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Omega-3 PUFAs: A Multifaceted Approach to Lifespan Brain Health, Neurodevelopment, and Precision Therapeutics with Implications for ASD, ADHD, and Cognitive Function

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Abstract: The pivotal role of omega-3 PUFAs in brain structure, function, and neurodevelopment underscores their importance across the lifespan, from prenatal stages to aging populations. This article discusses emerging evidence supporting their therapeutic potential in neurodevelopmental and psychiatric disorders such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), highlighting their neuroprotective, anti-inflammatory, and immunomodulatory properties. While significant strides have been made in understanding their mechanisms, this article discusses the need for future research to prioritize longitudinal studies, explore genetic factors, and investigate synergistic effects with nutrients. Additionally, the gut-brain axis offers a promising avenue for understanding how omega-3 PUFAs influence neuroinflammation and immune health. Addressing challenges such as optimizing dosage, refining patient selection criteria, and standardizing methodologies will enhance the reliability and applicability of findings. By advancing precision nutrition and integrative therapeutic strategies, omega-3 PUFAs hold potential to revolutionize approaches to brain health, offering hope for conditions ranging from ASD and ADHD to age-related cognitive decline.

Keywords: Omega-3 polyunsaturated fatty acids (PUFAs); Brain health; Neurodevelopment; Gut-brain axis; Autism spectrum disorder (ASD); Attention-deficit/hyperactivity disorder (ADHD).

Introduction

Omega-3 polyunsaturated fatty acids (PUFAs) have emerged as vital components of lipid metabolism in mammals, playing a central role in brain health and development. Characterized by their distinctive chemical structure containing multiple double bonds, omega-3 PUFAs include three key fatty acids: docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), and eicosapentaenoic acid (EPA)[1–3]. These lipids are integral to the brain's composition, where DHA predominates, constituting approximately 40% of total brain fatty acids, while EPA represents a much smaller proportion. Considering that lipids account for 50–60% of the brain's dry weight, with omega-3 PUFAs contributing around 35% of this lipid composition, their importance for neuronal function and structure cannot be overstated[2,4,5].

The significance of omega-3 PUFAs is particularly pronounced during critical periods of brain growth and development, such as the later stages of pregnancy and the first 18 months of life[6]. During these phases, DHA is essential for optimal cognitive and visual development, prompting its inclusion in infant formulas to mimic the benefits of breast milk, a natural source of DHA[7,8]. Despite mammals' limited capacity to synthesize DHA endogenously, its intake through diet or supplementation is crucial for supporting the rapid neuronal growth that occurs during early life[9].

Beyond development, omega-3 PUFAs offer neuroprotective benefits that span the human lifespan. Extensive research highlights their role in enhancing cognition, preserving neuronal integrity, and mitigating neurodegenerative processes[2,10]. These effects are mediated through mechanisms such as improving neuronal membrane fluidity, facilitating neurotransmitter release, and reducing apoptosis by counteracting reactive oxygen species[2,10,11]. Such properties make omega-3s invaluable in addressing age-related cognitive decline and disorders like Alzheimer's disease[12].

In recent years, systematic reviews and longitudinal studies have underscored the broader cognitive benefits of omega-3 supplementation. Higher intake of omega-3s has been associated with improved memory, learning, and cerebral blood flow across diverse populations[13,14]. Interestingly, while DHA supplementation primarily supports memory and learning, EPA has been linked to enhanced overall cognitive function, including improvements in verbal memory and reduced cognitive impairments associated with loneliness and aging[15–17].

Given the favorable safety profile and extensive benefits of omega-3 PUFAs[18], their role in promoting brain health through

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dietary sources or supplementation is increasingly recognized[2]. This article explores the multifaceted contributions of omega-3 fatty acids to brain development, cognitive performance, and neuroprotection, providing a comprehensive overview of their potential in mitigating cognitive impairments and fostering lifelong neurological well-being.

The literature search for this article was conducted to investigate the role of omega-3 PUFAs in brain health and neuroprotection. Databases such as PubMed, Scopus, Google Scholar, and Web of Science were searched for peer-reviewed articles published between January 2000 and December 2024. Keywords including "omega-3 PUFAs," "DHA," "EPA," "brain health," "neurodevelopment," "cognitive function," "ASD," "ADHD," "neuroprotective effects," and related terms were used, combined with Boolean operators. The search included randomized controlled trials, meta-analyses, and reviews that examined the effects of omega-3 PUFAs on brain structure, cognitive function, and their therapeutic potential in neurodevelopmental and neurodegenerative disorders, particularly ASD and ADHD. Priority was given to high-quality, peer-reviewed research, with an emphasis on mechanistic studies related to neuronal function and the modulation of inflammation. This search identified key trends and gaps in the therapeutic applications of omega-3 PUFAs.

This article discusses the pivotal role of omega-3 PUFAs in neurodevelopment and their potential therapeutic applications in conditions like autism spectrum disorder (ASD) and Attention-deficit/hyperactivity disorder (ADHD), highlighting their neuroprotective, anti-inflammatory, and neurotransmitter-modulating properties. It emphasizes the need for future research to explore personalized treatment strategies based on genetic, metabolic, and biochemical markers, as well as the integration of omega-3s with other therapies. Additionally, the article calls for addressing research gaps such as dosage optimization, standardized methodologies, and long-term studies to unlock the full therapeutic potential of omega-3 PUFAs for improving cognitive and neurological health across the lifespan.

Omega-3 PUFAs: Brain Health and Cognitive Function

Essential Role of Omega-3 PUFAs in Brain Structure, Function, and Lifespan Cognitive Health

Omega-3 PUFAs are essential components of brain structure and function, including DHA, ALA, and EPA, with DHA being the most abundant and biologically significant[11,19]. DHA serves as a crucial structural element of neuronal membranes, especially within the central nervous system, while EPA, though less prevalent, contributes significantly to maintaining brain health[11,20,21]. Since mammals have limited capacity for endogenous DHA synthesis, dietary intake —primarily from sources such as fish oils—is critical[5,22].

DHA is concentrated in the gray matter of the brain, where it is essential for maintaining the integrity and functionality of neuronal membranes[23]. The high concentration of DHA in neuronal tissues supports several critical processes, including membrane fluidity, signal transduction, and synaptic plasticity[5,24]. The need for DHA is especially pronounced during critical periods of brain development, such as late pregnancy and early childhood. It is during these stages that DHA facilitates cognitive development, visual acuity, and general brain maturation[25,26].

Given the importance of DHA, it is no surprise that breast milk serves as the primary natural source of DHA during infancy[27]. For infants who are not breastfed, DHA is often added to infant formulas to support early neurodevelopment[28]. The reliance on DHA during early development underscores its pivotal role not only in brain structure but also in lifelong cognitive health[26]. As a consequence, DHA intake remains crucial across the lifespan, from infancy through old age, to ensure optimal brain structure and function.

The Role of Omega-3 PUFAs in Cognitive Function, Neurological Health, and Neurodevelopmental Disorders

Omega-3 PUFAs contribute to a range of brain functions, including cognitive performance, memory, learning, and neuronal protection[13]. DHA and EPA enhance neuronal health through several mechanisms, such as increasing membrane fluidity, facilitating neurotransmitter release, and modulating the expression of apoptotic proteins[29,30]. These effects support neuronal survival and communication, which are crucial for cognitive function. Moreover, the antioxidant properties of omega-3 PUFAs help to reduce the production of reactive oxygen species (ROS)[31,32], thereby protecting neurons from oxidative stress that could otherwise lead to neurodegeneration.

One of the most significant benefits of omega-3 supplementation is its ability to protect against cognitive decline and age-related neurological disorders[33]. Studies have shown that individuals who consume diets rich in omega-3s —especially those that include oily fish —experience enhanced brain circulation, improved oxygen saturation, and increased neuronal activity[10,34]. DHA supplementation has been particularly beneficial for older adults, mitigating cognitive deficits associated with aging, such as memory loss and slower processing speed. For instance, individuals following Mediterranean diets, which are rich in DHA, tend to exhibit delayed onset of dementia and slower cognitive decline, suggesting the neuroprotective effects of DHA[14,35].

While DHA plays a critical role, EPA has also been shown to contribute significantly to cognitive function, especially in enhancing mood and reducing symptoms of depression[36]. Some studies suggest that EPA supplementation can yield more pronounced improvements in cognitive function, particularly in individuals with mild cognitive impairments or those suffering from mental health disorders[36,37]. The variability in the efficacy of omega-3 supplementation may be influenced by genetic factors, including the presence of the apolipoprotein E4 (APOE4) allele, which is associated with an increased risk of Alzheimer's disease[38,39]. This variability highlights the importance of considering genetic differences when evaluating the effectiveness of omega-3 supplementation.

Omega-3 supplementation has been explored for its potential therapeutic effects in neurodevelopmental disorders such as ASD and ADHD. However, the findings from research in this area have been inconsistent[40]. Some studies indicate that omega-3 supplementation, particularly with DHA and EPA, may enhance social interaction, communication, and behavioral symptoms in children with ASD, while others report minimal or no effects[40–42]. Similarly, the impact of omega-3 supplementation on behavioral symptoms of ADHD has shown variable outcomes[43,44]. These discrepancies highlight the need for further research to better understand the potential benefits of omega-3s in

these populations. This article will examine the effects of omega-3 PUFAs on ASD and ADHD from various perspectives.

Despite promising evidence, several challenges persist in omega-3 research. Many studies have been constrained by small sample sizes, short supplementation durations, and moderate dosages, potentially limiting the ability to assess the long-term effects of omega-3 supplementation[29]. Furthermore, the interactions between omega-3 PUFAs and other nutrients or vitamins remain underexplored, despite their potential to modulate the efficacy of omega-3s in both the short and long term[45,46]. This article discusses these limitations and proposes future research directions, emphasizing the need to examine the long-term effects of omega-3 supplementation, investigate genetic factors that may influence individual responses, and explore nutrient interactions that optimize brain health.

The Critical Role of PUFAs in Neurodevelopment, Neuroimmune Regulation, and the Gut-Brain Axis: Implications for Maternal and Early Childhood Nutrition

PUFAs are fundamental components of cell membranes, essential for cellular structure, signaling, and functional integrity[47]. In human physiology, critical PUFAs include linoleic acid (LA, 18:2n-6), α-linolenic acid (ALA, 18:3omega-3), and their biologically active derivatives, such as arachidonic acid (AA, 20:4n-6), (EPA, 20:5omega-3), and (DHA, 22:6omega-3)[48]. Among these, ALA, as the precursor to omega-3 fatty acids, undergoes enzymatic conversion to EPA and subsequently to docosapentaenoic acid (DPA) and DHA[49,50]. These derivatives play indispensable roles in regulating neural processes and immune responses.

