Enhancing Brain Health through Omega Fatty Acids: The Role of Ahiflower Oil and Oleic Acid in Modulating the Microbiome-Gut-Brain Axis

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Abstract

Neurodegenerative disorders are emerging as a major global health issue with increasing prevalence in every geographic location. This has prompted researchers to investigate the role of dietary factors in the development and progression of conditions such as Alzheimer's, Parkinson's, and other age-related cognitive disorders. This comprehensive review explores the relationship between omega fatty acids, brain health, and the gut-brain axis, focusing on Ahiflower oil (*Buglossoides arvensis*) and oleic acid (OA; 18:1*n*-9) as possible dietary therapeutics. It examines the benefits of omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) on brain health, while also investigating the potential synergistic or additive effects of monounsaturated fatty acids (MUFAs) like oleic acid. The analysis reveals promising evidence for the neuroprotective properties of Ahiflower oil and oleic acid, particularly in modulating the gut-brain axis and influencing microbiome composition. Based on the reviewed evidence, increasing omega-3 intake can provide neurological benefits regardless of omega-6 and omega-9 levels. While these findings reveal potential dietary interventions for neurological health, they also demonstrate the complex relationship between fatty acids and brain function. This review identifies significant limitations in current research, emphasizing the need for long-term human trials with diverse populations to fully elucidate the combined effects of these fatty acids on neurological health. Future directions include exploring the potential of incorporating unique plant-based omega-3 sources, such as Ahiflower oil, into dietary guidelines for brain health. This approach could benefit those following plant-based diets as well as individuals with limited access to or sensitivity towards marine-based omega-3 sources.

Keywords: Neurodegenerative disorders, omega fatty acids, Ahiflower oil, oleic acid, gut-brain axis, neuroprotection

1. Introduction

The prevalence of neurodegenerative conditions has become a major concern in global health, impacting the lives of countless individuals and significantly contributing to worldwide disability and loss of life.[1] Current data reveals that brain-related illnesses constitute a substantial portion of the global disease burden, accounting for over 11% of disability-adjusted life years (DALYs) and more than 16% of total mortality.[1] Among these, Alzheimer's disease (AD) and Parkinson's disease (PD) stand out as the two most common neurodegenerative diseases. AD, the leading cause of dementia, affects an estimated 24 million people globally and accounts for 60-80% of all dementia cases.[2] PD, the second most common neurodegenerative disorder, is characterized by movement impairments and affects millions worldwide, with prevalence rates reaching up to 2% in individuals aged 65 years and older.[3]

Interestingly, countries with higher sociodemographic indices (SDIs) such as the United States, Japan, and several Western European nations seem to experience a disproportionate impact from certain disorders when compared to nations with lower SDIs, including Bangladesh, Nepal, and many African countries.[1,2] Various aspects of contemporary living in developed countries, including eating habits, exercise routines, and social dynamics are under scrutiny. [4,5] Of particular interest is the potential role of nutrition in both preventing and managing brain-related disorders. This focus on dietary interventions has led to a shift in the field, with many healthcare professionals advocating for the incorporation of dietary strategies in the management of neurological disorders.[4,5]

In recent years, the concept of the microbiome-gut-brain axis (MGBA) has emerged as a crucial factor in understanding the development and progression of neurodegenerative diseases.[5] This bidirectional communication system links the gut microbiota with both the central and enteric nervous system through various pathways, including neural, endocrine,

immune, and humoral links. The gut microbiome plays an instrumental role in the development and maturation of both the enteric and central nervous systems, influencing stress reactivity, anxiety-like behavior, and the hypothalamic-pituitary-adrenal (HPA) axis activity.[5] Changes in microbial composition can modulate these pathways, suggesting that the MGBA plays a significant role in brain health and disease progression.

The rising prevalence of neurodegenerative disorders has prompted a re-evaluation of current treatment approaches. While conventional therapies such as acetylcholinesterase inhibitors for Alzheimer's disease offer symptomatic relief, their effectiveness is limited due to their inability to slow disease progression, and costs can be prohibitive.[6] This has led to growing interest in nootropic foods—natural compounds believed to enhance cognitive functions and influence the gut-brain axis through mechanisms, which result in anti-inflammatory and antioxidant effects. Foods like eggs, fatty fish, and blueberries have been recognized for their brain health benefits, though scientific validation remains limited.[4,6]

The Mediterranean diet, characterized by an abundance of plant-based foods, moderate consumption of fish and wine, and limited intake of red meat and processed foods, has been linked to a lower risk of chronic diseases and increased longevity.[7] An integral component of this diet is the inclusion of omega-3 (ω-3) polyunsaturated fatty acids (PUFA), which are essential for humans due to our inability to synthesize them *de novo*.[7,8] These omega-3s, primarily sourced from fatty fish such as salmon, sardines, and mackerel, are known for their role in reducing inflammation, promoting heart health, and supporting cognitive function.[8]

Omega-3 PUFAs, particularly eicosapentaenoic acid (EPA; 20:5*n*-3) and docosahexaenoic acid (DHA; 22:6*n*-3) serve as building blocks for various compounds that help resolve inflammation and protect neural tissue, such as resolvins, protectins, and maresins.[4,8,9] These lipid mediators play vital roles in neuroprotection by actively promoting the resolution of neuroinflammation and facilitating tissue repair. In fact, omega-3 fatty acids are known to activate the anti-inflammatory pathway and are essential in disease defense.[4,9] DHA is abundant in the membranes of brain cells, where it significantly contributes to the development of the nervous system, promotes synaptic plasticity, and supports neurogenesis.[4] EPA, although less prevalent in brain tissue, is believed to contribute to reduced inflammation by modulating the production of pro-inflammatory cytokines and protecting nerve cells from damage.[4] Together, these fatty acids form an important part of the brain's defense and maintenance systems, helping to regulate inflammation, protect against oxidative stress, and maintain cognitive function.

