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Review Article

Emerging Role of Polyunsaturated Fatty Acids (PUFAs) on Human Brain Development and Neurological Diseases: A Systematic Review

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ABSTRACT

Polyunsaturated fatty acids (PUFAs) are essential components of neural membranes, contributing to membrane fluidity, receptor function, and neurotransmission. Healthy fats, like omega-3 fatty acids, play a crucial role in brain development, enhancing mood, and neurodegenerative processes. This systematic review examines the growing incidence of neurological and neuropsychiatric disorders in recent decades, underscoring the urgent need for new therapies that target these conditions while minimizing adverse effects. Research suggests that omega-3 polyunsaturated fatty acids (n-3 PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential for maintaining nerve cell function, neurotransmission, and modulating inflammatory and immunological responses. To identify relevant studies, electronic databases such as Science Direct, Scopus, EBSCO, Medline, PubMed, Embase, SID, and Iran Medex were searched, resulting in the inclusion of 15 experimental and epidemiological studies. These studies provided a robust basis for conducting clinical trials to evaluate the efficacy of n-3 PUFAs in treating various neurological and psychiatric disorders. This review summarizes recent findings on the therapeutic potentials of n-3 PUFAs for a range of neuropsychiatric conditions and explores the underlying molecular mechanisms. It also addresses common methodological challenges in clinical research on n-3 PUFAs and offers recommendations for enhancing future study designs.

Keywords: Neurological disorders, Psychiatric disorders, Neuropsychiatric disorders, Omega-3 polyunsaturated fatty acids.

Introduction

The greasy substances present in the tissues of plants and animals are known as "fats." These are found in foods such as meat, eggs, dairy products, and certain plant-based foods like nuts, avocados, and olive oil. Lipids consist of fatty acids, esters, and derivatives of fatty acids. Dietary fats primarily consist of triglycerides, along with more complex lipids like phospholipids. Fat has historically been considered an unnecessary component of the diet, contributing to weight gain, type 2 diabetes, cardiovascular diseases, and cancer. However, growing evidence suggests that replacing dietary fats with refined sugars can have adverse effects, while essential fats and components of cooking oils, such as vitamin E, phytosterols, and polyphenols, have beneficial effects on health. The primary role of dietary fat is to provide energy to the body. It also aids in the absorption of fat-soluble vitamins (A, D, E, and K) and supplies essential fatty acids. Fat is a functional ingredient, acting as a carrier of flavours and providing desirable textures and mouthfeel to many foods.

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Polyunsaturated fatty acids (PUFAs) are essential components of neural membranes, contributing to membrane fluidity, receptor function, and neurotransmission. Long-chain (LC) PUFAs, such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and Arachidonic acid (ARA), modulate phospholipid composition, membrane fluidity, enzyme function, receptors, ion channels, and neurotransmission.[3] They also play a role in dendritic growth, neuronal synaptogenesis, and inflammation regulation. EPA, for instance, has anti-inflammatory properties, while ARA has pro-inflammatory effects.[4, 5] DHA, a metabolite from the docosanoid family, helps inactivate pro-apoptotic and pro-inflammatory signalling but does not produce eicosanoids. A higher intake of omega-6 PUFAs, which have pro-inflammatory properties, can enhance competition between alpha-linolenic acid (ALA) and linoleic acid (LA) as enzyme substrates, reducing the conversion of alpha-linoleic acid to DHA. This may result in lower DHA levels in both the fetus and the mother.[2, 6] Optimal DHA intake during pregnancy and the postnatal period is crucial,[7] with global recommendations suggesting a minimum of 200 mg/day for pregnant and lactating women. Neurological diseases (NDs) are often overlooked in developing countries due to illiteracy and superstitions surrounding these conditions. Many developing nations lack basic epidemiological data on the prevalence of NDs, and the available data is often unreliable due to poor methodologies and limited research.[8] Pakistan is among the developing countries in Asia with few epidemiological studies on diseases, including NDs. Fats provide 9 kcal (37 kJ)/g of energy, more than double the energy provided by proteins and carbohydrates, which supply 4 kcal (18 kJ) per gram. Human milk derives nearly half of its energy from fats, which are vital for infant growth and development. The high caloric density of fats helps to meet the overall energy needs of the diet, meaning even a small amount of fat can significantly increase the caloric content of food.[9] Conversely, removing animal fats from the diet can substantially lower the energy content of the foods we

