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A Review on Neurodegenerative Diseases – The Effect of Omega-3 Fatty Acids on Neuroinflammation

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ABSTRACT: A nutritional approach could be a promising strategy to prevent or slow the progression of neurodegenerative diseases such as Parkinson's and Alzheimer's disease, since there is no effective therapy for these diseases so far. The beneficial effects of omega-3 fatty acids are now well established by a plethora of studies through their involvement in multiple biochemical functions, including synthesis of anti-inflammatory mediators, cell membrane fluidity, and intracellular signaling.

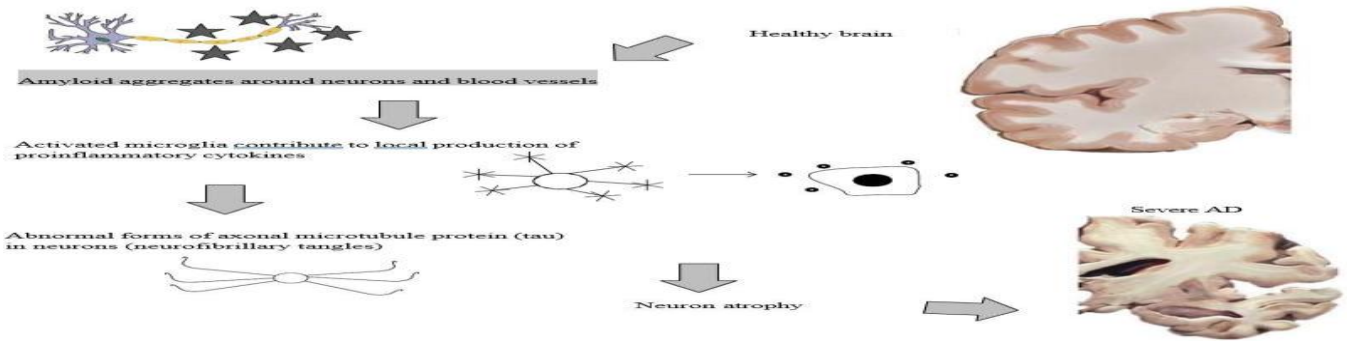
KEYWORDS: Omega-3 polyunsaturated fatty acids; Parkinson's disease; Alzheimer's disease; clinical trial.

I.INTRODUCTION

Several cerebral functions are determined by some nutrients, such as omega-3 polyunsaturated fatty acids (PUFAs), which are parts of the plasma membrane implicated in several processes, including increased synaptic development and functionality, effects on synaptic integrity and plasticity , contributing to neuroplasticity and subsequent enhancement of cognitive activity . There is accumulating scientific evidence on the possible efficacy of PUFAs supplementation in neurodegenerative disorders, such as Parkinson's (PD) and Alzheimer's disease (AD). Although dietary recommendations are far from being a treatment for PD or AD, they may be able to alleviate some of the symptoms or slow the cognitive and physical decline.

What Is Alzheimer's Disease?

Pathophysiology of Neurodegenerative Diseases. Neurodegenerative diseases represent major unmet challenges for therapeutic intervention. Neurodegenerative disorders can be considered in 3 main groups: (1) protein misfolding disorders, (2) mechanical injury and ischemia-reperfusion injury, and (3) myelin and lipid storage disorders. These disorders arise from inflammatory, neurodegenerative, metabolic, or ischemic primary insults. Generally, the risk of developing a neurodegenerative disease increases with aging.



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II.BACKGROUND

Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), represent a significant public health burden, especially among the aging population. These disorders are marked by progressive neuronal loss, cognitive dysfunction, and structural degeneration of the brain. While the clinical features and pathological mechanisms of AD and PD differ—AD is characterized by amyloid-beta plaques and neurofibrillary tangles, while PD is defined by dopaminergic neuronal loss and α-synuclein aggregation—both conditions share common underlying processes, including neuroinflammation, mitochondrial dysfunction, and oxidative stress.