Recent studies have expanded our understanding of omega-3 fatty acids and brain health by exploring their potential synergistic effects when combined with plasmalogens.[10] Plasmalogens have demonstrated important neuroprotective properties and play a key role in maintaining synaptic integrity.[10,11] Plasmalogens have demonstrated important neuroprotective properties and play a key role in maintaining synaptic integrity. Research has shown that supplementation with omega-3-enriched plasmalogens can lead to improvements in cognitive function and reduce markers of neuroinflammation and oxidative stress in the brain, two key factors in age-related cognitive decline and neurodegenerative diseases.[10,11]

The importance of omega-3 fatty acids is reflected in dietary recommendations, although intakes vary globally due to differences in dietary habits and food access. For instance, the Japanese consume between increased amounts of EPA and DHA, almost 3 to 4 times high than typical Westerners, primarily due to their high fish consumption[12,13]. This higher intake is associated with lower incidences of neurodegenerative diseases in Japan.[13] While national and international authorities recommend a daily intake of 200–500 mg of EPA and DHA, these recommendations are not uniform across countries due to differing genetic responses, health priorities and dietary habits.[14] Nonetheless, the variability in intake has

significant impact on neurological health, as higher EPA and DHA consumption is linked to reduced risks of cognitive decline and brain-related diseases.[12-14]

Seafood is traditionally the main source of EPA and DHA, which can be problematic for individuals with sensitivity to marine sources or following plant-based diets, as their intake of these fatty acids is often insufficient.[9] In response to this nutritional gap, Ahiflower oil, extracted from the seeds of *Buglossoides arvensis*, has emerged as a promising plant-derived alternative.[15] This oil has a distinctive composition of omega-3 fatty acids, particularly a very high concentration of stearidonic acid (SDA; 18:4*n*-3) and γ-linolenic acid (GLA; 18:3*n*-6) compared to marine and other plant sources (Table 1).[15,16] The composition of Ahiflower oil allows it to overcome certain metabolic hurdles in omega-3 synthesis, potentially enhancing its absorption and utilization in the body, which may contribute to its neuroprotective potential.[15]

In addition to examining Ahiflower oil, this review also investigates the potential synergistic or additive effects of oleic acid (OA), a monounsaturated omega-9 fatty acid, known for its anti-inflammatory properties and role in supporting neuronal development.[17] By analyzing the combined effects of Ahiflower oil and oleic acid, the aim is to provide a comprehensive understanding of how different types of fatty acids interact to promote brain health and cognitive function. This approach considers the complex interplay between omega-3, omega-6, and omega-9 fatty acids in neuroprotection with a particular focus on their roles in modulating the gut-brain axis and reducing neuroinflammation.

This review will explore the fatty acid profiles of Ahiflower oil and oleic acid, focusing on their underlying mechanisms of action and potential synergistic interactions. This review also examines how these fatty acids may influence the production of short-chain fatty acids (SCFAs), key microbial metabolites that are emerging as agonists in modulating the brain lipidome, inducing neuronal cell death, and affecting mitochondrial morphology and physiological function.[18] In contrast, other research has shown that SCFAs play a role in maintaining gut barrier integrity and reducing neuroinflammation. By interacting with the gut microbiome, Ahiflower oil and oleic acid may promote cognitive health through their effects on SCFA production, gut-brain axis modulation, and neuroprotective mechanisms.

2. Ahiflower Oil: A Novel Plant-Based Omega-3 Source

Ahiflower oil, extracted from the seeds of *Buglossoides arvensis*, is gaining recognition as a potent natural product for enhancing brain health.[15] This natural product has garnered attention due to its distinctive omega fatty acid composition, positioning it as a compelling plant-based alternative to conventional marine-derived oils. Its distinctive omega fatty acid composition, particularly the presence of stearidonic acid (SDA), positions Ahiflower oil as a unique dietary therapeutic option for supporting brain health and cognitive function.[15]

2.1 Fatty Acid Composition and Metabolic Advantages

Ahiflower oil demonstrates a distinctive fatty acid composition, with omega-3 fatty acids constituting the highest proportion (66.67%) among common plant-derived oils, as shown in Figure 1 and detailed in Table 1. The oil's omega-3 content comprises 46.1-47.9% α-linolenic acid (ALA; 18:3*n*-3) and 17.3-20.1% stearidonic acid (SDA) while its omega-6 fatty acids includes 11.4-11.8% linoleic acid (LA; 18:2*n*-6) and 4.9-5.8% gamma-linolenic acid (GLA).[19,20] The remaining composition consists of monounsaturated oleic acid (18:1*n*-9; 7.5-9.4%) and smaller amounts of saturated fatty acids, such as palmitic (16:0; 4.7-5.2%) and stearic (18:0; 1.8-1.9%) acids.[19,20] While chia seed oil shows comparable total omega-3 levels (59.8-63.8%), its higher omega-6 content (18.9-20.4%) results in a less favorable omega-6/omega-3 ratio of 1:3 compared to Ahiflower oil's 1:4 (Table 1).[19-21] The superior omega-3

profile of Ahiflower oil (63.4-68.0%) surpasses that of other renowned plant oils, including flaxseed (56.4-58.2%), echium (41.3-44.9%), and hemp seed (18-22.3%).[21-25] This composition, particularly the presence of SDA, which converts more efficiently to EPA than ALA, makes Ahiflower oil an attractive plant-based alternative for individuals seeking to increase their omega-3 intake without relying on marine sources.

