; He et al., 2009).

At the membrane level, DHA incorporation reorganizes lipid rafts and modulates ion channels, receptor dynamics, and intracellular signaling cascades, optimizing neuronal responsiveness and signal transduction (Salem et al., 2001; Bazinet & Layé, 2014). These membrane effects underlie observed associations between omega-3 status and cognitive and affective performance.

Antioxidant and neuroprotective properties add resilience to neural circuits. Omega-3s reduce oxidative stress and support mitochondrial function; DHA-derived neuroprotectin D1 shows antiapoptotic and anti-inflammatory actions that protect neurons from oxidative injury. Improved energy metabolism and reduced oxidative damage help restore neuronal function compromised in depression (Bazan, 2007; Maes et al., 2011).

Omega-3s also influence the gut–brain axis by modulating gut microbiota composition, reducing intestinal inflammation, and strengthening barrier integrity. These changes lower systemic inflammatory signaling and alter microbial metabolites that affect central neurotransmission and immune responses, which can translate into reduced neuroinflammation and improved mood via neural, endocrine, and immune pathways (Cryan et al., 2019; Costantini et al., 2017).

Together, these mechanisms align with measurable biomarkers—CRP, IL-6, TNF-α, BDNF, cortisol, the omega-3 index, and microbiome-derived metabolites—supporting biomarker profiling to identify likely responders. By targeting inflammation, neurotransmitter preservation, neurogenesis, membrane stabilization, oxidative protection, and gut microbial balance, omega-3s offer a multimodal, biologically plausible intervention suited for personalization within nutritional psychiatry.

6. Personalized Nutritional Psychiatry: A Biomarker-Guided Framework

Personalized nutritional psychiatry applies precision-medicine principles to depression by integrating biomarker data with clinical, dietary, genetic, and lifestyle information to tailor nutritional interventions—particularly omega-3 therapy—rather than using one-size-fits-all recommendations (Marx et al., 2021; Fernandes et al., 2017). Conventional depression treatment shows marked heterogeneity in response, with around one-third of patients failing first-line antidepressant remission (Rush et al., 2006). Because omega-3 responsiveness varies among individuals and omega-3s target inflammation, neuroplasticity, oxidative stress, and neuroendocrine pathways, a biomarker-guided approach can help identify those most likely to benefit (Mocking et al., 2016).

The rationale for biomarker-guided omega-3 therapy rests on biological heterogeneity in depression and mechanistic alignment between omega-3 actions and modifiable pathophysiological processes. For example, patients with elevated inflammatory markers—C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α)—may constitute an "inflammatory depression" subgroup that responds preferentially to EPA-rich formulations due to EPA's potent anti-inflammatory effects (Miller et al., 2009; Rapaport et al., 2016). Likewise, low baseline omega-3 status (measured by the omega-3 index) or a high omega-6/omega-3 ratio may identify nutritional deficiency–associated depression amenable to supplementation (Harris & von Schacky, 2004). Reduced brain-derived neurotrophic factor (BDNF) and elevated cortisol identify neuroplasticity- and stress-related phenotypes, respectively, which could benefit

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from interventions that restore neurogenesis and mitigate HPA-axis dysregulation (Duman & Monteggia, 2006; Pariante & Lightman, 2008). Genetic variants in FADS1 and FADS2 may predict metabolic responsiveness to supplementation and guide dosing choices (Simopoulos, 2010).

A practical clinical framework involves four steps: comprehensive clinical assessment (psychiatric evaluation, dietary history, comorbidities), biomarker evaluation (inflammatory panel, omega-3 index, omega-6/omega-3 ratio, BDNF, cortisol, and selected genetic markers), biological phenotyping (stratifying patients into inflammatory, nutritional deficiency, stress-related, neuroplasticity-impaired, or mixed subtypes), and personalized intervention (targeted omega-3 strategies combined with standard treatments and lifestyle changes). Ongoing monitoring of symptoms and biomarkers completes the pathway and allows iterative adjustment (Fernandes et al., 2017).

Integration with multi-omics and digital psychiatry can enhance precision: lipidomics and metabolomics provide detailed profiles of fatty-acid metabolism and inflammatory/metabolic signatures, while microbiome profiling informs gut–brain interactions. Wearables, mobile health apps, and AI-driven predictive models enable real-time symptom and adherence monitoring and can fuse multidimensional data into predictive algorithms for treatment selection (Penninx et al., 2021; Fernandes et al., 2017).

However, significant challenges impede widespread implementation. Scientific barriers include lack of universally validated biomarkers, methodological variability, inconsistent thresholds, and underlying biological heterogeneity. Clinically, access to advanced testing, costs, clinician training, and absence of standardized guidelines are limiting. Research gaps include insufficient large-scale prospective trials and validation of optimal biomarker combinations and predictive algorithms across diverse populations. Addressing these limitations will require well-powered randomized trials that integrate inflammatory, lipidomic, genetic, neuroendocrine, and microbiome markers, alongside machine-learning approaches to refine prediction.

