International Journal of Pharmacy and Industrial Research (IJPIR)
IJPIR | Vol.15 | Issue 2 | Apr – Jun - 2026
www.ijpir.com
ISSN: 2231-3656
DOI: https://doi.org/10.61096/ijpir.v15.iss2.2026.508-523

Review Article on Omega-3 Fatty Acids and Polysaccharides on Neurodegenerative Disorders

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Published by: 04.04.2026

Abstract: There is marked heterogeneity in the clinical response to omega-3 fatty acid therapy with many authors documenting futility in large-scale trials, secondary re-analysis, and meta-analysis. The question of failure in the context of omega-3 therapy is multifactorial and complicated by the observation that fish intake has been broadly linked to significant risk reductions across a range of conditions. The question that remains is how can we resolve the discrepancy between pre-clinical evidence and epidemiology, which dually emphasize the benefit of omega-3 therapy against the limited success of large-scale clinical trials and smaller scale clinical studies that do not consistently report benefit and may even report harm, especially as it pertains to atrial fibrillation. We present three primary considerations that may clarify the supposed failures of omega-3 therapy: 1) correction for omega-3:omega-6 ratio and competition, 2) variation in the fatty acid composition and quality of omega-3 products, and 3) fundamental concerns pertaining to the omega-3 vehicle and its impact on omega-3 metabolism. While the predominant source of omega-3 therapy is supplements, they are typically not regulated prior to market like drugs and have significant variability in fatty acid composition, vehicle, oxidation, and quality control. Further, the individual response to omega-3 therapy is likely variable and dependent on ambient dietary conditions and inherited differences in endogenous desaturase activity, which has infrequently been accounted for in large studies. The net effect of these concerns should engender pharmaceutical and consumer companies alike to consider 1) refining trial design and 2) consider the role of oxidation in the failure of omega-3 products.

Keywords: Omega-3 Fatty Acid Therapy, Omega-3, Fatty Acid

Introduction:-

A class of polyunsaturated fatty acids known as omega-3 fatty acids is necessary for human health maintenance, normal growth, and development Because the human body cannot synthesise them in sufficient numbers, they are referred to as necessary. They must therefore be acquired from diet. Alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are the three main forms of omega-3

fatty acids[1]. Green leafy vegetables, walnuts, chia seeds, mustard oil, and flaxseed are the primary plant sources of ALA. The main marine sources of EPA and DHA include fish oil, salmon, mackerel, sardines, and tuna. Cell membrane fluidity and appropriate cell signalling are maintained by omega-3 fatty acids, which are essential components of cell membranes. This characteristic makes them advantageous for inflammatory conditions such inflammatory bowel illness, asthma, and rheumatoid arthritis. Both visual development and brain function depend on these fatty acids. Adequate consumption of DHA is particularly crucial during pregnancy, infancy, and childhood because it is a fundamental structural component of the brain and retina. Omega-3 fatty acids Cellulose is a crucial part of dietary fibre and provides the structural underpinning for plant cell walls[2]. Cellulose is essential for preserving digestive health and avoiding constipation even though humans are unable to digest it[3]. Polysaccharides therefore play a major role in maintaining nutritional balance. Numerous naturally occurring polysaccharides have biological functions include wound-healing, immuno-modulatory, anti-inflammatory, and antioxidant qualities. For instance, pectin lowers cholesterol, while beta-glucans are believed to improve immunological response. The gelling and stabilising qualities of certain marine polysaccharides, such as alginate and carrageenan, make them useful in the food and pharmaceutical industries[4].Their significance in therapeutic applications is increased by these functional characteristics. Polysaccharides are widely employed as excipients in formulation develop-ment in the pharmaceutical sciences. They serve as stabilisers, thickeners, suspending agents, disintegrates, and binders. Drug delivery systems that are regulated and sustained make use of natural polymers such chitosan, alginate, dextran, and xanthan gum[5].

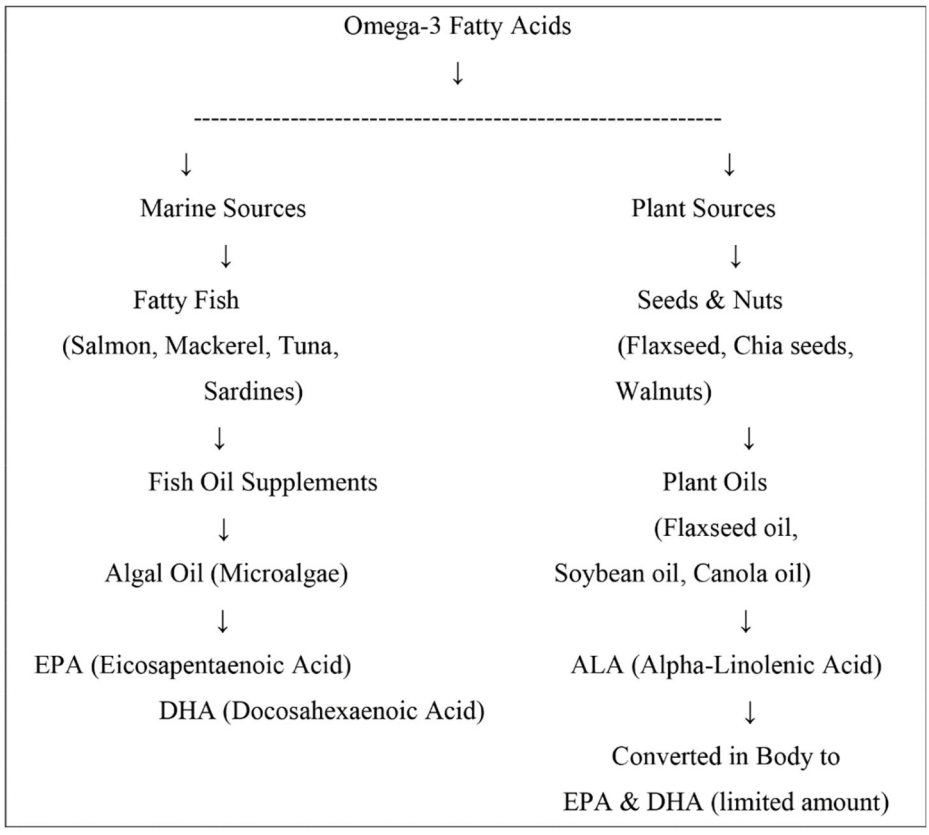

Fig 1: Sources of Omega-3 Fatty Acids

Alpha-linolenic acid (ALA), a necessary precursor of other omega-3 forms, is found in plant-based foods that are the primary source of omega-3 fatty acids. Flaxseed, chia seeds, walnuts, soybean oil, canola oil, and mustard oil are examples of common plant sources. Small