In humans, the conversion of ALA to longer-chain *n*-3 PUFAs like EPA and DHA (omega-3 pathway) is limited by the inefficient activity of delta-6 desaturase.[16] Studies using stable isotope tracers have shown minimal increases in brain tissue levels of these fatty acids following ALA intake, demonstrating this metabolic inefficiency.[19,20] By providing SDA directly, Ahiflower oil allows consumers to bypass this metabolic bottleneck, potentially leading to greater tissue accumulation of longer-chain omega-3 PUFAs such as EPA and DPA (22:5*n*-3) in the brain.[15,16] Additionally, Ahiflower oil contains modest amounts of omega-6 fatty acids, including GLA, which may complement the omega-3 effects by supporting neuronal membrane integrity and modulating neuroinflammatory processes.[15]

A recent study investigated the effects of dietary supplementation with ALA and SDA on EPA status in humans.[26] The researchers found that SDA was significantly more effective than ALA in increasing EPA levels in vivo, with consumption of SDA leading to a substantial improvement in plasma EPA levels from 0.2% to 0.6% of total fatty acid methyl esters.[26] These findings suggest that SDA-rich plant oils may serve as an effective and sustainable alternative to marine-derived omega-3 sources for improving EPA status in humans.

Another crucial aspect of Ahiflower oil is its favorable omega-6 to omega-3 ratio.[15] Many dieticians and the American Heart Association recommend an optimal omega-6:3 balance between 1:1 and 3:1.[15] However, the typical Western diet often has a ratio between 10-20:11, primarily due to high consumption of omega-6-rich oils in processed foods. Ahiflower oil's 1:4 ratio of omega-6:3 fatty acids can help reset this balance, potentially mitigating the pro-inflammatory effects associated with excessive omega-6 intake.[15]

2.2 Neuroprotective Effects and Mechanisms

The neuroprotective potential of Ahiflower oil stems from the unique composition of polyunsaturated fatty acids (PUFAs), particularly its high content of stearidonic acid and α-linolenic acid.[27] As integral components of neuronal membranes, these omega-3 fatty acids regulate membrane fluidity and facilitate synaptic plasticity, neurotransmission, and cellular signaling pathways. Maintaining optimal levels of these essential fatty acids in brain tissue may help protect against neuroinflammation and oxidative stress, two key factors implicated in the development and progression of neurodegenerative diseases.[27]

Recent studies have demonstrated the neuroprotective effects of omega-3 fatty acids, particularly DHA and EPA. In a mouse model of Alzheimer's disease, DHA supplementation significantly reduced amyloid-β plaque burden by 40% and phosphorylated tau by 60% in the hippocampus.[28] This reduction in pathological markers was accompanied by enhanced cognitive function. Similarly, a study found that DHA supplementation, particularly at doses exceeding 900 mg/day for 5 months or longer, improved various aspects of memory and cognitive performance in individuals with mild cognitive impairment.[29] These findings show the importance of ensuring adequate intake of omega-3 fatty acids. While DHA is not directly present in plant-based sources, it can be synthesized from EPA, which is more efficiently produced from the SDA content found in some plant oils.[9,25,26]

The brain's fatty acid profile shows a high degree of evolutionary conservation across mammalian species, with arachidonic acid (AA; 20:4*n*-6) and DHA as the principal long-chain fatty acid.[4,28,29] DHA, in particular, is rapidly incorporated into neural phospholipid membranes and is concentrated in photoreceptors and synaptic signaling sites. This conservation suggests the critical nature of these fatty acids for brain function.[4,28,29]

In a human clinical trial, Ahiflower oil supplementation demonstrated the ability to enhance the production of interleukin-10 (IL-10), a cytokine with potent anti-inflammatory effects.[20] Participants who received the highest dose of Ahiflower oil (9.7 mL/day) showed a 45% increase in IL-10 production from lipopolysaccharide-stimulated whole blood samples. The ability of Ahiflower oil to boost IL-10 levels is significant for neuroprotection. IL-10 is important in regulating neuroinflammation, which is implicated in various neurodegenerative processes.[20]

Omega-3 fatty acids, including EPA and DHA, have been shown to reduce oxidative stress in neuronal cells by enhancing antioxidant enzyme expression and decreasing reactive oxygen species production.[30] The ability of Ahiflower oil to increase tissue EPA levels efficiently suggests it may offer similar neuroprotective benefits, positioning it as a promising plant-based alternative for cognitive enhancement and neuroprotection.[20]

In addition to omega-3s, Ahiflower oil contains omega-6 and omega-9 fatty acids, which are essential for brain health.[15,16,19,20] Omega-6s like linoleic acid can be metabolized into AA, playing a role in cellular signaling and neuroinflammation regulation.[30] Some gut bacteria can convert linoleic acid into conjugated linoleic acids (CLA), which have anti-inflammatory properties, potentially benefiting neuroprotection.[31]

Omega-9 fatty acids are known for their anti-inflammatory effects.[17] Research using male Wistar rats demonstrated that a high omega-9 diet (17.5% for 90 days) significantly reduced pro-inflammatory cytokines like IL-1β, TNF-α, and MCP-1, suggesting omega-9's role in modulating inflammation, a key factor in neurodegenerative diseases.[17]

Based on the given evidence, Ahiflower oil offers a promising plant-based alternative to traditional marine-based omega-3 sources. As dietary trends increasingly prioritize sustainability, incorporating Ahiflower oil could enhance cognitive resilience and potentially delay the onset of neurodegenerative conditions.[9,15] This aligns with current nutritional strategies focused on optimizing fatty acid intake for neurological health and longevity.[7] The varied fatty acid composition of Ahiflower oil provides a comprehensive approach to neuroprotection, making it an option for those seeking to support brain health. Its unique profile offers a holistic solution that may contribute to reducing the risk of cognitive decline and promoting overall neurological well-being.