Critical Roles of Omega-3 and Omega-6 Fatty Acids in Neurodevelopment and Neuroimmune Regulation

DHA, the most abundant omega-3 fatty acid in the brain, is critical for a spectrum of neurological functions. It supports cognitive processing, neurite outgrowth, synaptic communication, and membrane fluidity while fostering neuronal survival[17,24,51]. DHA's neuroprotective attributes also mitigate neurodegenerative processes, underscoring its importance during pregnancy and early childhood, when the brain undergoes rapid growth and functional maturation[9,26]. Inadequate maternal DHA intake during these crucial periods can result in irreversible deficits in neurodevelopment and cognitive function in offspring[52].

Conversely, arachidonic acid, a prominent omega-6 PUFA, is a precursor to proinflammatory mediators like prostaglandins and leukotrienes[50,53]. These molecules are implicated in various inflammatory conditions, including those linked to the pathophysiology of ASD. The balance between omega-6-derived inflammatory mediators and omega-3 metabolites such as EPA-derived resolvins is pivotal in maintaining immune homeostasis and mitigating inflammation[54]. Emerging research highlights that up to 60% of individuals with ASD display systemic immune dysfunction, often exacerbated by an imbalance in the omega-6/omega-3 ratio. Children with ASD frequently exhibit reduced levels of long-chain omega-3 PUFAs, particularly DHA and EPA, which correlates with heightened production of proinflammatory cytokines linked to omega-6 PUFA metabolism[55,56]. This disruption exacerbates immune dysregulation and is associated with elevated autoantibody levels targeting neuronal and glial structures, suggesting a mechanistic interplay between lipid metabolism and neuroimmune dysfunction[57].

PUFA in Neurodevelopmental Disorders: Intersections of Metabolic Imbalance, Gut-Brain Axis, and Therapeutic Potential

The metabolic imbalances of PUFAs are not limited to ASD but extend to overlapping conditions like ADHD[58]. Studies reveal that children with ASD and ADHD have reduced omega-3 levels and elevated AA/EPA ratios[59]. These biochemical alterations amplify oxidative stress, enhance proinflammatory cytokine production, and disrupt neurotransmitter systems, worsening neurodevelopmental and behavioral symptoms[56,59,60]. Interventions, including omega-3 supplementation combined with vitamin D, have shown promise in modulating inflammation and improving symptomatology in these populations[61,62].

The gut-brain axis (GBA) emerges as a critical mediator linking dietary PUFAs to neurodevelopmental outcomes and behavior[63]. Omega-3 PUFAs enhance the proliferation of beneficial probiotic bacteria like *Bifidobacterium* and *Lactobacillus*, which fortify gut health and positively influence the hypothalamic-pituitary-adrenal (HPA) axis under stress[64–66]. These probiotics, in turn, support the integrity of the intestinal epithelium and regulate neuroinflammatory responses, ultimately modulating behavior and cognitive function. Omega-3 supplementation has also been linked to increased microbial diversity and the promotion of gut integrity, reinforcing its role in the GBA[64,67].

In contrast, excessive dietary omega-6 PUFAs are associated with reductions in beneficial gut microbiota populations, compromised epithelial barrier function, and increased gut permeability[68,69]. These effects amplify systemic inflammation, highlighting the necessity of a balanced omega-3 to omega-6 ratio for optimal gut and immune health[70,71]. A disproportionate omega-6/omega-3 ratio has been implicated in various inflammatory and neurodevelopmental conditions, further emphasizing the need for dietary precision[72].

Omega-3 PUFAs in Maternal and Early Childhood Nutrition: Implications for Neurodevelopment, Immune Regulation, and ASD Risk Reduction

The role of omega-3 PUFAs in maternal nutrition during pregnancy is pivotal for neurodevelopmental outcomes in offspring. Adequate maternal intake of DHA and EPA is essential for fetal brain development, influencing key processes such as microglial activity, neuroinflammatory regulation, and synaptic plasticity[26,73,74]. Research has identified a correlation between elevated maternal omega-6/omega-3 ratios and adverse neurodevelopmental trajectories, including an increased risk of ASD traits in children[75]. Notably, prospective studies demonstrate a 40% reduction in ASD risk when omega-3 intake is optimized during the second half of gestation[60,76,77]. These findings emphasize the importance of dietary interventions focused on increasing omega-3 consumption while minimizing excessive omega-6 intake during critical periods of development[78].

Beyond the prenatal period, early childhood represents another crucial window where omega-3 PUFAs significantly influence neurodevelopmental and immune health[79]. Omega-3 intake dur-

ing this stage has been shown to modulate gut microbiota composition, strengthen the gut-brain axis, and promote social behavior, cognitive performance, and overall well-being[80,81]. The therapeutic potential of omega-3 PUFAs in managing neurodevelopmental disorders, including ASD, is increasingly supported by emerging evidence, with significant implications for dietary guidelines and public health strategies[41].

Omega-3 PUFAs are integral to immune regulation and inflammation control, primarily through their incorporation into immune cell membranes such as macrophages, T-cells, neutrophils, and microglia[10,82] (Fig. 1). Once embedded in the phospholipid bilayer, Omega-3 PUFAs modulate lipid raft formation, altering receptor signaling pathways that drive immune responses[83]. This incorporation induces a functional shift in macrophages from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 state, enhances regulatory T-cell activity, limits excessive neutrophil infiltration, and suppresses overactivation of microglia[84–86]. Collectively, these actions create an anti-inflammatory and neuroprotective environment that supports immune tolerance, resolves inflammation, and maintains tissue homeostasis.

Additionally, Omega-3 PUFAs are metabolized into specialized pro-resolving mediators (SPMs), including resolvins, protectins, and maresins, which counteract the pro-inflammatory effects of Omega-6-derived eicosanoids[87–89]. These SPMs inhibit neutrophil overactivation, promote apoptotic cell clearance, and facilitate tissue repair[90,91]. Omega-3 PUFAs further regulate cytokine activity by suppressing pro-inflammatory cytokines while enhancing anti-inflammatory cytokines[54,88] (Fig. 1). Dysregulation of these pathways contributes to chronic inflammatory and neurodegenerative diseases, including neurodevelopmental disorders such as ASD and ADHD[55,92] (Fig. 1). The immunomodulatory and neuroprotective properties of Omega-3 PUFAs underscore their therapeutic potential in treating autoimmune diseases, inflammatory disorders, and neurological conditions.

Omega-3 PUFAs play a pivotal role in neurodevelopment, immune regulation, and gut health. Their influence on the gut-brain axis and neuroimmune interactions suggests significant therapeutic potential for neurodevelopmental and psychiatric disorders[93,94]. Omega-3 PUFAs contribute to membrane fluidity, synaptic plasticity, and anti-inflammatory signaling pathways, which can modulate both central nervous system (CNS) development and peripheral immune responses[95].

A balanced dietary intake of omega-3 and omega-6 PUFAs during pregnancy and early childhood is critical for optimal neurological and immune function. Disruptions in the omega-3 to omega-6 ratio, with excessive omega-6 consumption, have been associated with pro-inflammatory states and increased neurodevelopmental risks[96]. The recommended dosage of omega-3 PUFAs during pregnancy includes approximately 200-300 mg of DHA per day[97]. However, precise therapeutic dosages for psychiatric and neurodevelopmental conditions remain to be fully established.

Further research is warranted to clarify the mechanistic pathways by which PUFAs influence neurodevelopment and immune regulation, such as their effects on microglial activity, blood-brain barrier integrity, and epigenetic modulation of neuroinflammatory genes are still poorly understood. Continued investigation will be essential for refining dietary and supplemental strategies to harness the full therapeutic potential of PUFAs for enhanced developmental and clinical outcomes.

The Complex Role of Diet, Gut Microbiome, Neuroinflammation, and Immune Pathways in Neurodevelopment and ASD

The human gut is home to a vast and intricate microbial ecosys-

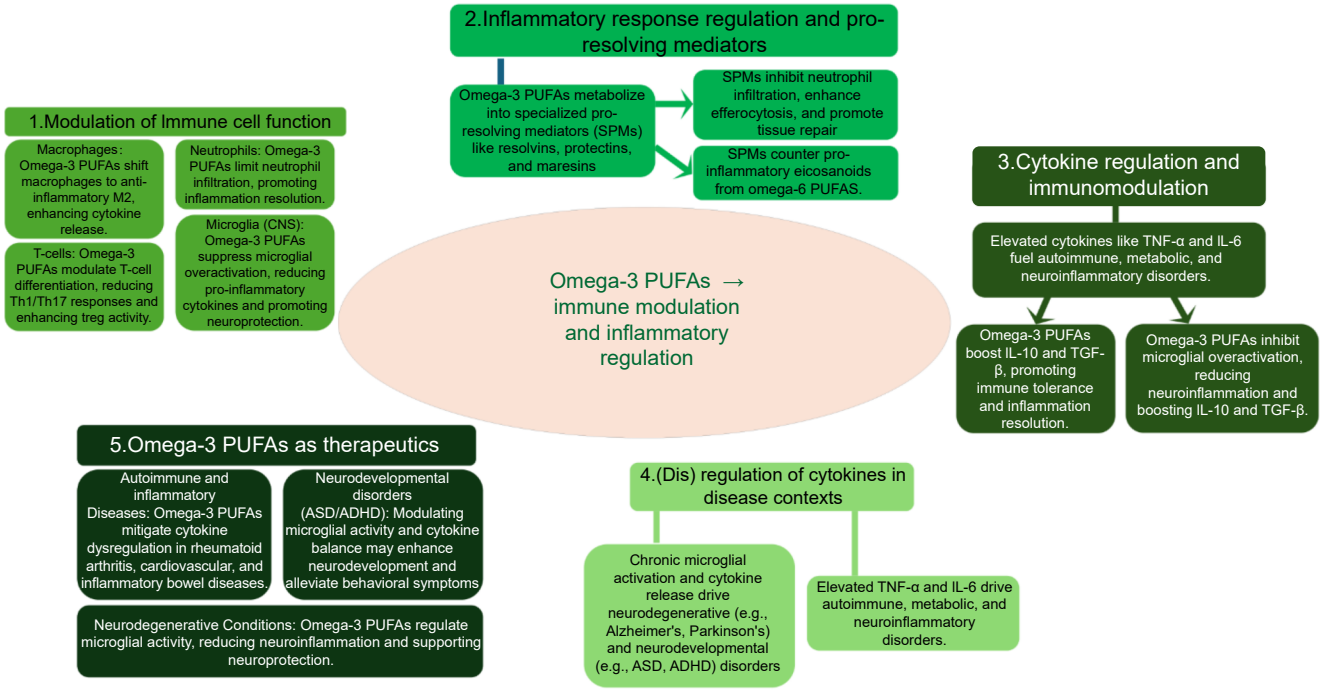

Fig. 1. Interconnection of Omega-3 PUFAs, Immune Response, and Inflammation.

tem, comprising approximately 100 trillion microbes, including more than 1,000 distinct bacterial species[98]. These microbes play critical roles in numerous physiological processes, such as digestion, metabolism, immune regulation, and increasing brain function[99]. Collectively known as the gut microbiome, this microbial community begins to develop soon after birth and is influenced by various factors including birth mode (vaginal or cesarean), genetics, feeding practices (breastfeeding or formula), antibiotic use, gastrointestinal infections, and environmental stressors[100,101]. In recent years, research has highlighted the essential role of gut microbiome in neuroinflammation and its bidirectional communication with the brain, a phenomenon known as the GBA. This axis allows gut microbes to influence brain function while also enabling the brain to regulate gut microbiota and gastrointestinal processes[63,65].