amounts are also found in green leafy vegetables like fenugreek and spinach[6]. Because they provide vital fatty acids needed for regular bodily activities, these meals are particularly significant for vegetarians. Although the human body can convert ALA into EPA and DHA, the conversion efficiency is limited, necessitating constant dietary consumption. Including oilseeds, nuts, and plant oils in regular meals promotes heart health, maintains lipid balance, and aids in healthy growth, development, and metabolism[7]. Omega-3 fatty acids, especially the physiologically active forms eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are thought to be most abundant and effective in marine diets. These long-chain omega-3 fatty acids are abundant in fatty fish, including salmon, mackerel, sardines, tuna, herring, and anchovies. Frequent consumption of fatty fish has been linked to increased brain function, less inflammation, and a lower risk of cardiovascular diseases[8]. To guarantee proper intake, fish oil and cod liver oil are frequently used as dietary supplements in the form of soft gels and capsules[9]. These marine sources offer readily usable EPA and DHA, which the body absorbs and uses more effectively than ALA produced from plants, making them extremely advantageous for both nutritional and medicinal uses. To help meet daily nutritional needs, omega-3 fatty acids can also be obtained through alternate sources and fortified meals. Omega-3 is added to a variety of widely eaten goods, including breakfast cereals, milk, yoghurt, eggs, and baby formulae, to increase their nutritional content10]. A significant vegetarian source of DHA is microalgae, and algal oil supplements are becoming more popular due to their sustainability and suitability for people who don't eat fish. Nuts like walnuts and seeds like chia and flaxseed are regarded as functional foods because they include antioxidants, fibre, and healthy fats[11]. Frequent consumption of these natural and fortified sources lowers the risk of chronic inflammatory diseases, promotes brain development, strengthens the immune system, and maintains cardiovascular health.

2. NEURODEGENERATIVE DISORDERS

A class of long-term, progressive illnesses known as neurodegenerative disorders is defined by the progressive loss of brain and spinal cord neuronal structure and function[12]. Huntington's disease, Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis are typical examples. Symptoms of these disorders include cognitive deterioration, tremors, memory loss, and poor coordination. The primary pathogenic mechanisms at play are aberrant protein build up, inflammation, mitochondrial dysfunction, and oxidative stress. Over time, the damage becomes irreversible since neurones have a limited capacity to recover. [13] A wide range of progressive illnesses known as neurodegenerative disorders are characterized by increasing clinical impairment in movement, cognition, or both, as well as selective neuronal vulnerability and cumulative loss of neuronal structure and function. These conditions include amyotrophic lateral sclerosis, frontotemporal dementia, Huntington's disease, Parkinson's disease, Alzheimer's disease, and multiple system atrophy, to name a few[14]. Protein misfolding and aggregation, mitochondrial dysfunction, poor proteostasis, synaptic failure, neuroinflammation, and disturbed axonal transport are common pathogenic features among many, despite their varied clinical manifestations and impacted brain systems. Although age is the primary risk factor, start and development are influenced by genetic predispositions, environmental exposures, metabolic comorbidities, and lifestyle factors.[15] Integrating molecular, cellular, circuit, and clinical viewpoints is necessary to comprehend neurodegeneration and relate early molecular insults to network failure and symptomatic decline. Aggregation and misfolding of proteins are key clinical characteristics of many neurodegenerative disorders[16]. Different proteins build up in ways that are specific to each disease: TDP 43 or SOD1 aggregates in subsets of amyotrophic lateral sclerosis, α synuclein in Parkinson's disease and related synucleinopathies, mutant huntingtin in Huntington's disease, and amyloid β and hyperphosphorylated tau in Alzheimer's disease. Misfolded species create insoluble fibrils and soluble oligomers that sequester vital proteins, impede synaptic transmission, and damage membrane integrity[17]. Aggregates can spread disease via interconnected networks by moving

across cells using prion-like mechanisms. ER stress, unfolded protein response, autophagy induction, and ubiquitin proteasome activation are examples of cellular responses that try to restore proteostasis but frequently fall short, hastening neuronal malfunction and death[18].