An increasing body of evidence highlights the role of nutritional factors in influencing the onset and progression of these neurodegenerative conditions. Omega-3 polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and docosapentaenoic acid (DPA), have attracted attention for their essential roles in brain development, synaptic plasticity, and inflammatory regulation. DHA is the most prevalent omega-3 PUFA in the brain, enriched in phosphatidylethanolamine and phosphatidylserine within neural membranes. EPA and DPA, though present in lower concentrations, may play specialized roles, particularly in signaling and lipid mediator synthesis. Age-related reductions in DHA levels have been observed in both AD patients and the aging brain, suggesting a possible link between omega-3 depletion and cognitive decline.

Notably, the transport of these fatty acids into the brain is a tightly regulated process. Unlike other nutrients, PUFAs require specific carrier molecules such as LysoPC-DHA and AceDoPC to cross the blood-brain barrier effectively. The unique fatty acid composition of the brain—high in DHA and arachidonic acid but low in EPA—points toward a highly selective enrichment process that may reflect the functional importance of these molecules in neuronal integrity and function. Furthermore, preclinical studies have shown that various PUFAs, including AA and DPAn-6, can bind to nuclear receptors like RXR, supporting the notion that their roles extend beyond structural incorporation to active signaling modulation.

III.METHODOLOGY AND DISCUSSION

To better understand the potential therapeutic effects of omega-3 fatty acids in neurodegenerative diseases, a variety of research methodologies have been employed. Clinical studies have primarily used oral supplementation of DHA, EPA, or mixed formulations in subjects ranging from healthy elderly individuals to patients with mild cognitive impairment (MCI) or established Alzheimer's disease. These trials have typically lasted from several weeks to over a year and involved cognitive assessments such as the Mini-Mental State Examination (MMSE), paired associate learning tasks, and memory recall evaluations. In some cases, plasma and erythrocyte fatty acid levels were measured to correlate biochemical changes with cognitive performance.

Preclinical studies, particularly in animal models of Parkinson's disease, have investigated the neuroprotective capacity of EPA and DHA. For example, one study administered a diet containing 0.8% EPA to mice and observed protective effects against a Parkinsonian neurotoxin. These studies have also highlighted the importance of understanding PUFA metabolism within the brain. Although EPA and DHA can cross the blood-brain barrier via passive diffusion, their levels in the brain are maintained not just by uptake but also through differential incorporation, elongation, oxidation, and phospholipid recycling mechanisms.

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The discussion surrounding DHA is complex; while it is widely recognized for its anti-inflammatory and synaptic-supportive properties, emerging evidence suggests that under certain conditions, DHA may contribute to α-synuclein aggregation, which is implicated in PD pathology. This dual nature underscores the importance of dosing, timing, and individual variability when considering omega-3 interventions for neurodegenerative conditions. Moreover, the presence of DHA, EPA, and DPA in different phospholipid subclasses of brain tissue may indicate unique functional roles that are not yet fully understood.