The Microbiota-Gut-Brain Axis and Its Role in Neurodevelopmental Disorders

Emerging evidence underscores the role of microbiota-GBA in neurodevelopmental disorders, with ASD being one of the most studied conditions[102]. Children with ASD often exhibit gastrointestinal symptoms, such as altered inflammatory cytokine profiles and increased intestinal permeability, which distinguish them from typically developing children[103,104]. One key mechanism through which the microbiome may influence brain function is the production of short-chain fatty acids (SCFAs) by gut microbes. SCFAs, including acetic, valeric, and propionic acids, are produced when gut bacteria ferment dietary fibers[105]. These SCFAs are capable of crossing the blood-brain barrier, directly impacting brain activity and neurophysiology. Furthermore, SCFAs play a crucial role in maintaining the integrity of the intestinal epithelial barrier, modulating immune responses, and supporting both innate and adaptive immunity[106].

The gut's immune system is closely intertwined with microbial activity. For instance, bacteria such as *Clostridia* species can release toxins that trigger localized immune responses. When these responses are dysregulated, they can lead to systemic inflammation[107]. This inflammatory cascade induces oxidative stress, which compromises the intestinal barrier and increases its permeability. As a result, bacteria and other pathogens may translocate into mesenteric lymphoid tissue, where immune cells such as macrophages and dendritic cells release proinflammatory cytokines[107,108]. These cytokines can then activate the vagus nerve or enter the bloodstream, reaching the brain and influencing the CNS. In the brain, these cytokines modulate microglial activity[109]. Microglia is essential for normal neural development and for responding to injury[110,111]. Dysregulated microglial activity, however, can disrupt normal brain function and contribute to neurodevelopmental disorders[112].

The interconnection between Omega-3 PUFAs, the gut microbiome, and the pathogenesis and management of ASD represents a critical area of research (Fig. 2). The gut microbiome plays a central role in immune regulation, metabolic functions, and neurological health, with dysbiosis contributing to ASD pathogenesis[113,114]. Omega-3 PUFAs can modulate immune responses, reduce neuroinflammation, and restore neurotransmitter balance, while promoting beneficial bacteria in the microbiome[10,64,115]. Disruptions in gut-brain communication and microbiota imbalances in ASD contribute to neurodevelopmental impairments through altered neurotransmitter production[116,117]. Omega-3 supplementation shows therapeutic potential by im-

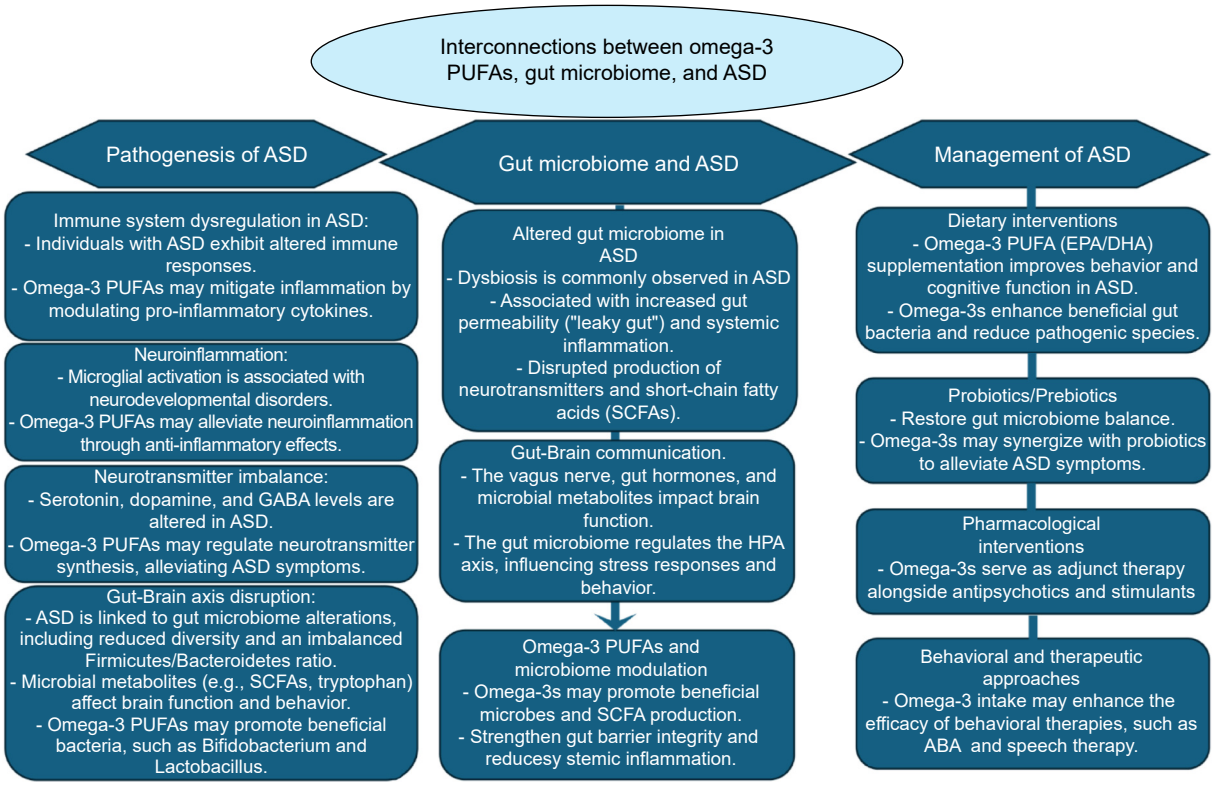

Fig. 2. Interconnection between Omega-3 PUFAs, the Gut Microbiome, and ASD Pathogenesis and Management.

proving gut integrity, reducing systemic inflammation, and enhancing gut-brain signaling, which are essential for managing ASD[55,118]. These fatty acids can be integrated into dietary interventions, combined with probiotics, or used adjunctively with conventional treatments to alleviate ASD symptoms[118,119].

Maternal Inflammation and Neurodevelopmental Disorders: Implications for ASD and Beyond

Epidemiological studies have established a strong association between maternal inflammation during pregnancy and an increased risk of ASD in offspring[120]. Maternal infections, inflammatory responses, and exposure to pathogens significantly elevate the likelihood of neurodevelopmental disorders[120]. The timing, intensity, and duration of the maternal immune response are critical factors influencing fetal brain development[121]. Pathogens and microbial metabolites in the mother can stimulate the release of proinflammatory cytokines, which can cross the placenta and interfere with fetal neurodevelopment[122]. This placental inflammation can initiate a systemic fetal inflammatory response, damaging critical brain regions, especially white matter. Elevated levels of inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), have been detected in the blood, cerebrospinal fluid, and brain tissue of individuals with ASD[123]. These cytokines disrupt CNS immune responses, activating microglia. Although this activation is initially protective, it can become maladaptive, leading to neuroinflammation, neurotoxicity, and neuronal damage[124,125].

Research has demonstrated that microglial activation is prominent in individuals with ASD, particularly in regions such as the dorsolateral prefrontal cortex[126]. Disruptions in microglial function during brain development are linked to an increased number of immature synapses, which are associated with cognitive impairments and behavioral disturbances commonly observed in ASD[126,127]. The ability of inflammatory cytokines to cross the blood-brain barrier provides a potential mechanism by which neuroinflammation may contribute to the onset of neurodevelopmental disorders[125,128]. This process may also contribute to conditions like cerebral palsy, schizophrenia, and other cognitive impairments. Although some interventions, such as supplementation with PUFAs, have shown promise in modulating inflammation and restoring the balance between proinflammatory and anti-inflammatory cytokines[46], the long-term effects of such interventions on neurodevelopmental outcomes remain unclear and warrant further investigation.

Modulation of Immune Responses in ASD: The Role of Proinflammatory Cytokines and PUFAs

Immunophenotypic analyses of individuals with ASD consistently reveal elevated levels of proinflammatory cytokines and chemokines, such as IL-1β, IL-6, interferon-μ (IFN-μ), TNF-α, interleukin 12 (IL-12) subunit p40, monocyte chemoattractant protein-1 (MCP-1), and transforming growth factor beta (TGF-β), along with hyperactive cellular immune responses[129,130] (Table 1). These immune markers are often associated with systemic inflammation and are believed to contribute to the neurodevelopmental impairments observed in ASD. However, the immune abnormalities in ASD arise from a multifactorial interplay of genetic, environmental, and lifestyle factors, including diet and maternal health[131]. This complexity presents a challenge in pinpointing clear causal relationships between these variables and the development of ASD[132].

Emerging research suggests that dietary interventions, particularly the inclusion of PUFAs, such as omega-3 fatty acids (EPA and DHA), may play a crucial role in modulating the inflammatory processes observed in ASD[55]. PUFAs are known to exert anti-inflammatory effects by reducing the levels of key proinflammatory cytokines, including IL-1β, IL-6, and TNF-α[31]

Table 1. Cytokine Dysregulation in ASD and Modulation by Omega-3 PUFAs.

Cytokine/ Immune Marker	Observed Level in ASD	Implications	Modulation by PUFAs	References
IL-1β	Elevated	Suggests involvement in neuroinflammation and immune dysregulation.	Omega-3 fatty acids (EPA/DHA) reduce IL-1β levels, helping to lower neuroinflammation.	[55,62]
IL-6	Elevated	Indicates systemic inflammation contributing to neurodevelopmental impairments.	Omega-3 fatty acids may reduce IL-6, modulating systemic inflammation.	[133,134]
TNF-α	Elevated	Increases microglial activation, which can lead to neurotoxicity and neuronal damage.	Omega-3 fatty acids decrease TNF-α levels, potentially reducing microglial activation and neurotoxicity.	[126]
IFN-μ	Elevated	Reflects heightened immune response, potentially impacting brain function and behavior.	PUFAs may regulate IFN-μ levels, helping to normalize immune responses.	[55,62,135]
IL-12 subunit p40	Elevated	Linked to proinflammatory cytokine production and immune activation.	Omega-3s can modulate IL-12 production, reducing proinflammatory responses.	[55]
MCP-1	Elevated	Promotes immune cell recruitment and inflammation, potentially exacerbating ASD-related symptoms.	PUFAs may reduce MCP-1 production, potentially mitigating immune cell recruitment.	[136−138]
TGF-β	Elevated	Involved in immune regulation, but can contribute to fibrosis and maladaptive immune responses.	Omega-3 fatty acids have been shown to regulate TGF-β, potentially reducing maladaptive immune responses.	[55,118]

(Table 1). These cytokines are key players in neuroinflammation and are believed to influence brain function and behavior. Through the regulation of immune cell activation and cytokine production, PUFAs may help restore immune balance, which is frequently dysregulated in individuals with ASD[139].