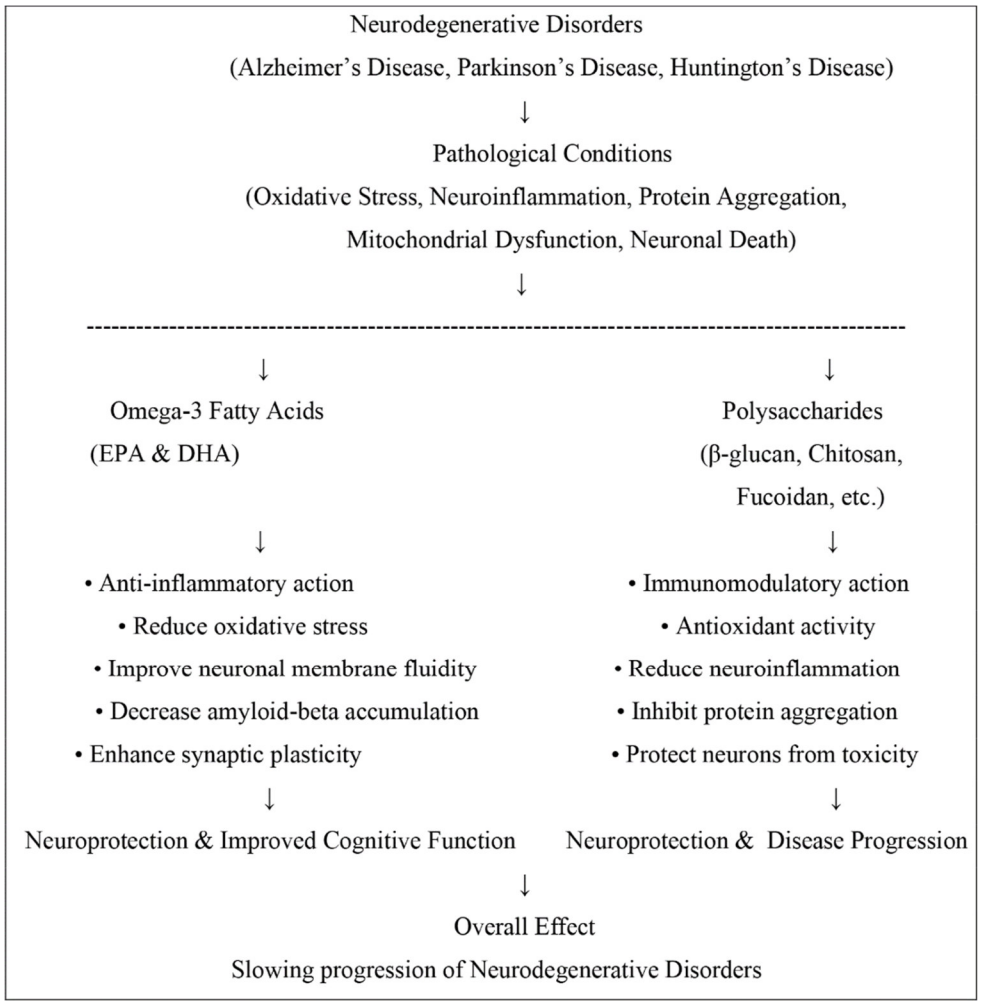

Fig 2: Neurodegenerative disorders

2.1. PARKINSON DISEASE

Bradykinesia, resting tremor, rigidity, and postural instability are among the motor dysfunctions that are the main characteristics of Parkinson disease, a progressive neurodegenerative illness[19]. Loss of dopaminergic neurons in the substantia nigra pars compacta and the resulting striatal dopamine deficit, which interferes with basal ganglia circuits that control movement, constitute the fundamental disease. Cognitive impairment, emotional disorders, autonomic dysfunction, sleep abnormalities, and olfactory loss are examples of nonmotor characteristics that are frequent and may occur years before motor indications[20]. Age-related increases in incidence are common, and although the majority of cases are idiopathic, environmental exposures and genetic alterations enhance risk and phenotypic heterogeneity. Multidisciplinary care is essential to management, and the diagnosis is still clinical, backed by imaging and dopaminergic medication response.[21] Biomarker development, disease-modifying treatments, and approaches to caregiver burden and health are among the research goals.

Pathology and Protein Aggregation

Many cases of Parkinson's disease are characterized by intracellular aggregation of misfolded proteins, with α synuclein producing Lewy bodies and Lewy neurites in afflicted

neurons. While bigger fibrils build up as inclusions, misfolded α synuclein can form soluble oligomers that hinder axonal transport, disrupt synaptic function, and undermine membrane integrity[22]. Evidence points to the progressive spread of pathology as a result of pathogenic α synuclein species propagating prion-like along interconnected brain circuits. Protein aggregation is accelerated by concurrent mechanisms that include mitochondrial failure, oxidative stress, defective autophagy and lysosomal degradation, and neuroinflammation. The molecular processes and therapeutic targets for regulating aggregation and improving proteostasis are revealed by genetic mutations in SNCA, LRRK2, GBA, and other genes.[23]

Clinical Features and Diagnosis

A variety of motor and nonmotor symptoms that change over time are present in Parkinson's disease[24]. Bradykinesia, resting tremor, rigidity, and postural instability are examples of cardinal motor symptoms that indicate nigrostriatal dopamine depletion and dysfunction in the basal ganglia. Cognitive decline, mood problems, autonomic dysfunction, sleep difficulties, hyposmia, and pain are examples of nonmotor symptoms that significantly lower quality of life and cause disability[25]. Dopaminergic responsiveness supports the clinical diagnosis, which is based on the patient's history and a neurologic examination showing bradykinesia along with tremor or rigidity. To help with differential diagnosis and rule out mimics, ancillary tests such structural MRI and dopamine transporter imaging (DAT SPECT) can be used.[26] The goal of multidisciplinary assessment is to maximize personalized therapy and long-term planning throughout illness phases by addressing the motor, cognitive, mental, and autonomic domains.

Pathogenesis and Risk Factors

The interaction of environmental exposures, aging-related processes, and hereditary susceptibility culminates in neuronal vulnerability and causes Parkinson disease. Genes including SNCA, LRRK2, PARK2, PINK1, and GBA have rare monogenic mutations that result in family forms and expose pathways related to lysosomal function, protein aggregation, and mitochondrial quality control[27]. Common risk loci linked to vesicular trafficking, immunological modulation, and lipid metabolism in sporadic disease are identified by genome-wide association studies[28]. Epidemiological studies have shown that physical exercise and coffee correspond with lower risk, but environmental factors such as head trauma, well water, rural life, and pesticide exposure have been linked to increased risk. Age continues to be the most significant risk factor, and somatic mutations, gene–environment interactions, and epigenetic modifications influence onset and progression globally[29].

2.2. ALZHEIMER DISEASE

The gradual deterioration of memory, executive function, language, and behaviour that eventually affects day-to-day functioning is the hallmark of Alzheimer disease, a neurological illness that progresses over time. Although early onset family forms do exist, it is the most frequent cause of dementia globally and primarily affects older persons. Alzheimer's disease is characterized pathologically by extracellular amyloid β plaques and intracellular neurofibrillary tangles made of hyperphosphorylated tau, along with brain atrophy, synapse loss, and neuronal death[30].The clinical appearance progresses from mild impairment and subtle cognitive complaints to full dementia with neuropsychiatric symptoms, gait abnormalities, and loss of independence. Clinical evaluation, cognitive testing, neuroimaging, and, more and more, fluid and molecular biomarkers are all integrated into diagnosis in order to stage the illness and direct treatment.