IV. SCOPE OF THE RESEARCH

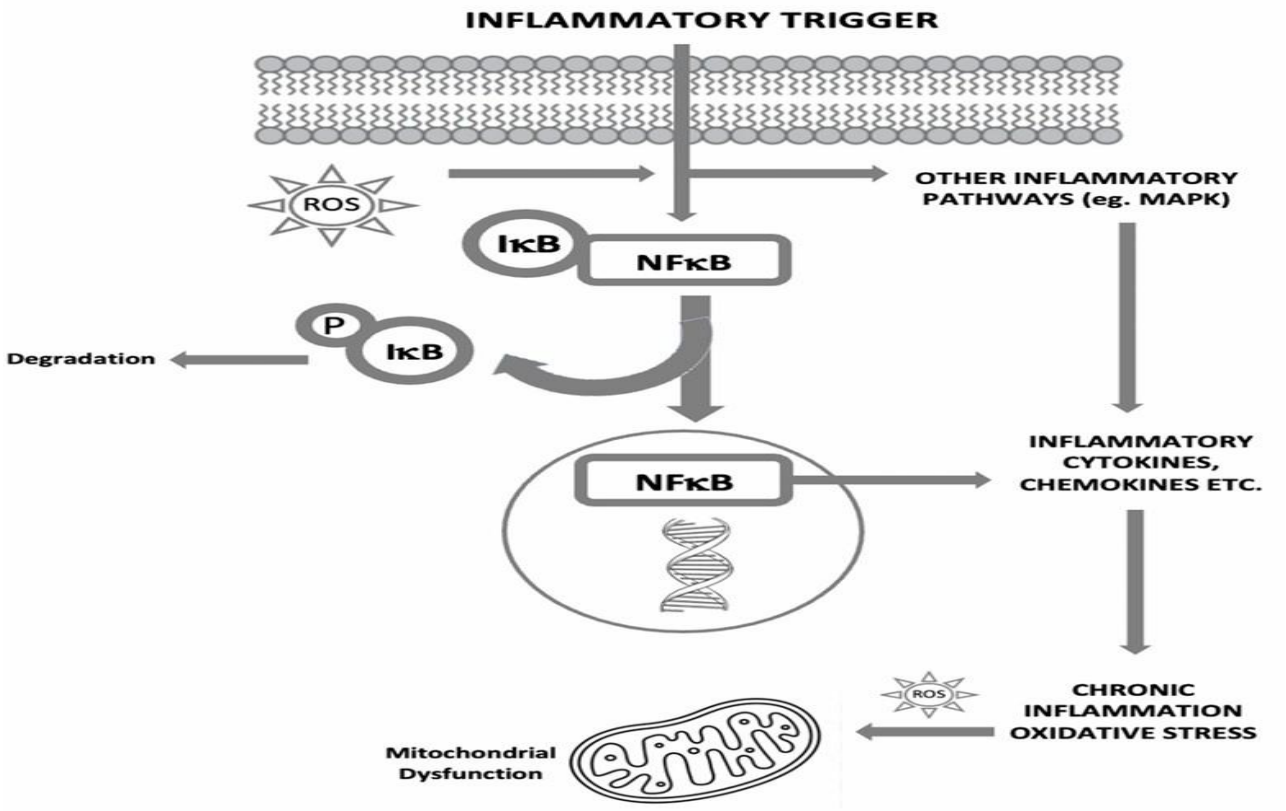

Figure: 02

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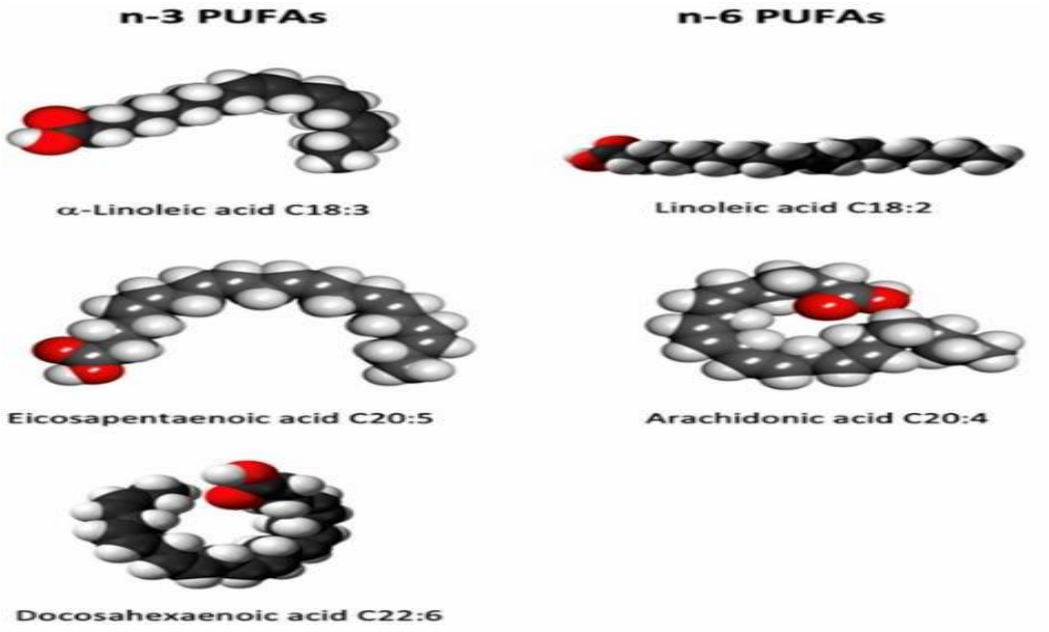
This review paper aims to evaluate the therapeutic relevance of omega-3 fatty acids in managing and potentially modifying the course of neurodegenerative diseases. It encompasses both Alzheimer's and Parkinson's diseases, considering their shared pathological mechanisms and the unique contributions of DHA, EPA, and DPA. The paper explores the nutritional modulation of brain function through dietary intake and supplementation of omega-3 PUFAs, examining their transport, metabolism, and interaction with cellular pathways in the central nervous system. Additionally, this study emphasizes the importance of personalized approaches in nutritional neuroscience, considering factors such as genetic predisposition, age, disease stage, and carrier mechanisms involved in PUFA delivery to the brain.

The goal is not only to summarize existing findings but also to highlight gaps in current research, especially the lack of large-scale, well-controlled clinical trials specifically focused on highly purified formulations of individual fatty acids. Through this synthesis, the study advocates for further investigation into targeted nutritional strategies that could serve as preventive or adjunctive therapies in neurodegenerative diseases.

V.EXPERIMENTAL RESULTS

A range of experimental outcomes across clinical and preclinical studies provides insight into the effectiveness of omega-3 fatty acids. In Alzheimer's research, a randomized controlled trial administering 2 grams of DHA per day over 18 months in patients with mild to moderate AD found no significant difference in cognitive decline compared to the placebo group, although a subgroup of ApoE4 non-carriers showed marginal benefits. Similarly, EPA supplementation at 1 gram per day in an open-label study increased erythrocyte EPA and