3. Synergistic Effects of Omega Fatty Acids on Brain Health

When selecting plant-based oils, the proportion of omega-3, omega-6, and omega-9 fatty acids should be a primary consideration. Oils rich in omega-3 fatty acids are generally considered more beneficial for brain health promotion.[15,16] However, only a few plant sources, such as Ahiflower and flaxseed oils, contain a predominant omega-3 component. Many other plant oils may inadvertently contribute to an excess of omega-6 fatty acids, as they typically contain higher levels of omega-6 compared to omega-3.[15] While omega-9 fatty acids offer health benefits in any quantity, achieving the right balance between these fatty acids is crucial, with omega-3s emerging as a key factor in this equilibrium.[32]

Oleic acid (OA; 18:1*n*-9), a monounsaturated omega-9 fatty acid, contributes significantly to brain development and protection.[17,32] Although the body can synthesize omega-9 fatty acids, their dietary intake can substantially impact health outcomes. OA contributes to myelin formation, which is essential for insulating nerve fibers and ensuring efficient signal transmission in the brain.[17,32] During neural development, OA acts as a neurotrophic factor, promoting axonal growth and synapse formation.[32] It interacts with peroxisome proliferator-activated receptors (PPARs), which are needed for neuronal differentiation. Studies have shown that OA's activation of PPARα upregulates proteins involved in neuronal growth, supporting brain development.[33]

Recent studies have shown OA's ability to reduce amyloidosis and attenuate microglial inflammatory responses, offering neuroprotection after cerebral ischemia.[34] It enhances neurogenesis by activating the TLX protein within neural stem cells, which supports learning, memory, and mood regulation.[35] These properties make OA a promising candidate for therapeutic strategies targeting neurodegenerative diseases such as Alzheimer's.

OA, in conjunction with omega-3 fatty acids like docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), enhances anti-inflammatory responses in the brain.[30,32] The anti-inflammatory properties of these fatty acids work synergistically to modulate microglial activation and reduce the production of pro-inflammatory cytokines.[32]

Integrating these fatty acids into our diet could be a valuable strategy for preventing or mitigating the effects of neurological disorders and promoting brain health. The combination of oleic acid with polyunsaturated fatty acids (PUFAs) in Ahiflower oil provides a balanced approach to maintaining homeostasis and preventing inflammation-related damage in the brain.[15,20,34]

Further research is needed to explore these interactions fully, but the promising results underscore the importance of these fatty acids in maintaining cognitive function and preventing neurodegenerative diseases.

4. The Microbiome-Gut-Brain Axis (MGBA) and Dysbiosis

The microbiome-gut-brain axis (MGBA) is a complex communication network linking the gut microbiota with brain function and behavior.[36,37] This bidirectional system allows signals from the brain to influence gut functions while metabolites from the gut microbiome affect brain development and function.[36] The human intestinal microbiome is highly diverse, comprising more than 1,000 bacterial species, with *Firmicutes* and *Bacteroidetes* making up approximately 90% of this population.[5,36,37] These bacteria maintain MGBA homeostasis through their crucial roles in gastrointestinal, immune, and neural functions.[5,37]

4.1 Communication in the MGBA

Communication within the MGBA occurs through several complex pathways that transmit sensory information from the gastrointestinal (GI) tract, converting it into hormonal, neural, and immunological signals.[37] These pathways encompass a network involving the gut lumen, intestinal epithelium, lamina propria, and ultimately the brain (Figure 2A).[37,38] The communication channels include chemical signaling via microbial metabolites, neurotransmitters, and hormones; neural pathways involving the vagus nerve; and immune system interactions via microglia-mediated effects and circulating cytokines.[37]

The gut lumen hosts a diverse microbial community where beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* maintain a balanced *Firmicutes*/*Bacteroidetes* (*F/B*) ratio.[36,37] These microorganisms are responsible for producing short-chain fatty acids (SCFA), including acetate (C2), propionate (C3), and butyrate (C4), through bacterial fermentation of dietary fibers in the colon.[18,36,37] These SCFAs are present in a natural molar ratio of 60:20:20 in healthy individuals and are essential for maintaining intestinal barrier integrity, mucus production, and anti-inflammatory effects.[18] Under normal conditions, systemic concentrations are approximately 60-100 µM for total short-chain fatty acids (SCFAs), with specific levels of 150-200 µM for acetate, 3-5 µM for propionate, and 7-9 µM for butyrate.[18] They can cross the blood-brain barrier (BBB), influencing microglial homeostasis and potentially modulate behavior.[18,36,37]

The intestinal epithelium comprises several specialized cell types, including enteroendocrine cells, goblet cells, and Paneth cells, each serving distinct functions in the MGBA.[36] Enteroendocrine cells act as sensory transducers, while goblet cells produce protective mucus, and Paneth cells secrete antimicrobial peptides.[36,37] This epithelial barrier

maintains tight junction integrity, allowing selective passage of beneficial compounds while preventing harmful substances from entering the circulation.[36]

Within the lamina propria, immune cells including macrophages, dendritic cells, and T cells interact with the enteric nervous system (ENS) and vagus nerve terminals, forming a complex communication network.[38] These immune cells work alongside beneficial gut microbiota to maintain homeostasis. The ENS, supported by astrocytes and other glial cells, forms an intricate network where the gut microbiota produces neurotransmitters such as gamma-aminobutyric acid (GABA), acetylcholine, noradrenaline, dopamine, and serotonin.[37,38] These neurotransmitters modulate neural signaling within the enteric nervous system (ENS) and can influence central nervous system (CNS) function through mechanisms like vagus nerve stimulation. Approximately 80-90% of vagal nerve fibers are afferent, carrying information from the gut to the brain.[36] These fibers can be activated by various gut-derived signals, including microbial metabolites and inflammatory mediators, as seen in Figure 2A, where beneficial metabolites interact with vagus nerve terminals. In healthy conditions, this communication supports optimal synaptic function and cognitive vitality.[36,37] The vagus nerve thus acts as a critical conduit for transmitting both beneficial and potentially harmful signals from the gut to the brain.[36] For instance, in Parkinson's disease, research has shown that alpha-synuclein aggregates can travel from the gut to the brain via the vagus nerve, potentially initiating or contributing to disease progression.[39] This is supported showing that individuals who underwent vagotomy (surgical removal of parts of the vagus nerve) had a significantly lower risk of developing Parkinson's disease, demonstrating the role of the vagus nerve in disease pathogenesis.[39] This entire network contributes to neuroprotection and enhanced neuroplasticity when functioning properly.