Epidemiology and risk factors

An important public health concern in aging societies is Alzheimer disease, whose incidence and prevalence increase sharply with age. Combinations of genetic variations, including pathogenic APP, PSEN1, and PSEN2 mutations for familial early onset disease, and the APOE ε4 allele for increased late onset risk, as well as family history and aging are factors that affect risk[31]. The following factors can be changed: sedentary lifestyle, poor diet, low cognitive engagement, obesity, diabetes, hypertension, vascular disease, and social

isolation. Additionally, traumatic brain damage and environmental exposures influence risk. Prevention efforts at the population level focus on social interaction, physical activity, cognitive stimulation, and cardiovascular risk reduction to lower incidence and postpone onset in various areas[32].

Molecular pathology and protein aggregation

At the molecular level, Alzheimer's disease is characterized by an accumulation of hyperphosphorylated tau that forms neurofibrillary tangles and misprocessed amyloid precursor protein fragments that aggregate into amyloid β plaques. Synaptic dysfunction and network disconnection are linked to amyloid β oligomers, whereas tau pathology is more closely associated with neuronal loss and clinical severity[33].Inhibited proteostasis, lysosomal and autophagic failure, mitochondrial stress, and oxidative damage are all interrelated with these proteinopathies. Misfolded proteins have the ability to disseminate pathology along brain circuits in a prion-like fashion. Microglia and astrocytes' neuroinflammatory reactions both try to eliminate damage and, in the long run, worsen it by releasing cytokines and activating complement [34].

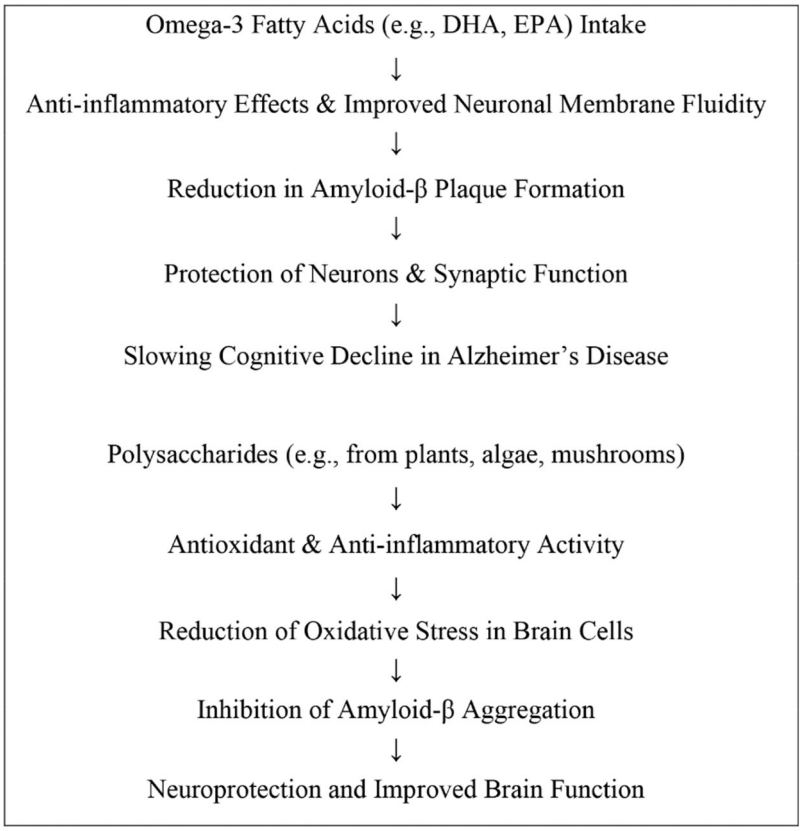

Fig 3: Role of omega-3 fatty acids in Alzheimer disease

2.3 HUNTINGTON DISEASE

A lengthy polyglutamine tract in the huntingtin protein is the result of an enlarged CAG trinucleotide repeat in the huntingtin (HTT) gene, which causes Huntington disease, an autosomal dominant, progressive neuro-logical illness. A trio of motor, cognitive, and mental abnormalities are clinically observed in HD: choreiform motions, diminished voluntary motor control, progressive executive dysfunction and memory loss, and mood disorders such as depression and irritability[35]. Juvenile variants result from extremely large expansions, and age upon onset is negatively correlated with CAG repeat length. The course of the disease causes growing impairment, loss of independence, and early death, usually due to complications like cardiovascular events or aspiration pneumonia. Genetic testing allows for predictive advice for relatives who are at risk and validates diagnoses[36].

Genetic basis and molecular pathology

Huntington disease is caused molecularly by the expansion of the CAG repeat in exon 1 of HTT, which codes for an enlarged polyglutamine tract that modifies the interactions and structure of huntingtin. Atypical proteolysis of mutant huntingtin results in N terminal fragments that are prone to misfolding and aggregation; these fibrillar and oligomeric species upset cellular homeostasis [37]. Transcriptional dysregulation, decreased axonal transport, mitochondrial dysfunction, altered calcium signalling, and poor protein quality control through the ubiquitin–proteasome and autophagy pathways are examples of pathogenic processes. The striatal medium spiny neurons and their cortical inputs are specifically affected by mutant huntingtin, which also disrupts neurotrophic support and synaptic function. The gradual neuronal malfunction and selective susceptibility typical of HD are caused by these converging cellular assaults[38].