The potential of PUFAs to modulate immune responses is of particular relevance within the context of gut microbiome alterations[140]. PUFAs are recognized to not only influence immune cell function but also impact the gut microbiota composition[64]. Changes in the gut microbiome, such as an imbalance in microbial populations, are known to contribute to immune system dysregulation[68,111]. By influencing both microbial diversity and immune function, PUFAs could potentially alleviate some of the inflammatory burden associated with ASD.

While the precise mechanisms underlying the effects of PUFAs on immune responses in ASD remain under investigation, current evidence suggests a promising therapeutic role. Omega-3 PUFAs, such as DHA and EPA, have been shown to influence immune balance and reduce neuroinflammation, potentially alleviating inflammation-associated symptoms in ASD[11,94].

The proposed mechanisms of action involve the modulation of inflammatory pathways through the conversion of PUFAs into bioactive lipid mediators, such as resolvins and protectins, which have anti-inflammatory and neuroprotective properties[95]. These lipid mediators can inhibit pro-inflammatory cytokine production and promote the resolution of inflammation, which may contribute to improved neurodevelopmental outcomes in ASD[141].

Clinically, PUFAs have been administered in varying dosages across studies, with omega-3 supplementation commonly ranging between 0.3 g and 3 g per day, depending on age, baseline nutritional status, and severity of ASD symptoms[142]. However, standardized dosing guidelines remain under development, emphasizing the importance of individualized assessments by healthcare professionals.

The multifactorial nature of ASD underscores the necessity for further research to fully elucidate how maternal inflammation, dietary components such as PUFAs, and gut microbiome composition interact to influence immune dysregulation and neurodevelopmental outcomes. The gut microbiome, a key regulator of neurodevelopment and immune function, has been increasingly recognized for its role in ASD pathophysiology[143]. The microbiota-gut-brain axis influences brain function, immune regulation, and gut health, highlighting the therapeutic potential of targeting both dietary factors and microbiome modulation[144].

Future investigations should focus on integrating genetic, environmental, and dietary factors to develop targeted therapeutic strategies that address the complex immunological mechanisms underlying ASD. A deeper understanding of these interactions may yield novel interventions aimed at restoring immune homeostasis and supporting neurodevelopment in ASD populations.

Omega-3 Fatty Acids in ASD Management: From Molecular Mechanisms to Clinical Applications

Exploring Omega-3 PUFAs as a Therapeutic Approach in ASD and Current Evidence

ASD is a complex neurodevelopmental disorder marked by a diverse range of symptoms that predominantly affect social communication, interaction, and behavior[145]. Individuals with ASD commonly face substantial challenges in both verbal and nonverbal communication, find it difficult to express emotions, and often struggle to form and maintain meaningful social relationships[146]. These core deficits are frequently accompanied by repetitive behaviors, restrictive interests, and a pronounced insistence on sameness, all of which can substantially impair daily functioning and hinder effective social integration[147]. Beyond these behavioral symptoms, individuals with ASD are often characterized by immune system dysregulation, heightened sensitivity to sensory stimuli, and notable alterations in brain function[148,149], further complicating the management of the condition.

While pharmacological treatments such as selective serotonin reuptake inhibitors (SSRIs) are often employed to alleviate certain symptoms of ASD, the effectiveness of these medications remains limited, and their side effects can be considerable[150]. This has led to an increasing exploration of alternative therapeutic strategies, including nutritional interventions, to complement traditional treatments. Among these alternatives, omega-3 PUFAs, particularly DHA, have emerged as a promising area of research due to their potential to modulate critical physiological processes implicated in the pathophysiology of ASD[55,118].

Epidemiological studies consistently show that children with ASD tend to have lower levels of DHA and EPA compared to neurotypical peers[59,151]. Furthermore, an imbalanced n-6 to omega-3 PUFA ratio is frequently observed in individuals with ASD, which may be attributed to restricted dietary preferences and impaired fatty acid metabolism[72]. This imbalance underscores the potential therapeutic value of supplementing omega-3 PUFAs as a means to correct these metabolic disturbances.

Clinical trials examining the impact of omega-3 PUFA supplementation on ASD symptoms have produced mixed results. Open-label studies have suggested that supplementation may improve various behavioral symptoms, including hyperactivity and stereotypy. However, randomized controlled trials (RCTs) have yielded inconsistent outcomes, with some studies reporting reductions in these behaviors while others show no significant changes in symptom severity or adaptive functioning[151–155]. Meta-analyses of RCTs have provided more nuanced insights. For example, one meta-analysis of four trials found improvements in social interaction and repetitive behaviors, though it noted the limitations of short trial durations and variability in participant age. Another meta-analysis revealed improvements in hyperactivity and stereotypy, but the effects on social skills and externalizing behaviors were less consistent. Variations in study designs, including differences in dosages (ranging from 200 mg/day to 1.5 g/day), treatment durations (6 to 24 weeks), and participant selection criteria, have hindered the ability to draw definitive conclusions[142,156].

The Role of Omega-3 PUFAs in Modulating Immune Dysregulation, Oxidative Stress, and BDNF in ASD

A growing body of evidence highlights the significant role of immune dysregulation and oxidative stress in the pathophysiology of ASD, leading researchers to investigate omega-3 PUFAs as a potential therapeutic intervention[55,157,158]. Many individuals with ASD exhibit immune-related abnormalities, including heightened activation of immune cells, alterations in cytokine profiles, and

the presence of autoantibodies. Additionally, compromised blood-brain barrier (BBB) integrity has been observed in these individuals, which allows neurotoxic substances to cross into the central nervous system and exacerbate neurological dysfunction[159,160].

Oxidative stress, another key feature of ASD, is characterized by elevated levels of inflammatory markers such as prostaglandin E2, leukotrienes, and 8-isoprostane, in conjunction with reduced antioxidant defenses[135]. This oxidative imbalance is believed to correlate with the severity of ASD symptoms, thus providing a rationale for the use of interventions targeting oxidative stress and immune dysfunction, such as omega-3 PUFA supplementation[135,161]. The neuroprotective properties of these fatty acids suggest that they could help mitigate the inflammatory and oxidative processes that contribute to the disorder.

ASD has been associated with structural abnormalities in key brain regions responsible for social communication, sensory processing, and the regulation of repetitive behaviors[148,162]. One critical factor implicated in these neurological deficits is brain-derived neurotrophic factor (BDNF), a protein essential for neuronal survival, synaptic plasticity, and myelination[163,164]. Dysregulation of BDNF levels has been implicated in many of the core symptoms of ASD, including impaired social interaction and communication. This suggests that modulation of BDNF expression may offer therapeutic benefits for individuals with ASD.

Recent research suggests that omega-3 PUFAs, particularly DHA, play a vital role in modulating BDNF expression. DHA supports neuronal health, promotes myelination, and helps protect against oxidative damage within the central nervous system[11,165]. Additionally, DHA exhibits immunomodulatory properties, reducing pro-inflammatory cytokines such as IL-6 and TNF-α, while inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a transcription factor central to inflammation[166,167]. These combined neuroprotective and immunomodulatory effects suggest that DHA may help address both the neurological and immune dysfunctions underlying ASD.

The effectiveness of omega-3 PUFAs in managing ASD symptoms may also be influenced by individual genetic and metabolic factors. Variants in genes involved in fatty acid metabolism, such as the fatty acid desaturase (FADS) genes, can significantly impact the body's ability to metabolize essential fatty acids[151,168]. Specifically, polymorphisms in the FADS2 gene, which are common in individuals with ASD, may hinder the conversion of essential fatty acids into their bioactive forms, exacerbating metabolic disturbances in these individuals[169,170].

Additionally, individuals carrying the APOE4 allele, which affects fatty acid metabolism, may face challenges in efficiently utilizing omega-3 PUFAs. Dysregulation of fatty acid-binding proteins (FABPs), including FABP7, has also been implicated in ASD-related phenotypes such as anxiety and hyperactivity[171,172]. These findings emphasize the complexity of genetic predispositions and metabolic processes in ASD, highlighting the need for personalized treatment strategies that take these factors into account.

Optimizing the Therapeutic Potential of omega-3 PUFAs in ASD: Addressing Variability, Personalization, and Future Research Directions

Omega-3 PUFAs, particularly DHA, have demonstrated significant potential as adjunctive therapies for ASD. However, the clinical evidence supporting their efficacy remains inconclusive. Several factors contribute to this uncertainty, including variability in study designs, differences in participant characteristics, and the influence of individual genetic and metabolic profiles[56,118,151]. These inconsistencies complicate the interpretation of existing results and hinder the establishment of definitive therapeutic guidelines for the use of omega-3 PUFAs in ASD management.

To more accurately assess the clinical benefits of omega-3 PUFAs for individuals with ASD, future research must address key areas of variability that may impact study outcomes. One critical aspect is the need for longer treatment durations and standardized dosing regimens. Short treatment periods and varying dosages across studies often lead to inconsistent findings, making it difficult to draw clear conclusions. Standardizing these elements would contribute to more consistent results and facilitate comparison across studies, ultimately strengthening the evidence base for omega-3 PUFA supplementation in ASD.

Additionally, expanding participant demographics is essential to capture the diverse range of genetic, environmental, and clinical factors that may influence treatment response. Current studies often have limited participant pools, which may not fully represent the broader population of individuals with ASD. Including a wider range of participants—considering variables such as age, sex, and comorbidities—could provide more comprehensive insights into how omega-3 PUFAs affect different subgroups within the ASD population. Such improvements in study design will help clarify the role of omega-3 PUFAs and ensure that the findings are generalizable to the broader population of individuals with ASD.

Moreover, personalized treatment strategies hold promises in optimizing the effectiveness of omega-3 PUFA supplementation. Variations in genes involved in fatty acid metabolism, particularly those related to the FADS family, can significantly affect how individuals metabolize and respond to omega-3 PUFAs[168]. For instance, certain genetic polymorphisms in the FADS2 gene, common in individuals with ASD, may impair the conversion of essential fatty acids into their bioactive forms, potentially exacerbating metabolic disturbances[169,173]. Understanding and accounting for these genetic factors could allow for more tailored interventions that maximize therapeutic outcomes and reduce the variability in responses.

Furthermore, genetic variants, such as those associated with the APOE4 allele, may affect fatty acid metabolism and influence the efficacy of omega-3 PUFAs[172]. Research that investigates these genetic and metabolic factors in greater detail will be crucial in developing personalized approaches to treatment. Tailoring interventions to an individual's unique genetic profile may enhance the therapeutic potential of omega-3 PUFAs, improving clinical outcomes and minimizing the inconsistencies seen in past studies.

By integrating personalized approaches, future research may unlock the full therapeutic potential of omega-3 PUFAs in ASD. These strategies could position omega-3 PUFAs as a valuable complement to current ASD treatment paradigms, particularly as adjunctive therapies. Ultimately, a deeper understanding of the complex interplay between genetics, metabolism, and neurobiology will be essential in establishing omega-3 PUFAs as a novel, evidence-based therapeutic option for individuals with ASD.

Such advancements have the potential to improve clinical outcomes and quality of life for individuals with ASD, offering a promising avenue for more effective and personalized care.