The immune aspect of this communication network holds significant importance, with microglia acting as the primary immune cells within the central nervous system (CNS).[5,36-38] These cells can be stimulated by signals originating from the gut, which in turn prompts the release of pro-inflammatory cytokines that influence the functioning of the hypothalamic-pituitary-adrenal (HPA) axis.[36-38] Such immune interactions are essential for maintaining homeostasis, as they ensure a balanced production of cytokines and regulate inflammatory responses, thereby supporting neuroprotection and promoting neuroplasticity (Figure 2A).

This intricate network of neural, immune, and endocrine communication pathways demonstrates the relationship between the gut and brain.[38] When functioning properly, these pathways collaborate to sustain optimal brain health through various mechanisms, such as the synthesis of neurotransmitters, immune system regulation, and the maintenance of barrier integrity. Understanding these complex interactions reveals the direct influence of gut health on neurological function and potential therapeutic targets for neurological disorders.[38]

4.2 Dysbiosis and Its Implications for Neurological Health

Gut dysbiosis—an imbalance in microbial composition—can disrupt the MGBA, leading to increased gut permeability and widespread inflammation.[17] As shown in Figure 2B, this condition involves a shift from beneficial microbiota (e.g., *Bifidobacterium*, *Lactobacillus*) to pathogenic microbiota (e.g., *Clostridium difficile*, *Ruminococcus*), resulting in a disrupted (*F/B*) ratio and elevated lipopolysaccharide (LPS) level.[17,36,37] These changes alter the intestinal environment, compromising barrier integrity and increasing BBB permeability.[17]

The dysbiotic state has been linked to various neurological disorders, including Alzheimer's and Parkinson's diseases—both characterized as proteinopathies due to abnormal protein aggregation such as amyloid-beta in Alzheimer's or alpha-synuclein in Parkinson's.[40] Proteinopathies involve proteins that misfold and aggregate into toxic structures within neurons or brain tissue. Dysbiosis-induced inflammation exacerbates these conditions by promoting protein misfolding through immune pathways that increase cytokine production.[36,40]

In these conditions, specifically in the gut lumen, decreased levels of beneficial metabolites (butyrate, propionate, acetate) and increased inflammatory compounds lead to dysfunction of the intestinal barrier.[18] SCFA concentrations fluctuate from 20 µM to over 1 mM[76], with propionate levels rising as high as 100 µM in pathological states, compared to control levels below 10 µM.[18] These elevated SCFA concentrations are indicative of gut microbiota imbalances and may contribute to neurodegenerative processes by impacting brain lipid metabolism and mitochondrial function.[18,37]

The compromised intestinal barrier allows increased translocation of harmful substances, leading to inflammation in the lamina propria (Figure 2B).[37-39] This inflammatory environment triggers the production of pro-inflammatory cytokines (IL-10, IL-6, IL-1β, TNF-α), creating a state of neuroinflammation and oxidative stress.[37,38] The altered microbial landscape favors the development of pro-inflammatory T cells (e.g., Th17) over regulatory T cells (Tregs), activating toll-like receptors (TLRs) and initiating an inflammatory cascade that extends beyond the gut.[36]

These inflammatory changes have been linked to various neurological disorders, particularly Alzheimer's (AD) and Parkinson's (PD) diseases. In AD, gut barrier dysfunction leads to peripheral inflammation, where inflammatory cytokines like IL-1β reduce amyloid-beta (Aβ) phagocytosis.[41] The inflammatory state activates the NLRP3-inflammasome, releasing caspase-1 and IL-18, which increase amyloid-beta deposits. These changes ultimately result in cognitive impairment and neuronal damage (Figure 2B).[41]

In PD patients, research has revealed lower fecal concentrations of acetate, propionate, and butyrate compared to controls, while plasma concentrations were elevated.[42] The increased plasma propionate levels correlate with disease severity, suggesting that altered SCFA absorption may contribute to neurodegeneration. These changes, combined with increased BBB permeability shown in Figure 2B, create an environment conducive to neurological dysfunction.[42]

The dysbiotic state plays a role in the development and progression of neurological disorders.[36] Alterations in microbial diversity, weakened protective barriers, and increased inflammatory responses, establishes an environment that significantly affects brain health.[36,37] These changes result in cognitive deficits, neuroinflammation, and oxidative stress, ultimately causing neuronal injury.[36,37]

4.3 Effects of Omega-3, -6, and -9 Fatty Acids on the MGBA

The intricate relationship between dietary fatty acids, gut microbiota, and overall health has become a focal point of research in recent years. While the exact causal relationship between gut microbiota and various pathological conditions remains unclear, it is evident that dietary habits significantly influence the composition of gut microbiota.[18,38,40,43] This microbial community plays a role in metabolizing dietary lipids, potentially impacting both gut and systemic health.[18]

In a healthy gut, omega-3 fatty acids, particularly EPA and DHA, have been shown to increase the abundance of beneficial bacteria such as *Bifidobacterium*, *Lactobacillus*, *Akkermansia*, and butyrate-producing bacteria like *Eubacterium*, *Roseburia*, and *Coprococcus*.[5,36] This shift in microbial composition may contribute to the beneficial effects of omega-3 fatty acids on health.[36] Moreover, a balanced intake of omega-3 and omega-6 fatty acids is associated with higher gut microbiome diversity, which is linked to better overall health.[32,36]

The gut microbiome's ability to biotransform dietary lipids adds another layer of complexity to understanding their effects on host health.[18] For instance, while omega-6 fatty acids are often associated with pro-inflammatory effects, some gut bacteria can convert linoleic acid (an omega-6) to conjugated linoleic acid, which has anti-inflammatory

properties.[32,43] This microbial modification of fatty acids may contribute to individual variability in susceptibility to metabolic disorders and inflammatory diseases.[43]