Selective neuronal vulnerability and circuit dysfunction

Medium spiny neurons in the striatum are among the first and most severely afflicted cell types in Huntington illness, which exhibits remarkable regional specialization and disrupts the circuits in the basal ganglia that control behavior and movement. Early changes in glutamatergic transmission, synaptic plasticity, and inhibitory control that show up as motor incoordination and cognitive inflexibility are signs of corticostriatal synaptic dysfunction, which occurs before overt cell death[39]. Widespread network disconnection results from progressive degeneration that spreads to cortical layers and other subcortical nuclei. Both hyperkinetic and later hypokinetic movements, as well as cognitive and psychiatric problems, are caused by circuit level disruption, underscoring the significance of synaptic and network preservation in treatment approaches [40].

Clinical course, phenotypic variability, and modifiers

The clinical trajectory of HD is variable: age at onset, symptom predominance, and progression rate differ across individuals and families. Longer CAG expansions generally predict earlier onset and more rapid decline, but genetic modifiers, somatic instability of repeats, and environmental factors also influence phenotype. Juvenile Huntington disease often presents with rigidity, bradykinesia, and seizures rather than chorea. Psychiatric manifestations can precede motor signs by years, complicating early recognition. Comorbidities, access to multidisciplinary care, and supportive interventions shape functional outcomes. Research into genetic modifiers and lifestyle influences aims to explain heterogeneity and identify targets to delay onset or slow progression[41].

Diagnostic approaches and biomarkers

Clinical evaluation backed by molecular genetic testing for the enlargement of the HTT CAG repeat is necessary for the diagnosis of Huntington disease; predictive testing procedures include psychosocial assistance and pre-test counselling. Advanced MRI and functional imaging identify early structural and connectivity alterations, while neuroimaging shows striatal atrophy and cortical thinning that correlate with illness stage. Neurofilament light chain and mutant huntingtin fragments are fluid biomarkers that have potential for monitoring neuronal damage and treatment response. In order to enable early intervention and more effective trial designs, biomarker development focuses on sensitive, repeatable measurements for prodromal staging, tracking the progression of disease, and assessing disease-modifying therapies in clinical trials[42].

3. Mechanisms of Action of omega-3 fatty acids and polysaccharides on neurodegenerative disorders

The incorporation of omega-3 fatty acids, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), into neuronal membranes increases fluidity and modifies the composition of lipid rafts[43].These biophysical modifications improve synaptic plasticity by modifying receptor conformation, synaptic vesicle fusion, and neurotransmitter release. The specialized pro-resolving mediators (resolvins, protections) that omega 3s are enzymatic precursors for actively reduce inflammation, decrease microglial activation, and encourage tissue repair interrupt chronic neuroinflammatory cycles linked to Parkinson's and Alzheimer's disease and support neuronal survival mechanisms in general[44].

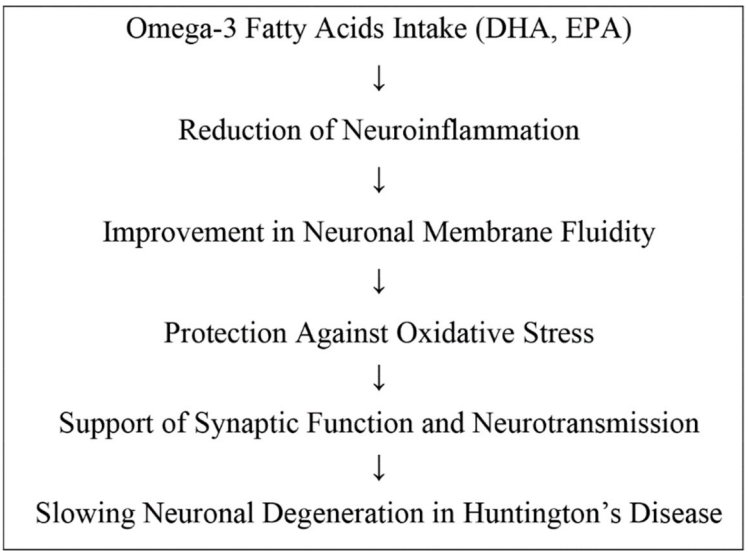

Fig 4: Omega-3 fatty acids pathway.

By stabilizing electron transport, lowering the generation of reactive oxygen species, and integrating into mitochondrial membranes, EPA and DHA affect mitochondrial function. They protect synapses and axonal transport by promoting mitophagy and maintaining ATP synthesis under stress. By upregulating neurotrophic factors and antioxidant enzymes and downregulating proinflammatory transcriptional programs, omega-3s control gene expression through nuclear receptors and epigenetic processes. Together, these transcriptional and metabolic actions strengthen neural resilience and may halt the advancement of sensitive populations[45].

Polysaccharides such β glucans and sulfated algal polysaccharides interact with pattern recognition receptors on peripheral immune cells and microglia, causing activation to shift toward anti-inflammatory and debris-clearing phenotypes. They inhibit complement activation, decrease proinflammatory cytokines, and encourage misfolded protein phagocytosis. Many polysaccharides also decrease oxidative damage to proteins and lipids by inducing endogenous antioxidant mechanisms. Polysaccharides indirectly shield synapses and neural networks from long-term inflammatory damage and improve clearance processes through immunological reprogramming and redox homeostasis[46].

Role of omega-3 fatty acids and polysaccharides on Parkinson disease

Membrane incorporation and synaptic stabilization by omega-3 fatty acids

Dopaminergic neurons and their synapses experience changes in membrane fluidity, curvature, and lipid raft composition due to the integration of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) into neuronal phospholipid bilayers. Synaptic vesicle fusion and neurotransmitter release are facilitated by these biophysical alterations, which also affect the conformation and trafficking of membrane proteins, such as dopamine transporters and receptors. DHA enrichment prevents excitotoxic susceptibility, maintains synaptic integrity, and promotes long-term potentiation in circuits damaged by Parkinson disease. Omega 3 fatty acids assist sustain neuro-transmission in the face of proteostatic stress and mitochondrial compromise by stabilizing presynaptic and postsynaptic membranes. This delays functional synaptic failure, which occurs before overt neuronal loss in nigrostriatal pathways[47].