Behavioral and Social Gains in ASD: The Promise of Omega-3 PUFAs

ASD is a neurodevelopmental condition marked by deficits in social communication, restricted interests, and repetitive behaviors[174]. Despite the lack of universally accepted pharmacological treatments, omega-3 PUFAs have gained attention as a potential therapeutic approach. EPA and DHA are essential fatty acids vital for brain development and function and have been primarily explored for their therapeutic potential in ASD. This section reviews RCTs investigating the effects of omega-3 supplementation on core ASD symptoms, particularly improvements in behavioral, social, and motor skills (Table 2)[77,175–180].

The Potential Benefits of Omega-3 Supplementation in Alleviating Core Symptoms of ASD: A Review of the Research

Research has demonstrated the potential benefits of omega-3 supplementation in alleviating core symptoms of ASD, including hyperactivity, lethargy, and stereotypical behaviors (Fig. 2)[118,152]. Several studies have reported significant improvements in behavioral outcomes, such as reductions in stereotypical behaviors, enhanced communication abilities, and improved concentration, eye contact, motor skills, and language development. These findings suggest that omega-3 fatty acids, such as DHA and EPA, may positively influence both core and associated symptoms of ASD, particularly when administered at appropriate doses over sustained periods[55,72,118].

In addition to behavioral improvements, omega-3 supplementation has shown promise in enhancing social-communicative and motor skills. Combining omega-3 with other nutrients, such as vitamin D, has been associated with significant improvements in social communication[10,118,158]. Modest symptom improvements have also been observed in specific populations, such as preterm children, highlighting the broad applicability of omega-3 interventions. While some studies note limited changes in specific areas, such as social interaction, the overall evidence suggests that omega-3 supplementation, particularly in combination with complementary nutrients, may offer a promising approach to addressing both core and broader behavioral aspects of ASD[181].

Therapeutic Potential of Omega-3 PUFA Supplementation in ASD: Impacts on Core Symptoms and the Need for Standardized Research Protocols

Omega-3 PUFA supplementation has garnered significant attention for its potential therapeutic effects on core symptoms of ASD, particularly in relation to stereotypical behaviors, social functioning, and communication skills. Several studies suggest that omega-3 supplementation may have a beneficial impact on these areas, potentially enhancing early language development, reducing hyperactivity, and improving motor skills[40,77,182,183]. Despite these promising findings, the evidence regarding omega-3's effect on reactive aggression and antisocial behavior remains inconclusive, with variability in results across studies.

A major challenge in drawing definitive conclusions arises from the methodological variability observed in existing research. Differences in omega-3 formulations, dosages, and supplementation durations have contributed to inconsistent findings, complicating efforts to establish clear clinical guidelines. This variability highlights the necessity for more standardized research protocols to fully assess the potential of omega-3 PUFAs as a treatment for ASD.

Despite these challenges, omega-3 PUFA supplementation continues to show promising therapeutic benefits, particularly in alleviating behavioral symptoms and enhancing social communication. These positive outcomes suggest that omega-3s could be a valuable adjunctive treatment for individuals with ASD. However, to optimize clinical application, further large-scale RCTs are essential. Such studies should aim to determine the most effective dosages, supplementation regimens, and explore the potential for combining omega-3 supplementation with other therapeutic strategies.

While further research is needed to clarify the optimal conditions for omega-3 supplementation in ASD, the current evidence supports its potential as a well-tolerated and effective adjunctive treatment for improving key behavioral and social communication symptoms in individuals with ASD.

Table 2. Impact of Omega-3 and Omega-6 PUFA Supplementation on Behavioral and Developmental Outcomes in ASD.

Participants	PUFA Formulation	Dosage	Duration	Outcomes	Reference
Children with ASD and hyperactivity	Omega-3 (EPA/DHA)	1.3 g/day	6 weeks	Reduced stereotypical behaviors and lethargy	[175]
Children with ASD	DHA, AA	High doses	16 weeks	Improvements in social withdrawal, stereotypy, communication	[176]
Children with ASD	DHA	200 mg/day	6 months	No improvements in core symptoms, improved communication	[177]
Children with ASD	DHA, EPA, AA	Combination	3 weeks	Behavioral improvements in concentration, eye contact, motor skills	[178]
Preterm children with ASD	Omega-3 and omega-6 PUFAs	Combination	12 weeks	Language development improvements	[77]
Individuals with ASD	Omega-3 PUFAs	Variable	12 weeks	Improved social motivation	[179]
Children with ASD	Omega-3 PUFAs	Variable	8 weeks	Reduced reactive aggression	[180]

The Role of Omega-3 PUFAs in ADHD Pathophysiology and Therapeutic Potential: Insights into Genetic, Metabolic, and Neuroinflammatory Mechanisms

Nutritional and Genetic Determinants of ADHD: A Focus on Omega-3 PUFA Deficiencies and Implications for Management

ADHD is a prevalent neurodevelopmental disorder affecting an estimated 5% to 10% of the global population, with the majority of cases occurring in children and adolescents[184,185]. ADHD is characterized by symptoms of inattention, hyperactivity, and impulsiveness. The disorder often co-occurs with various psychiatric conditions, such as mood disorders, anxiety, conduct disorders, and substance use disorders[184,186,187]. The untreated consequences of ADHD are substantial, manifesting in increased absenteeism from work, higher school dropout rates, frequent motor vehicle accidents, substance misuse, and decreased economic productivity. Furthermore, children with ADHD frequently experience strained familial relationships, particularly with their mothers, which further exacerbate the difficulties they face[188,189].

The pathophysiology of ADHD is multifactorial, involving complex interactions between genetic, environmental, and neurobiological factors. Recent research has highlighted the potential role of omega-3 PUFAs in the development and progression of ADHD[43,190,191]. Both DHA and EPA are essential components of neuronal cell membranes, where they modulate membrane fluidity, synaptic plasticity, and neurotransmitter signaling—all processes that are frequently disrupted in individuals with ADHD (Fig. 3)[10,11,24].

Epidemiological studies suggest that insufficient maternal intake of DHA and EPA during pregnancy—often due to inadequate seafood consumption or low dietary intake of omega-3 PUFAs—may contribute to neurodevelopmental impairments in offspring[26,192,193]. Children born to mothers with low levels of omega-3 PUFAs are more likely to exhibit deficits in motor coordination, verbal communication, and social behaviors, all of which are hallmark features of ADHD[60,73,194]. These early-life deficiencies may set the stage for the later development of ADHD symptoms.

Clinical studies examining the effects of omega-3 PUFA supplementation on ADHD have yielded mixed results. Some studies report improvements in clinical symptoms and cognitive performance, particularly with DHA supplementation, while others have found negligible or inconsistent effects[182,195,196]. The variability in outcomes may be attributed to differences in supplementation types (e.g., DHA versus EPA), doses, durations, and study designs. Many studies have used relatively low doses of omega-3 PUFAs, typically below 500 mg/day, which could explain the inconsistencies observed[44,197]. These findings highlight the need for more rigorous and well-designed research to determine the most effective therapeutic strategies involving omega-3 PUFAs for ADHD.

Despite substantial evidence supporting the role of omega-3 PUFAs in ADHD, several key questions remain unanswered. For example, it is unclear whether DHA alone, EPA alone, or a combination of both is most effective in alleviating ADHD symptoms. Furthermore, the optimal dosage and duration of omega-3 PUFA supplementation for therapeutic benefit have yet to be definitively determined. These gaps highlight the necessity for further clinical trials to establish the most effective formulation, dosage, and duration of omega-3 PUFA supplementation in ADHD management.

Children diagnosed with ADHD often exhibit physical signs of essential fatty acid (EFA) deficiency, including dry skin, brittle nails, and eczema, which are clinically correlated with reduced plasma levels of DHA and EPA. These symptoms are associated with more severe ADHD characteristics, such as inattention, impulsivity, and hyperactivity[42,43,198]. Moreover, alterations in fatty acid profiles, such as a lower overall omega-3 PUFA content and an elevated omega-6 to omega-3 ratio in red blood cell membranes, further support the hypothesis that imbalances in PUFAs play a significant role in the etiology of ADHD[30,60,197,199].

Deficiencies in essential nutrients, particularly omega-3 PUFAs, have been implicated in various neurodevelopmental dis-

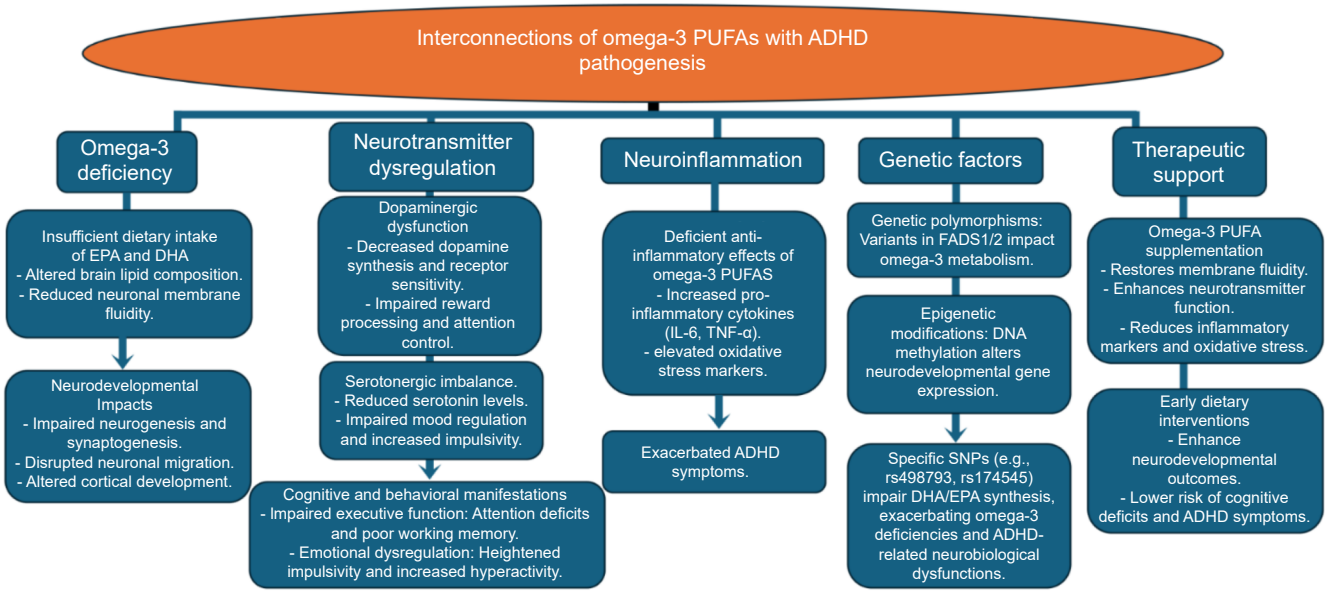

Fig. 3. The Interconnection Between Omega-3 PUFAs and ADHD Pathogenesis.

orders, with ADHD being a notable example (Fig. 3)[43,44]. The maternal diet during pregnancy plays a critical role in shaping the neurodevelopmental trajectory of offspring. Specifically, maternal intake of omega-3 PUFAs has been linked to improved developmental outcomes in children, such as enhanced social behavior, fine motor skills, verbal communication, and overall cognitive development. Adequate maternal consumption of these fatty acids during pregnancy is associated with a reduced risk of developmental deficits[200,201]. These findings underscore the importance of omega-3 PUFAs in early brain development, particularly during the rapid growth and differentiation of the fetal brain.