In dysbiotic conditions, the interplay between omega-3, omega-6, and omega-9 fatty acids becomes even more crucial.[32] Omega-3 PUFAs can help revert the microbiota composition in inflammatory bowel diseases, increasing the production of anti-inflammatory compounds like short-chain fatty acids.[32,36] They have also been shown to decrease the *Firmicutes*-to-*Bacteroidetes* ratio, which is often elevated in obesity and other metabolic disorders.[36,43] Conversely, high omega-6 intake, particularly in the context of a Western diet, can contribute to dysbiosis, reducing bacterial diversity and increasing pro-inflammatory taxa.[43]

Omega-9 fatty acids, primarily oleic acid, demonstrate significant beneficial effects on gut health, working synergistically with Ahiflower oil to enhance neuroprotection through their complementary actions (Figure 2C).[32,43] While oleic acid supports intestinal barrier integrity and reduces inflammation, its combination with Ahiflower oil's unique blend of omega fatty acids (18:3*n*-3, 18:4*n*-3, and 18:3*n*-6) creates a powerful synergistic effect that promotes optimal gut-brain communication.[5] This synergy suggests that oleic acid's benefits may be enhanced when combined with other beneficial fatty acids, though further research is needed to fully understand the molecular mechanisms underlying these interactions, particularly in the context of dysbiosis.

Overall, a balanced intake of omega-3, omega-6, and omega-9 fatty acids appears to be beneficial for maintaining a healthy gut microbiome and potentially reversing dysbiosis.[32] These fatty acids, particularly those found in Ahiflower oil and oleic acid, show promise in promoting beneficial bacteria and reducing inflammation in dysbiotic conditions to support optimal gut-brain communication (Figure 2C). However, more research is needed to fully understand the complex interactions between these fatty acids and the gut microbiome, especially in the context of various health conditions and neurological disorders.[43]

5. Integration of Research Implications

This review has explored the intricate relationships between polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids (MUFAs), the gut microbiota, and neurodegenerative diseases. Recent findings show the significant roles of omega-3, omega-6, and omega-9 fatty acids in preserving neurological health and shaping the gut microbiome composition.[32]

The gut microbiome has been identified as a component in lipid metabolism, influencing both the utilization and production of fatty acids.[5,43] Advances in chemical analysis and lipidomics have enhanced our understanding of how lipids impact human health.[43] Microbial-derived lipids can directly affect host cells through metabolic and immunological mechanisms, influencing chronic inflammation, autoimmune disorders, cardiovascular function, and metabolic health.[43]

The ratio of omega-6 to omega-3 fatty acids may be more critical than their absolute quantities in modulating neuroinflammation and oxidative stress.[15,43] This balance appears to influence the composition of the gut microbiome, which in turn affects the production and absorption of short-chain fatty acids (SCFAs).[43] These SCFAs have been shown to cross the blood-brain barrier and directly impact neuronal function, potentially offering a novel pathway for therapeutic interventions in neurodegenerative diseases.[18,38,40,43]

The interaction between omega-9 fatty acids and the gut microbiome has revealed unexpected effects on the enteric nervous system, which may indirectly influence central nervous system function through the gut-brain axis.[18,38] This finding suggests that the traditional focus on direct brain effects of fatty acids may be too narrow, and a more holistic approach considering the entire neuroendocrine system could yield new perspectives on disease prevention and treatment.

Recent studies have stated the individual and potentially complementary roles of omega-3, omega-6, and omega-9 fatty acids in brain health and function.[32] While research on their combined effects is limited, evidence suggests that these fatty acids can influence various aspects of neuronal health, including gene expression patterns related to neuroplasticity and neuroprotection.[32]

While many individuals consume adequate amounts of omega-6 fatty acids, there is often a deficiency in omega-3 and omega-9 intake.[32] Balancing these fatty acids in the diet can be achieved through simple dietary modifications. Incorporating Ahiflower oil, a novel plant-based oil rich in omega-3 and omega-6 content, provides a good alternative to fatty fish.[15,26] These dietary adjustments may contribute to maintaining the health of various organs, including the brain, and potentially mitigate the risk of neurodegenerative diseases.

6. Conclusion and Future Directions

The findings of this comprehensive review underscore the role of omega fatty acids in neurological health and the relationship between dietary lipids, gut microbiota, and brain function. Ahiflower oil emerges as a promising plant-based alternative to traditional marine-derived omega-3 sources, offering a fatty acid profile that may confer substantial neuroprotective benefits.[9,15,16] Therefore, this review concludes that the synergistic effects of omega-3, omega-6, and omega-9 fatty acids, particularly when combined in optimal ratios, appear to regulate neuroinflammation, oxidative stress, and microbiome composition in ways that could potentially mitigate the risk of neurodegenerative diseases.[32]

Despite the promising findings, several limitations in current research must be acknowledged. Many studies have been short-term and focused on specific populations, which limits our understanding of the long-term impacts of these fatty acids on brain health and the gut-brain axis.[11,16,19,20] The effects of various factors such as age, health status, and genetic background on the efficacy and safety of increased omega 3, -6, and -9 consumption remain unclear.[5,30,36,37] Many studies focus on individual omega fatty acids rather than their combined effects, making it difficult to understand how omega-3, omega-6, and omega-9 interact in the context of the gut-brain axis.[5,32] This approach overlooks the potential synergistic or antagonistic effects that may occur when these fatty acids are consumed together, as they typically are in a balanced diet. While associations between fatty acid intake and neurological health have been observed, the precise mechanisms underlying these effects are not fully understood.[5,37,40] More research is needed to understand the molecular and cellular pathways through which these fatty acids influence brain function and gut-brain communication.