Anti-inflammatory and pro-resolving signalling of omega-3 metabolites

Enzymatic conversion of EPA and DHA into specific pro-resolving mediators (SPMs) such resolvins, protections, and maresins that actively reduce inflammation goes beyond their structural functions. Chronic microglial

activation in Parkinson disease maintains a neurotoxic environment; SPMs increase phagocytic clearance of debris without causing significant bystander harm, downregulate inducible nitric oxide synthase, and decrease microglial production of proinflammatory cytokines (TNF α, IL 1β). Additionally, these mediators limit peripheral to central inflammatory signalling by modifying peripheral immune cell trafficking and blood–brain barrier integrity.[28] A two-tiered anti-inflammatory mechanism that can reduce increasing inflammatory damage to susceptible dopaminergic neurons is produced when membrane incorporation and SPM production are combined[48].

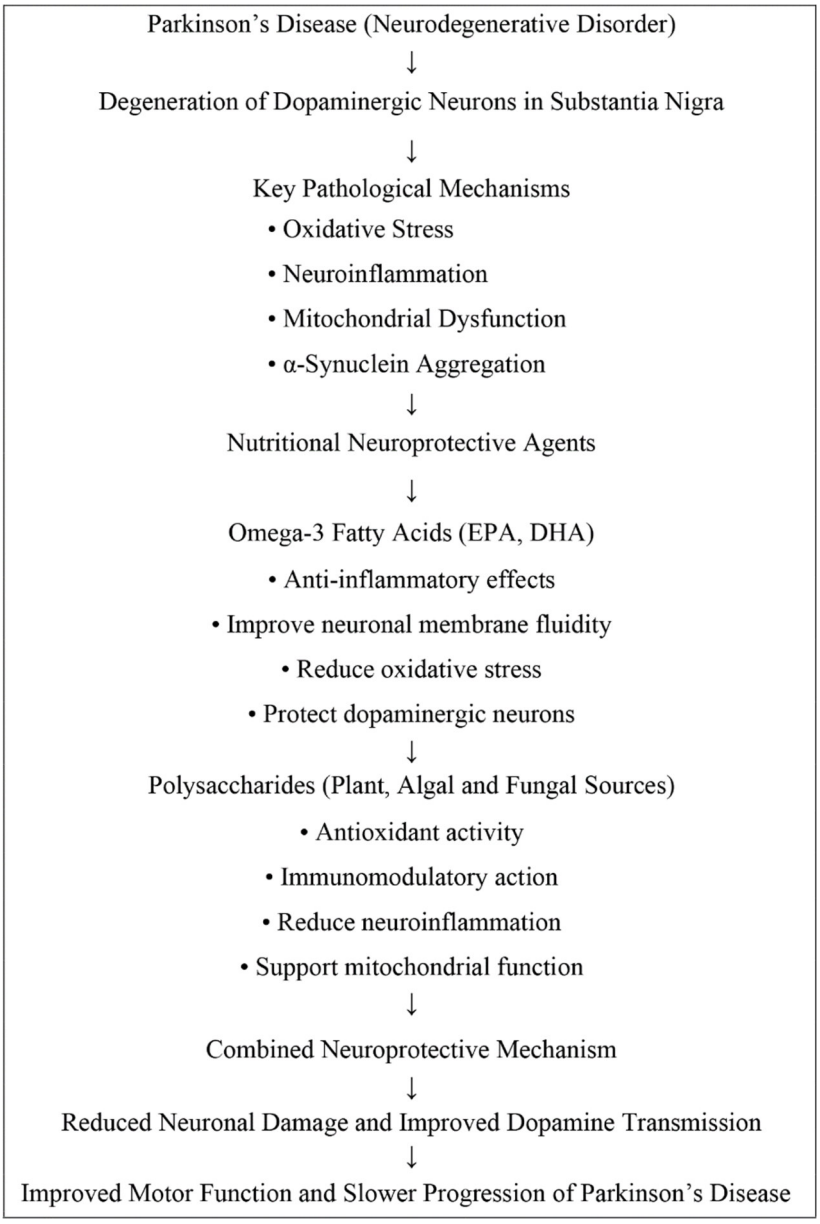

Fig 5: Role of omega-3 fatty acids in Parkinson's Disease

Mitochondrial protection and gene regulatory effects of omega-3s

In neuronal mitochondria, omega-3 fatty acids improve electron transport efficiency and decrease the production of reactive oxygen species by influencing mitochondrial membranes and bioenergetics. DHA incorporation maintains ATP production under metabolic stress, stabilizes mitochondrial membranes, and promotes mitophagy—all of which are essential

for long projection nigrostriatal neurons [49].Through nuclear receptors and epigenetic processes, omega 3 fatty acids also alter transcriptional programs, downregulating proinflammatory and apoptotic genes and upregulating neurotrophic factors (BDNF) and antioxidant enzymes. If used early or as an adjuvant therapy, this combination metabolic and gene regulatory effects may halt degeneration by increasing neuronal resilience to oxidative and proteotoxic insults that are typical of Parkinson pathogenesis[50].

Immunomodulation and antioxidant actions of polysaccharides

Polysaccharides, including as β glucans, sulfated algal polysaccharides, and certain plant heteropolysaccharides, interact with peripheral immune cells and microglia's innate immune receptors (dectin 1, TLRs) to rewire activation states. These medicines decrease the release of proinflammatory cytokines, improve the phagocytosis of aggregated α synuclein, and change microglia toward balanced, debris-clearing phenotypes in Parkinson models. In addition to immediately scavenging reactive oxygen species and inducing endogenous antioxidant defenses (Nrf2 pathway), several polysaccharides also reduce oxidative damage to proteins and lipids. Polysaccharides may enhance the removal of harmful protein species from impacted brain areas by reducing secondary inflammatory cascades that intensify neuronal damage through immunological balance and redox modulation [51].