DPA levels without improving cognitive scores. However, more encouraging results have been observed in healthy elderly individuals and patients with MCI. For example, a study with 900 mg of DHA over 24 weeks led to significant improvements in verbal memory and learning performance. Combinations of DHA and EPA, such as 1.3 g + 0.45 g and 1.7 g + 0.6 g respectively, administered over 6 to 12 months, resulted in enhanced short-term and working memory functions.



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In Parkinson's disease models, mice receiving EPA-enriched diets demonstrated reduced neurotoxin-induced damage. Nevertheless, the translation of these findings to clinical practice remains limited. A study on schizophrenia patients with tardive dyskinesia using 2 g/day EPA showed only mild, short-lived improvements in newly diagnosed individuals. Additionally, an ongoing clinical trial (NCT01563913) is evaluating DHA's role in mitigating dyskinesias in PD. While these efforts are promising, there remains a need for caution, as some experimental data suggest DHA may exacerbate protein aggregation under certain conditions, raising concerns about safety in vulnerable populations.

VI.CONCLUSION

Neurodegenerative diseases like Parkinson's and Alzheimer's pose a growing global challenge, with current treatments largely limited to symptom management. Omega-3 fatty acids offer promising potential due to their anti-inflammatory and neuroprotective effects. While observational studies suggest a reduced disease risk with higher omega-3 intake, randomized trials have shown mixed results, possibly due to differences in study duration and disease stages. Individual responses and lifestyle factors also influence outcomes. Nevertheless, omega-3 supplementation is generally safe and may serve as a valuable component of early, personalized strategies for managing neurodegenerative conditions.

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