To address these limitations, future research should conduct longer-term studies across diverse populations, investigating the combined effects of omega fatty acids, and further exploring the molecular and cellular pathways through which these fatty acids influence brain function and gut-brain communication. Investigation into potential interactions with medications commonly used in neurodegenerative diseases is also necessary. Research should focus on determining the optimal ratios of omega-3, omega-6, and omega-9 fatty acids for different health conditions and age groups.

Research on the gut-brain axis and the impact of dietary lipids on neurological health continues to reveal the potential of omega-3, omega-6, and omega-9 fatty acids in preventing and managing neurodegenerative diseases.[32] Addressing current research gaps will enable the development of targeted, evidence-based dietary strategies that harness these essential nutrients to improve brain health and combat neurological disorders. The fatty acid profiles found in plant-based sources offer promising avenues for further investigation, potentially leading to more effective approaches in supporting cognitive function and overall neurological well-being.

7. CRediT authorship contribution statement

Anita Fuambi: Conceptualization; Writing - original draft; Writing - review & editing; Visualization. Ramak Esfandi: Writing - review & editing; Proofreading. Raymond H. Thomas: Supervision; Conceptualization; Writing - review & editing; Proofreading.

8. Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. Fatty acid composition, including individual and total fatty acid ranges, and omega-6/omega-3 ratios of selected plant-derived oils from *Buglossoides arvensis* (Ahiflower), *Linum usitatissimum* (Flaxseed), *Salvia hispanica* (Chia Seed), *Cannabis sativa* (Hemp Seed), and *Echium plantagineum* (Echium). Values compiled from literature presents ranges of individual fatty acids (C16:0 to C18:4), totals of saturated (SFAs), monounsaturated (MUFAs), and polyunsaturated fatty acids (PUFAs), as well as omega-6/omega-3 ratios, all expressed as percentage of total fatty acids, to show the nutritional significance of these plant-derived oils.

Fatty Acids	Ahiflower Oil[19,20]	Flaxseed Oil[21]	Chia Seed Oil[21]	Hemp Seed Oil[22,23]	Echium Oil[24,25]
Palmitic acid (16:0)	4.7-5.2	5.1-5.4	7.0-7.1	5.9-6.1	6.9-7.0
Stearic acid (18:0)	1.8 -1.9	3.2-3.3	2.8-3.2	2.2-2.5	3.6-3.9
Oleic acid (18:1*n*-9)	7.5-9.4	18.1-18.7	7.3-10.5	9.0-10.7	15.2-15.5
Linoleic acid (18:2*n*-6)	11.4-11.8	15.3-16.1	18.9-20.4	55.3-55.9	15.2-16.5
Alpha-linolenic acid (18:3*n*-3)	46.1-47.9	56.4-58.2	59.8-63.8	16.7-20.3	30.2-32.8
Gamma-linolenic acid (18:3*n*-6)	4.9-5.8	-	-	4.0-4.4	10.4-10.8
Stearidonic acid (18:4*n*-3)	17.3-20.1	-	-	1.3-2.0	11.1-12.1
Total SFAs	6.5-7.1	8.3-8.7	9.8-10.3	8.1-8.6	10.5-10.9
Total MUFAs	7.5-9.4	18.1-18.7	7.3-10.5	9.0-10.7	15.2-15.5
Total PUFAs	79.7-85.6	71.7-74.3	78.7-84.2	77.3-82.6	66.9-72.2
Omega-6: Omega-3 ratio	1:3.9	1:3.6	1:3.1	2.7:1	1:1.6