Children with ADHD are often found to have more pronounced deficiencies in omega-3 PUFAs compared to their typically developing peers (Table 3)[43,58,182,197,202–211]. These deficiencies are reflected in physical symptoms such as dry skin, eczema, and dry eyes, which correlate with reduced plasma DHA levels. Specifically, lower DHA levels are associated with more severe ADHD symptoms, indicating that DHA is integral to the neurobiological mechanisms underlying the disorder[43,182]. Biochemical markers further support the role of omega-3 PUFAs in ADHD pathophysiology. Children with ADHD typically show reduced omega-3 PUFA levels in their red blood cells and a higher omega-6 to omega-3 ratio compared to typically developing children (Table 3). This altered fatty acid composition correlates closely with the severity of ADHD symptoms, especially those related to attention and hyperactivity. Numerous studies have reported significantly lower concentrations of DHA, EPA, and total omega-3 PUFAs in the blood of children with ADHD[197], reinforcing the hypothesis that omega-3 PUFA deficiencies contribute to the disorder's pathophysiology.

Genetic factors may exacerbate omega-3 PUFA deficiencies in individuals with ADHD. Variations in genes involved in the metabolism of essential fatty acids, such as FADS1 and FADS2, have been implicated in ADHD pathogenesis[43,212]. These genes encode enzymes that are crucial for converting plant-derived precursors into long-chain omega-3 fatty acids, including DHA and EPA. Single nucleotide polymorphisms (SNPs) in these genes, such as rs498793 in FADS2 and rs174545 in FADS1, can impair the body's ability to synthesize omega-3 PUFAs, potentially worsening the neurobiological dysfunctions associated with ADHD (Fig. 3)[41,206].

Genetic variations in FADS1 and FADS2, which encode enzymes responsible for converting dietary PUFAs into bioactive metabolites, are critical to the synthesis of long-chain omega-3 PUFAs like DHA and EPA. Specific genetic variations, including SNPs in these genes, have been linked to ADHD, particularly in children exposed to alcohol in utero[168,213,214]. These genetic variations may impair the body's ability to efficiently convert omega-3 PUFAs into their active forms, potentially increasing the risk of ADHD. Individuals with prenatal alcohol exposure, already at an elevated risk for ADHD, may experience additional disruptions in PUFA metabolism due to these genetic variants[215].

The interplay between genetic factors, metabolic inefficiencies, and environmental influences underscores the complexity of ADHD pathophysiology. This multifaceted relationship highlights the importance of considering individual genetic profiles in the development of personalized therapeutic strategies, including targeted interventions to address omega-3 PUFA deficiencies.

The Role of PUFA Metabolism in Neuroinflammation and ADHD: Implications of Enzymatic Regulation

The metabolism of PUFAs, orchestrated by enzymes such as phospholipase A2 (PLA2) and cyclooxygenase-2 (COX2), plays a critical role in the production of bioactive lipid mediators with significant implications for conditions like ADHD[216,217] (Table 4)[4,11,30,43,54,217–231].

PUFA metabolism begins with PLA2, which releases free fatty acids from phospholipids. The two major isoforms, iPLA2 and cPLA2, have distinct roles. iPLA2 primarily influences the metabolism of DHA, an omega-3 fatty acid essential for brain function and synaptic plasticity[165,232,233]. In contrast, cPLA2 is responsible for the release of arachidonic acid, an omega-6 fatty acid, which can be converted into pro-inflammatory eicosanoids, including prostaglandins such as prostaglandin E2 (PGE2)[222,234]. These pro-inflammatory mediators are linked to neuroinflammation and disorders such as ADHD. Imbalances between omega-3 and omega-6 fatty acids exacerbate inflammation, contributing to neuroinflammation in ADHD[197].

COX2 catalyzes the conversion of AA into prostaglandins, including PGE2, playing a pivotal role in inflammatory responses[224]. In the context of ADHD, COX2 activation is implicated in the dysregulated inflammatory processes observed in the brain, contributing to symptoms such as inattention, hyperactivity, and impulsivity[223]. Elevated levels of pro-inflammatory cytokines and eicosanoids, including those derived from COX2, can disrupt synaptic plasticity and neurotransmitter signaling, which in turn impairs cognitive functions[125,235].

Table 3. Key Factors Linking Omega-3 PUFAs to Neurodevelopmental Outcomes and ADHD.

Factor	Finding	Implication	Reference
Maternal diet	Adequate maternal intake of omega-3 PUFAs during pregnancy improves developmental outcomes.	Emphasizes the importance of maternal nutrition for offspring brain development.	[202,203]
Omega-3 PUFA deficiency in ADHD	Children with ADHD often have lower DHA and total omega-3 PUFA levels, and a higher omega-6 to omega-3 ratio.	Suggests a direct link between omega-3 PUFA deficiency and ADHD symptoms.	[43,58,204]
Biochemical markers	Reduced omega-3 PUFAs in red blood cells in ADHD children.	Indicates potential biomarkers for diagnosing and assessing ADHD severity.	[182,197,205]
Genetic factors	SNPs in FADS1 and FADS2 genes are associated with impaired omega-3 PUFA metabolism.	Genetic variations may increase the risk of ADHD through disrupted PUFA metabolism.	[206–208]
Clinical trial outcomes	Mixed results with DHA supplementation showing improvements in some studies, but inconsistencies in others.	Calls for larger, more standardized clinical trials to determine optimal treatment.	[209–211]

Table 4. Metabolism of PUFAs and Their Implications for Neuroinflammation and ADHD Pathophysiology.

Process/Enzyme	Description	Implications for ADHD	References
Phospholipase A2 (PLA2)	Releases free fatty acids from phospholipids. Includes two isoforms: iPLA2 and cPLA2.	iPLA2 influences DHA metabolism (omega-3), crucial for brain function. cPLA2 releases arachidonic acid (AA, omega-6), leading to pro-inflammatory eicosanoids.	[217−219]
iPLA2 (Type I)	Primarily involved in DHA metabolism, an omega-3 fatty acid vital for synaptic plasticity and brain function.	Deficient DHA metabolism may impair cognitive function and neuroplasticity, potentially exacerbating ADHD symptoms.	[4,30,220]
cPLA2 (Type II)	Releases arachidonic acid (AA), which can be converted into pro-inflammatory eicosanoids, including prostaglandins.	Elevated AA release leads to production of inflammatory mediators like PGE2, which can exacerbate neuroinflammation and ADHD-related symptoms (inattention, hyperactivity, impulsivity).	[221,222]
Cyclooxygenase-2 (COX2)	Catalyzes the conversion of AA into prostaglandins, including PGE2, involved in inflammatory responses.	COX2 activation contributes to dysregulated inflammation in the brain, impairing cognitive function, and worsening ADHD symptoms.	[223−225]
Pro-inflammatory mediators (e.g., PGE2)	Prostaglandins produced from AA catalyzed by COX2 play a central role in inflammatory responses in the brain.	Elevated PGE2 and other pro-inflammatory cytokines disrupt synaptic plasticity, neurotransmitter signaling, and cognitive functions, contributing to ADHD pathophysiology.	[226−228]
Neuroinflammation	Excessive immune response in the brain, marked by an imbalance favoring pro-inflammatory mediators like PGE2.	Impairs neuroplasticity and contributes to cognitive and behavioral deficits in ADHD.	[227,229]
Omega-3 Fatty Acids (DHA, EPA)	Anti-inflammatory properties that help modulate brain inflammation and support neuronal membrane structure.	DHA and EPA help resolve inflammation and support synaptic plasticity, potentially alleviating neuroinflammation and ADHD symptoms when balanced with omega-6 intake.	[11,30,43,54]
Omega-6 Fatty Acids	In excess, may promote inflammation in the brain.	Excess omega-6 fatty acids without adequate omega-3 intake can exacerbate neuroinflammation, worsening ADHD symptoms.	[230,231]

Neuroinflammation, a central factor in the pathophysiology of ADHD, is characterized by an excessive immune response in the brain. An imbalance favoring pro-inflammatory mediators, such as PGE2, impairs neuroplasticity and contributes to cognitive and behavioral deficits[236,237]. Omega-3 fatty acids, such as DHA and EPA, are known for their anti-inflammatory properties and help modulate brain inflammation by supporting neuronal membrane structure and producing lipid mediators that resolve inflammation. In contrast, omega-6 fatty acids may exacerbate neuroinflammation if not balanced by adequate omega-3 intake[54,238,239].

Targeting PUFA metabolism offers a promising therapeutic strategy for ADHD. Omega-3 supplementation, particularly with DHA and EPA, has shown potential in reducing brain inflammation and alleviating ADHD symptoms (Table 4). Genetic factors, such as polymorphisms in the FADS1 and FADS2 genes, which affect omega-3 conversion, could guide personalized treatment approaches. Individuals with impaired PUFA metabolism may benefit from direct omega-3 supplementation or dietary adjustments aimed at improving neuroinflammation and cognitive function in ADHD.

The Role of omega-3 PUFAs in the Management of ADHD: Insights from Meta-Analyses and Clinical Trials

Challenges in Meta-Analyses and the Need for Focused Investigations

Research into the therapeutic potential of omega-3 PUFAs for managing ADHD has produced mixed results, primarily due to methodological inconsistencies in earlier studies. These studies were often characterized by small sample sizes, inadequate control of confounding variables, and varied supplementation protocols, which limited the ability to draw definitive conclusions about the efficacy of omega-3 PUFAs in alleviating ADHD symptoms.

Meta-analyses investigating the effects of omega-3 PUFAs in ADHD face additional challenges stemming from the heterogeneity of clinical samples. Participants in these studies frequently span a wide range of age groups and present with diverse comorbid conditions, introducing significant variability into the results and complicating the accurate assessment of omega-3 PUFA effects. Furthermore, many studies employ mixed supplementation regimens, combining omega-3 PUFAs with other nutrients such as vitamins or minerals. This approach makes it difficult to isolate the specific therapeutic effects of omega-3 fatty acids on ADHD symptoms.

These methodological challenges emphasize the critical need for focused research on omega-3 PUFA monotherapy in ADHD treatment. Prioritizing the control of variables, such as comorbidities and co-supplements, is essential for accurately evaluating the therapeutic potential of omega-3 PUFAs. Selecting well-defined patient populations and implementing standardized treatment protocols can minimize confounding factors and improve the reliability of findings. By employing rigorous methodologies, researchers can gain a clearer understanding of the role omega-3 PUFAs play in managing ADHD symptoms, ultimately facilitating the development of more effective and targeted therapeutic strategies.