In sum, biomarker-guided omega-3 therapy exemplifies how personalized nutritional psychiatry could shift depression care from symptom-based to biologically informed treatment. With validated biomarker panels, multi-omics integration, and digital tools, omega-3 interventions could be targeted to those most likely to respond, improving efficacy, efficiency, and mechanistic precision in depression management.

7. Challenges and Limitations

Despite growing evidence supporting the role of omega-3 fatty acids in depression, several challenges limit their integration into biomarker-guided clinical practice. First, depression is a highly heterogeneous disorder with diverse biological mechanisms, making it unlikely that a single biomarker can reliably predict treatment response across all patients. Although inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) have shown promise, their predictive value remains inconsistent across studies (Miller et al., 2009).

Second, considerable variability exists among clinical trials regarding study design, sample size, diagnostic criteria, omega-3 dosage, EPA:DHA composition, treatment duration, and outcome measures. Such heterogeneity complicates the interpretation and generalization of findings (Mocking et al., 2016). Additionally, standardized reference ranges for biomarkers such as the omega-3 index, BDNF, and inflammatory cytokines have not been universally established in psychiatric settings.

Practical barriers also exist, including the cost and limited availability of advanced biomarker testing, genetic profiling, and multi-omics technologies. Furthermore, most evidence remains derived from observational studies and short-term clinical trials, while long-term effectiveness and implementation strategies are insufficiently explored. Therefore, large-scale prospective studies are needed to validate biomarker panels and establish standardized protocols for personalized omega-3 therapy in depression.

8. Future Directions

Future research should focus on advancing biomarker-guided approaches to optimize the use of omega-3 fatty acids in depression. Although current evidence supports the potential role of inflammatory markers, neurotrophic factors, and

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fatty acid profiles in predicting treatment response, larger prospective studies are required to validate their clinical utility. Standardized biomarker panels incorporating C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), brain-derived neurotrophic factor (BDNF), cortisol, and the omega-3 index may improve patient stratification and facilitate precision-based interventions.

Emerging multi-omics technologies, including genomics, metabolomics, lipidomics, proteomics, and microbiome analysis, offer new opportunities to better understand the biological heterogeneity of depression and identify novel predictors of omega-3 responsiveness. Future randomized controlled trials should integrate these biomarkers into study designs to establish evidence-based algorithms for personalized nutritional psychiatry.

In addition, advances in artificial intelligence and machine learning may enable the integration of clinical, biological, dietary, and lifestyle data to generate individualized treatment recommendations. Long-term studies assessing sustainability, safety, cost-effectiveness, and real-world implementation are also needed. Ultimately, combining biomarker profiling with targeted omega-3 interventions may facilitate a shift from symptom-based treatment toward precision psychiatry, improving therapeutic outcomes and promoting more personalized management of depressive disorders.

9. Conclusion

Depression is a multifactorial and biologically heterogeneous disorder characterized by complex interactions among inflammatory, neuroendocrine, neuroplastic, metabolic, and genetic pathways. Increasing evidence suggests that omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), exert antidepressant effects through mechanisms that extend beyond traditional neurotransmitter modulation. Their ability to reduce neuroinflammation, enhance neuroplasticity, improve membrane function, regulate stress responses, and influence the gut–brain axis provides a strong biological rationale for their use in depression management.

Clinical studies and meta-analyses indicate that omega-3 supplementation may be especially beneficial in specific patient subgroups rather than universally effective across all individuals with depression. This variability in treatment response highlights the importance of identifying biomarkers capable of predicting therapeutic outcomes. Biomarkers such as C-reactive protein, interleukin-6, tumor necrosis factor-α, brain-derived neurotrophic factor, cortisol, the omega-3 index, and genetic variants involved in fatty acid metabolism represent promising tools for patient stratification and treatment optimization.

The integration of biomarker profiling with nutritional interventions reflects the emerging paradigm of personalized nutritional psychiatry. By shifting from a symptom-based approach to a biologically informed framework, clinicians may be better positioned to identify individuals most likely to benefit from omega-3 therapy. Although challenges related to biomarker validation, standardization, and clinical implementation remain, ongoing advances in multi-omics technologies, precision medicine, and digital health are expected to accelerate the development of individualized treatment strategies.

In conclusion, biomarker-guided use of omega-3 fatty acids represents a promising avenue for advancing precision psychiatry and improving outcomes in depressive disorders. Future research focused on validating predictive biomarkers and integrating biological phenotyping into clinical practice will be critical for translating personalized nutritional psychiatry from concept to routine patient care.

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