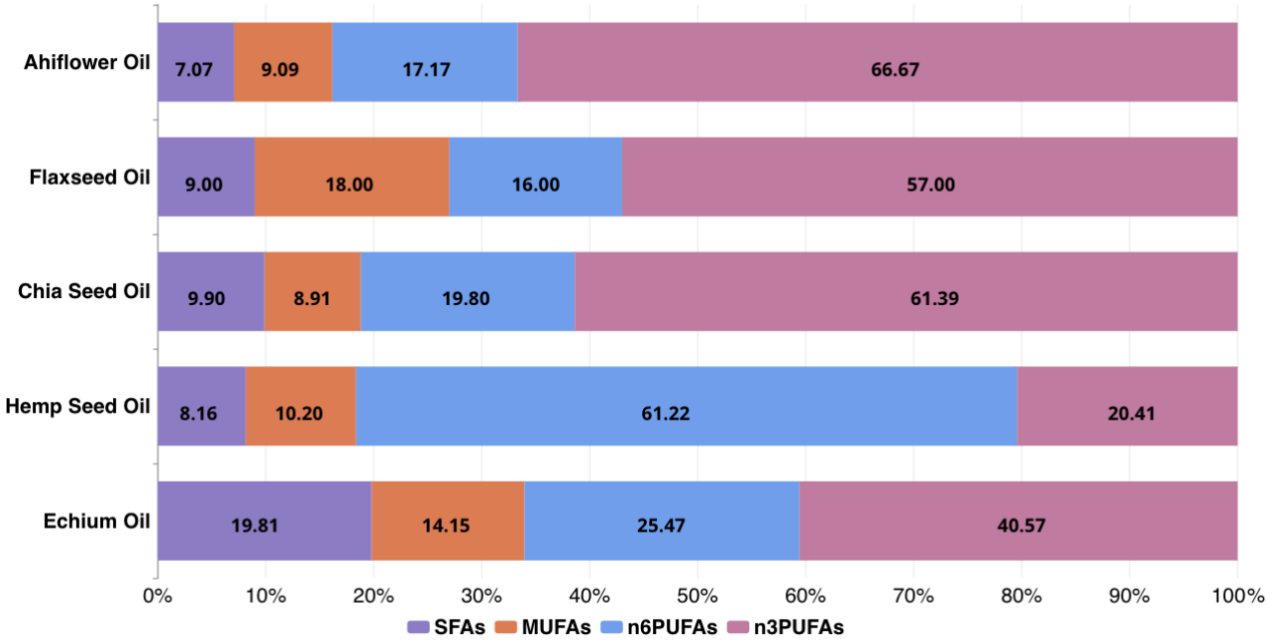


Figure 1. Comparative Fatty Acid Profiles of Plant-Derived Oils. Normalized fatty acid composition (100% stacked horizontal bars) shows the distribution across five plant-derived oils: *Buglossoides arvensis* (Ahiflower), *Linum usitatissimum* (Flaxseed), *Salvia hispanica* (Chia Seed), *Cannabis sativa* (Hemp Seed), and *Echium plantagineum* (Echium). Data represents averaged values from Table 1 compiled from literature sources, demonstrating the relative distribution of major fatty acid classes. Fatty acid classes are represented as: saturated fatty acids (SFA: palmitic acid C16:0, stearic acid C18:0); monounsaturated fatty acids (MUFA: oleic acid C18:1*n*-9); omega-3 polyunsaturated fatty acids (n3PUFA: α-linolenic acid C18:3*n*-3, stearidonic acid C18:4*n*-3); and omega-6 polyunsaturated fatty acids (n6PUFA: linoleic acid C18:2*n*-6, γ-linolenic acid C18:3*n*-6). Figure created with Visual Paradigm.

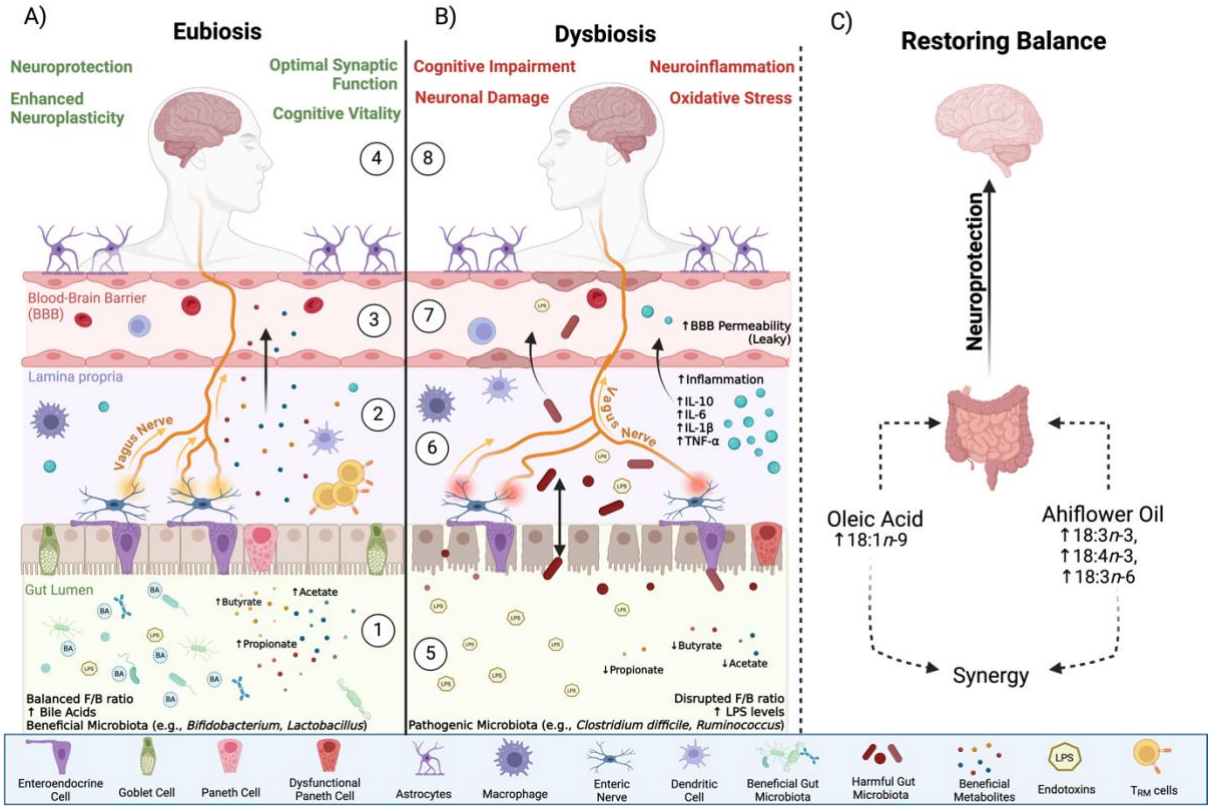


Figure 2. Microbiome-Gut-Brain Axis Conditions and Therapeutic Intervention in Neurological Health**.** In eubiotic conditions (A), the gut maintains a balanced *Firmicutes/Bacteroidetes* (*F/B*) ratio with beneficial microbiota (e.g., *Bifidobacterium*, *Lactobacillus*) in the gut lumen (1), producing optimal levels of metabolites like butyrate, propionate, and acetate. These metabolites support the integrity of the blood-brain barrier (BBB) (3) and enhance synaptic function and neuroplasticity (4), contributing to neuroprotection and cognitive vitality. Communication via the vagus nerve (2) plays a role in maintaining this balance. During dysbiosis (B), pathogenic microbiota such as *Clostridium difficile* and *Ruminococcus* proliferate, disrupting the *F/B* ratio and increasing lipopolysaccharide (LPS) levels (5). This leads to compromised BBB integrity (7), triggering neuroinflammation through elevated inflammatory markers like IL-10, IL-6, IL-1β, and TNF-α (6), resulting in neuronal damage, oxidative stress, and cognitive impairment (8). The therapeutic intervention (C) demonstrates the potential synergistic effects of oleic Acid (18:1n-9) and Ahiflower Oil, rich in omega-3 and omega-6 fatty acids, in promoting neuroprotection through modulation of the gut-brain axis. Figure created with BioRender.com.

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