Optimizing omega-3 PUFA Supplementation in ADHD: A Meta-Analysis of EPA Doses, Treatment Duration, and Personalized Approaches

A targeted meta-analysis of six RCTs involving 524 children diagnosed with ADHD revealed significant improvements across multiple domains, including inattention, overall ADHD symptom severity, and cognitive function (Table 5)[182,195,240–245]. Notably, a subanalysis within this meta-analysis emphasized the efficacy of supplementation with EPA at doses of 500 mg/day or higher. These doses were particularly effective in mitigating hyperactivity and impulsiveness, highlighting EPA's pivotal role in ADHD management.

In support of these findings, a comprehensive review of 10 clinical trials, encompassing approximately 700 predominantly male children, reinforced the critical importance of EPA supplementation. This review identified that doses ranging from 1 to 2 g/day were necessary to achieve meaningful reductions in ADHD symptoms (Table 5)[182,230,246]. Together, these studies provide robust evidence for the therapeutic potential of EPA in addressing core ADHD symptoms, particularly in the context of hyperactivity and impulsivity

The therapeutic benefits of EPA are likely attributable to its anti-inflammatory and antidepressant properties, which may counteract arachidonic acid and associated inflammatory processes, further supporting its role in ADHD treatment[43,247]. Notably, these findings suggest that formulations with higher EPA-to-DHA ratios—or even EPA monotherapy—could yield superior clinical outcomes compared to supplements focusing on DHA or low-dose combined DHA and EPA formulations, which have generally shown limited efficacy.

Moreover, the data indicate that the beneficial effects of omega-3 PUFA supplementation may be more pronounced in individuals with an EPA deficiency, a fatty acid critical for brain function and neurodevelopment[2,72]. These insights emphasize EPA's pivotal role in targeting the neurobiological mechanisms underlying ADHD, positioning it as the most essential omega-3 PUFA for therapeutic interventions in this context.

The duration of treatment significantly influences the extent of clinical improvement. Cognitive performance enhancements were typically observed after 16 weeks of supplementation, while stable red blood cell PUFA levels required at least 24 weeks[10,17,248]. Behavioral changes, however, necessitated treatment durations of up to 52 weeks to manifest significant improvements (Table 5). These findings underscore the importance of sustained supplementation for achieving comprehensive therapeutic outcomes across cognitive, physiological, and behavioral domains.

Identifying specific patient subgroups that are most responsive to omega-3 PUFA therapy could optimize treatment efficacy. Recent clinical trials have shown that high-dose EPA supplementation, particularly at 1200 mg/day, improved cognitive function in children with low endogenous EPA levels, which may indicate elevated inflammation. In contrast, children with moderate to high endogenous EPA levels exhibited minimal cognitive improvements[42,43,249,250]. These results suggest that stratification based on biomarkers such as inflammation levels or endogenous PUFA concentrations could enable more personalized and effective treatment strategies for ADHD.

The implications of omega-3 PUFA supplementation extend to adult ADHD, which often persists from childhood and is frequently accompanied by comorbid depression. Studies indicate that adults with ADHD exhibit lower erythrocyte omega-3 PUFA levels and higher n-6/omega-3 ratios. Supplementation with omega-3 PUFAs has demonstrated benefits in improving cognitive function and reducing these unfavorable ratios in adults[43,44,60,182,230]. Moreover, given the high comorbidity between ADHD and depression, omega-3 PUFAs could provide dual therapeutic benefits, addressing both cognitive and mood-related symptoms in adult populations.

Omega-3 PUFA supplementation, particularly with higher doses of EPA, demonstrates significant potential in managing ADHD[43,241]. However, further investigation is needed to establish optimal dosages and treatment durations, explore stratified treatment approaches based on clinical characteristics—such as inflammation levels or endogenous PUFA concentrations—and extend research to adult populations with persistent ADHD symptoms. By tailoring interventions to individual clinical profiles, omega-3 PUFAs could become a valuable component of ADHD treatment, offering safe and effective therapeutic outcomes for both children and adults.

Table 5. Key Insights on Omega-3 PUFA Efficacy and Mechanisms in ADHD Management.

Aspect	Findings	Key Insights	Reference
Heterogeneity in meta-analyses	Variability in age groups, comorbid conditions, and mixed regimens complicates result consistency.	Focused analyses on monotherapy are required for accurate conclusions.	[215,242]
Effective doses	EPA doses ≥ 500 mg/day alleviate hyperactivity and impulsivity; 1–2 g/day improves overall symptoms.	EPA demonstrates superior therapeutic effects compared to DHA.	[41,42,60]
Mechanism of action	EPA's anti-inflammatory and antidepressant properties counteract arachidonic acid and inflammation.	Suggests a role of immune modulation in ADHD pathophysiology.	[43,243]
Duration of treatment	Improvements in cognition (16 weeks), red blood cell stability (24 weeks), and behavior (52 weeks).	Longer treatments are necessary for sustained benefits.	[244,245]
Personalized treatment	High-dose EPA effective in children with low endogenous EPA; less effective in those with higher levels.	Stratification based on inflammation or endogenous PUFA levels enhances treatment outcomes.	[42,43,212]
Adult ADHD	Adults with ADHD show low omega-3 PUFA levels; supplementation improves cognitive function and omega-6/omega-3 ratios.	Omega-3 PUFAs may address ADHD and depression in adult populations.	[42–44]

Inflammation and Omega-3 PUFAs in the Pathogenesis and Management of ADHD: Exploring Cytokine Modulation

Inflammation has gained increasing recognition as a crucial factor in the pathophysiology of ADHD. Several interconnected mechanisms, including immune system dysfunction, neuroinflammatory responses, and alterations in the HPA axis, have been proposed to contribute to the onset and exacerbation of ADHD[227,228,251]. Understanding how omega-3 PUFAs, particularly EPA, may modulate these inflammatory pathways and potentially offer therapeutic benefits in managing ADHD symptoms is crucial.

The Inflammatory Basis of ADHD: Exploring the Role of Cytokines and Immune Dysregulation

Epidemiological studies have consistently linked ADHD with a higher prevalence of inflammatory and autoimmune disorders, suggesting a possible inflammatory basis for the condition. ADHD often co-occurs with conditions such as asthma, atopic dermatitis, and psoriasis, indicating a shared inflammatory etiology[252,253]. Furthermore, a family history of autoimmune diseases —including thyrotoxicosis, type 1 diabetes, autoimmune hepatitis, and psoriasis —has been associated with an elevated risk of developing ADHD[254,255]. This association points to the potential role of chronic inflammation and continuous cytokine release in altering brain function and contributing to ADHD.

Cytokines, which are signaling molecules produced during systemic inflammation, can cross the blood-brain barrier and exerting significant effects on brain function. Once inside the CNS, cytokines can affect processes such as synaptic plasticity, neurogenesis, and neuroinflammation, all of which are critical to maintaining proper cognitive function[256,257]. Research has highlighted the impact of inflammatory cytokines on the prefrontal cortex, a brain region essential for executive functions like attention and impulse control, which are often impaired in individuals with ADHD[227,258]. This suggests that inflammatory processes may directly disrupt the neural circuits involved in these functions, contributing to ADHD pathology.

Further supporting the inflammatory hypothesis of ADHD, studies have found higher rates of T-cell mediated neuroinflammation in individuals with ADHD. This immune response, which involves the activation of immune cells in the brain, may play a critical role in the development and exacerbation of ADHD symptoms[227]. Moreover, maternal inflammation during pregnancy has been linked to an increased risk of ADHD in offspring[259], suggesting that prenatal inflammatory exposures may lead to long-term neurodevelopmental consequences.

Although there is evidence of an inflammatory component to ADHD, the findings regarding specific inflammatory biomarkers have been inconsistent. Some studies have found elevated levels of pro-inflammatory cytokines such as IL-6, as well as anti-inflammatory cytokines like IL-10, in individuals with ADHD. These findings suggest a dysregulated immune response in ADHD. However, other studies have reported no significant differences in cytokine levels between ADHD and typically developing children, underscoring the need for further research to clarify the relationship between inflammation and ADHD[228,260,261].

The Role of Omega-3 PUFAs in Modulating Inflammation and Protecting Against ADHD

Omega-3 PUFAs, particularly EPA, have been shown to play a vital role in modulating the immune response and reducing inflammation. EPA exerts its anti-inflammatory effects by reducing the levels of AA, a pro-inflammatory omega-6 fatty acid, and by inhibiting the synthesis of prostaglandin E2 (PGE2), a molecule involved in promoting inflammation[50,68,88]. By regulating these pathways, EPA may help to mitigate the inflammatory processes that contribute to ADHD and other comorbid conditions.

Beyond reducing pro-inflammatory signaling, omega-3 PUFAs such as EPA and DHA are known to modulate oxidative stress and free radical generation, both of which are implicated in inflammation[31,249]. These fatty acids help maintain cellular integrity by regulating lipid raft signaling platforms on cell membranes, which are involved in neurotransmitter release and immune function[50,86,262]. Through these mechanisms, omega-3 PUFAs can exert protective effects on the brain and help balance immune system activity.

Emerging evidence highlights the potential benefits of omega-3 supplementation, particularly during critical periods of brain development. Maternal systemic inflammation during pregnancy has been linked to adverse effects on fetal brain development, including heightened inflammation and cognitive deficits in offspring[263,264]. However, an adequate omega-3 intake during pregnancy appears to mitigate these impairments, suggesting a protective role for omega-3 PUFAs. These findings underscore the importance of maternal nutrition in safeguarding fetal neurodevelopment and reducing the risk of neurodevelopmental disorders such as ADHD.

Inflammation is increasingly recognized as a central mechanism in the pathogenesis of ADHD, with immune dysfunction, neuroinflammatory responses, and prenatal factors all playing a role in its development[227,251]. Omega-3 PUFAs, particularly EPA, offer a promising therapeutic strategy for modulating these inflammatory pathways. By reducing systemic inflammation, protecting against neuroinflammation, and supporting proper brain development, omega-3 PUFAs may contribute to mitigating ADHD symptoms[88,138]. A better understanding of the specific mechanisms through which omega-3 PUFAs exert their effects, as well as determining the optimal conditions for their use in clinical interventions for ADHD, is essential.

Advancing ADHD Treatment: The Role of omega-3 PUFAs and Personalized Approaches in Managing Neurobiological Dysfunction

Pharmacological interventions, including stimulant medications such as methylphenidate and amphetamines, as well as non-stimulant options like atomoxetine and guanfacine, remain the cornerstone of ADHD treatment, with efficacy in alleviating symptoms in 60-80% of patients by improving attention, impulse control, and behavior regulation[184,265]. However, these medications do not provide universal efficacy, as approximately 20-40% of individuals experience inadequate symptom control or intolerable side effects, such as sleep disturbances, appetite suppression, or irritability. These limitations have led to growing interest in exploring al-

ternative or adjunctive treatment approaches, particularly nutritional interventions like omega-3 PUFAs. Supplementation with omega-3 PUFAs, especially DHA and EPA, has emerged as a promising adjunct to pharmacotherapy, offering potential benefits for managing ADHD symptoms, particularly for patients who do not respond well to conventional treatments or experience significant side effects[43,60,266].