Extracellular matrix interactions, anti-aggregation, and translational challenges of polysaccharides

Sulfated and charged polysaccharides have the ability to stabilize less toxic soluble conformers, bind misfolded proteins, and prevent pathogenic aggregation by preventing α synuclein fibrillization. Glycosaminoglycan-like substances may improve the glymphatic elimination of proteinaceous waste by influencing the nature of the extracellular matrix and perivascular clearance routes. These external effects lessen oligomer toxicity and synaptic impairment by enhancing intracellular proteostasis systems. To achieve consistent CNS delivery and assess clinical efficacy in Parkinson disease, standardized extraction, structural characterization, and formulation strategies (e.g., nanoparticle carriers) are required. Translational barriers include heterogeneity in molecular weight and sulfation patterns, variable bioavailability, and limited blood–brain barrier penetration[52].

Role of omega-3 fatty acids and polysaccharides in Alzheimer disease

The fluidity and stability of neuronal membranes are vitally dependent on omega-3 fatty acids, especially docosahexaenoic acid (DHA). The characteristic of Alzheimer's disease is synaptic dysfunction, and DHA improves neurotransmission by stabilizing synaptic membranes. These fatty acids also lower oxidative stress and alter the expression of genes linked to neuroplasticity. Omega-3 fatty acids decrease cognitive decline and enhance general brain health by promoting neuronal resilience and counteracting the gradual synapse loss associated with Alzheimer's [53].

Anti-Inflammatory Effects of Omega-3s

Alzheimer's disease pathogenesis is significantly influenced by chronic neuro-inflammation. Omega-3 fatty acids reduce pro-inflammatory cytokines like TNF-α and IL-6 to produce their anti-inflammatory effects. Along with actively reducing inflammation, they also encourage the synthesis of specific pro-resolving mediators including protections and resolvins. This decrease in neuroinflammation slows the development of tau pathology and amyloid-beta toxicity, two key characteristics of Alzheimer's disease, by shielding neurons from more harm [54].

Omega-3s and Amyloid-Beta Clearance

Amyloid-beta plaque buildup is one of the hallmarks of Alzheimer's disease. The removal of amyloid-beta deposits is facilitated by omega-3 fatty acids, which increase microglial phagocytosis. Additionally, DHA affects the lipid raft composition of neuronal membranes by decreasing the breakdown of amyloid precursor proteins into harmful amyloid-beta peptides. Omega-3 fatty acids directly target one of the most harmful pathological processes in Alzheimer's disease by promoting plaque clearance and decreasing amyloidogenic processing, which slows the illness's progression [55].

Polysaccharides and Antioxidant Properties

Natural sources of polysaccharides, such as marine life and medicinal plants, have potent antioxidant properties. Oxidative stress triggers amyloid-beta aggregation and speeds up neuronal damage in Alzheimer's disease. The endogenous antioxidant enzymes catalase and superoxide dismutase are enhanced by polysaccharides, which also reduce reactive oxygen species. As two major factors in Alzheimer's pathogenesis, mitochondrial malfunction and DNA damage are prevented by this antioxidant defence, which lessens oxidative damage to neurons [56].

Role of omega-3 fatty acids and polysaccharides in Huntington disease

Huntington disease-affected striatal and cortical neurons' fluidity, lipid raft composition, and receptor function are all changed by the incorporation of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) into their membranes. These biophysical modifications stabilize corticostriatal synapses that are susceptible to mutant huntingtin by enhancing synaptic vesicle dynamics, neurotransmitter release, and receptor trafficking. Omega 3s can reduce early synaptic dysfunction that precedes neuronal loss and clinical decline in Huntington disease and increase stress tolerance by maintaining membrane integrity and synaptic transmission [57].

Anti-inflammatory and pro-resolving signalling of omega-3s

Enzymatic antecedents of specific pro-resolving mediators that actively reduce inflammation, such as protections and resolvins, are EPA and DHA. These mediators decrease proinflammatory cytokines, microglial activation, and the removal of cellular debris in Huntington models without causing undue harm to bystanders. In damaged basal ganglia circuits, omega 3-derived mediators reduce oxidative stress, restrict chronic neuro-inflammation caused by mutant huntingtin, and improve neuronal survival by reorienting innate immune responses toward resolution [58].

Mitochondrial and metabolic support by omega-3s

In susceptible neurons, omega-3 fatty acids maintain ATP production by improving the composition of the mitochondrial membrane, lowering the production of reactive oxygen species, and promoting mitophagy. These metabolic actions stabilize synapse function and axonal transport by compensating for energy shortages brought on by mutant huntingtin. Through nuclear receptors and epigenetic processes, omega 3 fatty acids also alter gene expression, downregulating proapoptotic pathways and upregulating neurotrophic factors and antioxidant enzymes. When used early or in addition to other treatments, these measures together strengthen neuronal resilience and may reduce the rate of development [59].

Polysaccharide immunomodulation in Huntington disease

By interacting with pattern recognition receptors on microglia and peripheral immune cells, polysaccharides such β glucans and sulfated algal polymers reprogram activation toward balanced, debris-clearing phenotypes. This lessens complement activation and chronic cytokine release linked to mutant huntingtin disease. Immune modulation brought on by polysaccharides promotes tissue repair pathways and improves the phagocytosis of misfolded proteins. Over time, these carbs indirectly shield neurons and synapses in striatal and cortical circuits impacted by Huntington disease by reducing maladaptive inflammation and encouraging clearance[60].

Anti-aggregation and extracellular effects of polysaccharides

The load of hazardous aggregates can be decreased by binding misfolded huntingtin fragments with sulfated and charged polysaccharides, which prevent oligomerization and fibril formation. The extracellular matrix composition and perivascular clearance are influenced by glycosaminoglycan-like molecules, which may improve the elimination of proteinaceous waste through lymphatic channels. By enhancing internal proteostasis systems, these external contacts reduce oligomer toxicity and maintain synaptic micro-environments. For clinical assessment and safety testing, consistent formulations and delivery methods are required due to translational obstacles like as heterogeneity, molecular weight variations, and blood–brain barrier penetration [61].