Given the neurobiological effects of DHA and EPA and their favorable safety profile, these fatty acids have shown promise in mitigating several neurobiological dysfunctions associated with ADHD, making them a viable adjunctive treatment option for individuals who either do not respond well to conventional pharmacological therapies or suffer from significant side effects.

Neuroprotective and Anti-Inflammatory Effects of Omega-3 PUFAs in ADHD: Mechanisms and Clinical Benefits

DHA and EPA are increasingly recognized for their neuroprotective and anti-inflammatory properties, offering significant potential in the treatment of ADHD. These omega-3 fatty acids are essential for maintaining brain structure and function[11,244]. DHA, in particular, serves as a major component of neuronal membranes, enhancing membrane fluidity, supporting synaptic plasticity, and facilitating neurotransmission. Deficiencies in DHA have been linked to alterations in the lipid composition of neuronal membranes, which can subsequently impair the functioning of key neurotransmitter systems, including serotonin, norepinephrine, and dopamine pathways[267–269]. These disruptions are often observed in ADHD and are linked to cognitive impairments, mood disorders, and behavioral dysregulation, which are hallmark features of the disorder.

In addition to their structural role, omega-3 PUFAs exert substantial effects on the brain's inflammatory pathways, which are increasingly recognized as playing a critical role in the pathophysiology of ADHD[44,266]. Neuroinflammation, characterized by an overactivation of microglia and an imbalance in pro-inflammatory and anti-inflammatory cytokines, has been proposed as a contributing factor to ADHD symptoms. Omega-3 fatty acids, particularly DHA and EPA, have been shown to modulate these inflammatory processes[270,271]. Specifically, they help to reduce the production of pro-inflammatory cytokines and eicosanoids, such as prostaglandins and leukotrienes, which are known to contribute to neuroinflammation. By enhancing the production of anti-inflammatory molecules, omega-3s can help restore the balance of the brain's immune response, potentially alleviating some of the neuroinflammatory contributions to ADHD[95,228].

Clinical studies investigating the therapeutic effects of omega-3 PUFA supplementation in ADHD have shown promising results. Supplementation with DHA and EPA has been demonstrated to improve cognitive function, particularly in areas such as attention, working memory, and processing speed, which are commonly impaired in individuals with ADHD[43,195,272]. Moreover, omega-3 PUFAs have been shown to reduce hyperactivity and inattention, two core symptoms of ADHD[273]. These improvements are thought to be mediated by omega-3's ability to enhance neurotransmission and synaptic plasticity, thereby supporting more efficient cognitive processing and reducing behavioral impulsivity.

Beyond cognitive and behavioral improvements, omega-3 supplementation has also been shown to have beneficial effects on mood regulation, a key concern in ADHD management[230]. Many individuals with ADHD experience co-occurring mood disturbances, including anxiety and depression, which can further complicate the management of the disorder. Omega-3 fatty acids, through their effects on the serotonin and dopamine systems, are thought to help stabilize mood and reduce symptoms of anxiety and depression in ADHD patients[230,268,274]. By supporting the optimal functioning of neurotransmitter systems involved in mood regulation, omega-3s may offer a valuable adjunct to traditional treatments for mood-related symptoms in ADHD.

Another significant benefit of omega-3 PUFA supplementation is its potential to reduce markers of neuroinflammation. Research has demonstrated that individuals with ADHD often exhibit elevated levels of inflammatory markers, such as cytokines and C-reactive protein (CRP)[43,275]. These markers are associated with increased neuroinflammation and are thought to play a role in the development and exacerbation of ADHD symptoms. Supplementation with omega-3 fatty acids has been shown to reduce these inflammatory markers, suggesting that omega-3s may help mitigate the inflammatory component of ADHD.

Therefore, the neuroprotective and anti-inflammatory properties of omega-3 PUFAs, particularly DHA and EPA, offer a multifaceted approach to managing ADHD. Their ability to enhance cognitive function, regulate mood, and reduce neuroinflammation positions omega-3 fatty acids as a promising adjunctive or alternative treatment for individuals with ADHD. However, further research is necessary to optimize treatment protocols, determine the most effective dosages and durations of supplementation, and better understand the mechanisms underlying the therapeutic effects of omega-3s.

Personalized Approaches to Omega-3 PUFA Supplementation: Optimizing ADHD Management through Biomarker-Driven Strategies

As research on omega-3 PUFA supplementation advances, there is growing recognition that a one-size-fits-all approach may not be the most effective strategy for managing ADHD. Personalized medicine, which takes into account individual biological markers such as baseline EPA levels and inflammatory markers, is emerging as a more effective way to optimize treatment outcomes.

For instance, children with elevated inflammatory biomarkers or low plasma EPA levels are more likely to experience symptom improvements with high-dose EPA supplementation[19,42,276]. In contrast, individuals with normal PUFA profiles may derive little benefit from such interventions. These findings underscore the importance of tailoring supplementation strategies to individual needs, which could enhance treatment efficacy while minimizing unnecessary treatments.

Omega-3 PUFAs, particularly EPA, represent a promising adjunctive therapy for ADHD, offering a safe and potentially effective approach to managing the disorder's neurobiological underpinnings[43,230]. However, the variability in treatment responses highlights the necessity of personalized approaches that account for individual genetic, metabolic, and inflammatory profiles.

By incorporating nutritional strategies into a comprehensive, patient-centered treatment plan, clinicians may improve the management of ADHD, offering safer and more effective options for individuals affected by the disorder. As the research landscape continues to evolve, omega-3 PUFAs could play a key role in re-

shaping ADHD therapy, complementing existing pharmacological treatments, and ultimately enhancing the quality of life for individuals living with ADHD.

While pharmacological treatments remain the cornerstone of ADHD management, omega-3 PUFA supplementation presents a viable alternative or adjunctive strategy for individuals who do not respond well to medications or prefer to avoid the side effects associated with pharmacotherapy. In particular, omega-3 PUFAs may be beneficial in addressing cognitive deficits, mood dysregulation, and neuroinflammation, which are often observed in ADHD[43,44].

Emerging evidence suggests that omega-3 PUFAs may hold significant therapeutic potential for managing ADHD. However, further research is necessary to refine clinical protocols for omega-3 PUFA supplementation, particularly emphasizing the identification of optimal dosage ranges, treatment durations, and patient populations most likely to benefit.

A critical aspect of this refinement is the investigation of both established and hypothetical mechanisms through which omega-3 PUFAs may influence ADHD symptomatology. These mechanisms include the modulation of neuroinflammation, neuronal membrane fluidity and signal transduction, and neurotransmitter regulation. Omega-3 PUFAs, particularly EPA and DHA, have been shown to reduce the production of pro-inflammatory cytokines. This reduction may help alleviate neuroinflammatory processes that contribute to the pathophysiology of ADHD[94]. By mitigating inflammation, omega-3 PUFAs may indirectly improve the neurological environment, potentially benefiting individuals with ADHD. DHA also plays a structural role in enhancing neuronal membrane fluidity, which is essential for maintaining proper synaptic function and neurotransmitter release. This function is critical for the effective transmission of signals across neurons, contributing to cognitive and behavioral regulation, which are often impaired in ADHD[277]. Moreover, omega-3 PUFAs may influence key neurotransmitter pathways, particularly those involving dopamine and serotonin, which are known to play a significant role in attention and mood regulation. This suggests a neurochemical basis for the beneficial effects of omega-3 PUFAs in the management of ADHD, potentially offering therapeutic avenues for improving these symptoms[92].

Personalized strategies for omega-3 PUFA supplementation in ADHD could be further enhanced through biomarker-driven approaches. For example, assessing baseline omega-3 index levels or inflammatory markers could guide individualized treatment plans, ensuring patients receive tailored interventions based on their specific neurobiological profiles[278]. Dosage optimization remains an area requiring clarification, with current studies suggesting therapeutic ranges of 500-1000 mg/day of combined EPA and DHA, though individual variability in absorption and metabolic response warrants further investigation[241].

Conclusion

The multifaceted role of omega-3 PUFAs in brain health, neurodevelopment, and the management of neurodevelopmental and neuropsychiatric disorders underscores their critical importance across the lifespan. These fatty acids, particularly DHA and EPA, contribute to structural integrity, functional optimization, and modulation of inflammatory and immune pathways in the brain. Despite significant progress, the field remains ripe for exploration, with future research needed to address key gaps and challenges.

For neurodevelopmental disorders like ASD and ADHD, omega-3 PUFAs show promise in mitigating core and associated symptoms through their neuroprotective, anti-inflammatory, and immunomodulatory properties. Personalized approaches that account for genetic predispositions, metabolic profiles, and individual dietary needs could maximize their therapeutic potential. Advances in biomarker identification and the integration of omega-3s with complementary therapies such as vitamin D, probiotics, or existing pharmacological treatments offer pathways to enhanced outcomes.

Additionally, the emerging interplay between omega-3 PUFAs and the gut-brain axis represents a compelling area of study. Investigating how these fatty acids influence the microbiome, and immune responses may unlock novel interventions for both neurological and systemic health. To advance clinical applications, addressing limitations in study design, standardizing methodologies, and extending treatment durations are essential. Longitudinal studies are particularly crucial for assessing sustained benefits and refining precision nutrition strategies.

By embracing a holistic and multidisciplinary perspective, the therapeutic potential of omega-3 PUFAs can be harnessed to transform public health approaches to brain health and neurodevelopmental disorders. These efforts hold the promise of innovative, individualized, and effective strategies that improve long-term outcomes and quality of life for affected individuals.

Abbreviation

ADHD, Attention-deficit/hyperactivity disorder; ALA, Alpha-linolenic acid; APOE4, Apolipoprotein E4; ASD, Autism spectrum disorder; BBB, Blood-brain barrier; BDNF, Brain-derived neurotrophic factor; CNS, Central nervous system; COX2, Cyclooxygenase-2; CRP, C-reactive protein; DHA, Docosahexaenoic acid, EFA, Essential fatty acid; EPA, Eicosapentaenoic acid; FABPs, Fatty acid-binding proteins; FADS, Fatty acid desaturase; GBA, Gut-brain axis; HPA, Hypothalamic-pituitary-adrenal; IFN-μ, Interferon-μ; IL-12, Interleukin 12; IL-1β, Interleukin-1β; IL-6, interleukin-6; MCP-1, Monocyte chemoattractant protein-1; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; PGE2, Prostaglandin E2; PLA2, Phospholipase A2; PUFAs, Omega-3 polyunsaturated fatty acids; RCTs, Randomized controlled trials; ROS, Reactive oxygen species; SCFAs, Short-chain fatty acids; SPMs, Specialized pro-resolving mediators; SSRIs, Selective serotonin reuptake inhibitors; TGF-β, Transforming growth factor beta; TNF-α, tumor necrosis factor-alpha.

Conflicts of Interest

The author declares no conflicts of interest.

Authors' contributions

OAAE, SG, and MMN equally contributed to the design and writing of the main manuscript text.

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