Combined strategies and research priorities

Immunomodulatory polysaccharides and omega-3 fatty acids may work in concert to stabilize membranes, reduce inflammation, improve clearance, and safeguard synapses. Preclinical research should assess formulation, timing, and dosage to optimize brain absorption and target engagement. Neurofilament light, imaging, and inflammatory panels can be used in biomarker-driven trials to detect mechanism-specific effects and stratify individuals. Standardized nutraceutical characterization, CNS delivery system optimization, safety evaluation, and well-powered randomized trials to ascertain therapeutic efficacy in individuals with Huntington disease are among the top priorities[62].

4. Supplementation Strategy

Randomized controlled trials (RCTs), observational studies, and meta analyses that examine impacts on heart disease, brain health, mood, metabolic indicators, and inflammation are examples of clinical research on EPA and DHA supplements. Large RCTs and pooled analyses were prompted by early observational work and mechanistic investigations that revealed broad effects. Much of the difference in outcomes can be explained by heterogeneity in dose, EPA:DHA ratio, baseline dietary intake, participant risk profile, and trial duration. It is important to pay attention to these methodo-logical nuances when analyzing any one study because modern reviews highlight that formulation and trial design—rather than a single universal effect—determine outcomes[63].

Cardiovascular outcomes and major trials

Cardiovascular trials have the most impact: many lower dose or mixed EPA+DHA trials were neutral, whereas EPA-dominated, high dose (≈4 g/day) trials revealed decreases in major adverse cardiovascular events among chosen high-risk patients. EPA-focused regimens are the most promising for secondary prevention, according to meta analyses, which also show that efficacy depends on formulation and dosage. Conflicting results can be explained by variations in baseline omega-3 status, trial populations, and background medications (such as statin use); when counseling high-risk patients, doctors should consider data from EPA-specific trials[64].

Cognitive, mood, and neurological findings

Studies on the impact of omega-3 fatty acids on depression, peripheral neuropathy, and cognition have shown mixed or negligible results. Large RCTs frequently fail to demonstrate clinically significant improvements across large populations, while some smaller or subgroup analyses suggest advantages for depressive symptoms or age-related cognitive decline in those with low baseline omega 3 levels. Systematic reviews demand longer, higher-powered studies for neurological outcomes such peripheral neuropathy before suggesting regular supplementation. Overall, the data points to potential benefits in particular subgroups rather than widespread use[65].

Dose, formulation, and methodological drivers

EPA versus EPA+DHA composition, total daily dose (low 250–1000 mg vs. high 2–4 g), length of therapy, and participant selection (primary vs. secondary prevention) are important factors influencing trial results. Studies measuring baseline omega-3 biomarkers (omega-3 index) frequently find more pronounced advantages in those who are lacking. Results are also influenced by concurrent drugs, placebo selection, and adherence. When putting trial results into practice, several methodological considerations are crucial: match formulation and dosage to the clinical question and, if available, take biomarker testing into account[66].

Practical takeaways and safety considerations

Consider omega-3 supplementation mainly for specific indications (e.g., high-risk cardiovascular patients under professional guidance) rather than widespread preventive use for individuals in Ambala and similar contexts. Therapeutic doses (2–4 g/day) call for medical care; common safe amounts for general health are up to 1 g/day. When possible, give dietary sources (fatty fish) priority and keep an eye out for anticoagulant interactions and minor gastrointestinal side effects. Using baseline diet, risk profile, and data from EPA-focused trials, clinicians should make customized judgments [67].

In animal and cellular models, polysaccharide supplementation (such as beta glucans, fucoidans, and chitosan derivatives) exhibits strong neuroprotective benefits through microglial regulation, prevention of protein aggregation, increase of neurotrophic signalling, and antioxidant activity. Preclinical research consistently demonstrates improved behavior, less neuronal loss, and reduction of characteristic diseases such amyloid and alpha synuclein aggregation. Small pilot trials and safety studies are the only human clinical data available; these indicate tolerability and sporadic cognitive or functional indications, but they lack the strength and consistency to support general clinical recommendations. One of the biggest obstacles to translation is standardization of molecular weight, purity, and dosage[68].

Combination and translational considerations highlight the physiologically plausible but clinically unproven nature of synergy: polysaccharides influence innate immunity and oxidative stress, while omega 3s reduce neuroinflammation and stabilize membranes, providing a basis for combined therapies. Variable compound quality, inconsistent dosing, short trial durations, and heterogeneous patient selection, however, limit clinical translation; future RCTs should employ standardized polysaccharide preparations, stratify by disease stage, and measure baseline biomarkers (inflammatory markers, the omega 3 index). Prioritize food sources (fatty fish, flaxseed, walnuts; mushrooms, seaweeds, whole grains), set aside supplements for specific purposes, and speak with local clinicians regarding interactions (anticoagulants) and proper monitoring for those living in[69]

Conclusion

The many neuroprotective effects of omega 3 long chain polyunsaturated fatty acids, particularly DHA and EPA, are closely related to neurodegenerative diseases. They promote the integrity of the dendritic spine, influence synaptic plasticity, and integrate into neuronal membranes to improve membrane fluidity and receptor function. In terms of biochemistry, omega 3s are precursors for certain pro-resolving mediators that actively reduce inflammation and encourage tissue repair, hence lowering chronic neuroinflammatory signalling linked to Parkinson's and Alzheimer's diseases. Additionally, these lipids affect oxidative stress responses and mitochondrial activity, maintaining neuronal energy metabolism in stressful situations. When taken as a whole, these mechanistic effects offer a tenable biological foundation for omega 3s' ability to halt or alter neurodegenerative processes in susceptible brain regions[70].

The results of observational research and randomized controlled trials on omega 3 supplementation in neurodegenerative illness vary depending on the time, dosage, and initial nutritional state. While trials in advanced disease frequently show little benefit, those conducted in early or prodromal phases and in people with low baseline omega 3 levels tend to reveal more favorable cognitive or functional signs[69]. Complicating synthesis is variation in formulations (DHA alone, EPA rich, or combination), length of treatment, and outcome measurements. Meta evaluations stress that omega 3s are more likely to be used as an adjuvant than as a stand-alone disease-modifying treatment, and they show small effect sizes for prevention or slowing of decline. Trial success may be enhanced by biomarker-guided methods and careful patient selection[71].

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