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consume. There are various categories of dietary fat, some of which are more beneficial than others. Trans and saturated fats can increase cholesterol levels and the risk of cardiovascular diseases, whereas unsaturated fats support health and are categorized as polyunsaturated or monounsaturated. The difference between dietary fats lies in their chemical structure. Fats are composed of chains of carbon atoms linked to hydrogen atoms.[1] In saturated fatty acids, the carbon atoms are fully saturated with hydrogen atoms. In unsaturated fats, fewer hydrogen atoms are attached to the carbon atoms. Consuming unsaturated fats as an alternative to saturated fats may help improve cholesterol levels. Monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids are derived from unsaturated fatty acids.[1] Monounsaturated fatty acids have only one double bond, which can be classified as a cis or trans isomer, depending on the position of the hydrogen atoms around the double bond. Most of the beneficial effects of MUFAs on the cardiovascular system are related to cis-MUFAs, particularly oleic acid, which is found in nuts, avocados, and vegetable oils such as peanut, olive, and canola oils.[10] Consuming foods high in monounsaturated fats may help lower cholesterol levels. Polyunsaturated fats are fatty acids characterized by the presence of two or more double bonds. This type of fat is primarily found in vegetable oils such as safflower, soybean, sunflower, sesame, and corn oils. Polyunsaturated fatty acids (PUFAs) are the main fats found in seafood. The position of the last double bond relative to the terminal methyl end of the molecule allows for the classification into n-3 or n-6 polyunsaturated fats. The two categories of PUFAs are omega-3 and omega-6 fatty acids. In omega-3 fatty acids, the first double bond appears on the third carbon atom, and they are found in plant-based foods such as walnuts, flaxseed, soybean, and canola oil. Omega-3s are also present in fatty fish and shellfish as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Salmon, sardines, herring, trout, anchovies, Atlantic mackerel, Pacific oysters, and Pacific mackerel are high in DHA and EPA and low in mercury. In omega-6 fatty acids, the double bond is present on the sixth carbon atom. These are found in liquid vegetable oils such as soybean oil, corn oil, and safflower oil. Cholesterol is a steroid found in animal tissues.[11] It is present in shrimp, beef, egg yolks, pork, poultry, cheese, and butter. According to National Health and Nutrition Examination Survey (NHANES) data on the American population (2005–2006), the top five sources of cholesterol are chicken, beef and related dishes, eggs and egg dishes, burgers, and regular cheese. Triglycerides are another type of fat and are the most common type found in the human body. Food sources include oils, butter, and other fats. Triglycerides are the excess calories consumed but not needed by the body.[12] The body converts these excess calories into triglycerides and stores them in fat cells. Neurological diseases, which damage the nervous system, are a significant and increasing cause of morbidity, mortality, and disability. In addition to compromising health, those suffering from these alarming conditions often face mistreatment, stigmatization, and discrimination. Stigmatization further limits patients' access to treatment and social activities.[13] These disorders, therefore, require special attention, especially in developing countries, where the burden of these diseases remains largely unrecognized. The challenges posed by such enduring neurological conditions are expected to be particularly overwhelming in poor populations. These conditions are emerging as severe public health concerns in developing countries due to factors such as ignorance, illiteracy, the large number of untreated individuals, and the lack of affordable yet effective treatments.[14] Unfortunately, reliable population-based data from developing countries, including Pakistan, on the epidemiology of neurological diseases is extremely limited.

However, some information on the epidemiological characteristics of neurological disorders is available from countries like Pakistan, Saudi Arabia, Iran, India, Sri Lanka, and China. Disease prevalence and patterns are influenced by geographical, religious, social, cultural, and ethnic factorss.[15] In this review, 209 studies on the burden and prevalence of hypertension, Alzheimer's disease, epilepsy, depression, stroke, and Parkinson's disease in Pakistan and neighboring countries were examined. The available data on the prevalence of epilepsy in Pakistan is very limited. According to the data, epilepsy is more prevalent in Pakistan than in other neighboring Asian countries. Approximately 2 million people in Pakistan suffer from epilepsy, most of whom are younger than 30 years. This figure accounts for about 10 percent of the global burden of epilepsy. Around 450,000 individuals in Pakistan suffer from Parkinson's disease, in a population of approximately 182 million, this amount to about 219 people with Parkinson's disease per 100,000 individuals. Epidemiological data on the prevalence of Alzheimer's disease in Pakistan is lacking. The limited available data indicates the incidence and occurrence of Alzheimer's disease in elderly individuals and its associations with other diseases.[16]

Methods

Literature search were conducted, and data retrieved from journals accessible through databases such as ScienceDirect, Scopus, EBSCO, Medline, PubMed, Embassy, SID, and IranMedex. Keywords such as polyunsaturated fatty acids (PUFAs), human brain development, and neurological disease were used to retrieve data from the various databases. Duplicate data were removed, while retaining only one version of each source.

PUFA and its Derivatives in Neurotransmission and Synapses

Research shows that long-chain polyunsaturated fatty acids (PUFAs) can effectively regulate synaptic transmission by affecting membrane fluidity and association, as well as regulating voltage-gated ion receptors and channels through by-products such as endocannabinoids and oxylipins. The mechanism of neurotransmission and its regulation by PUFAs is through the following steps. In the first step, the presynaptic element of a chemical signal binds to an axon terminal close to the dendritic bouton of the postsynaptic element, separated by a gap called the synaptic cleft.[16] In the second step, the neurotransmitter binds to receptors on the postsynaptic membrane, initiating the process of neurotransmission. In the third step, this triggers a series of events,[17] resulting in membrane-bound PUFAs being activated into their free form with the help of phospholipase A2. In the fourth step, free PUFAs are converted into their by-products, either oxylipins, which activate the process of neurotransmission (Step 5), or endocannabinoids (Step 6), which bind to activating receptors known as endocannabinoid receptors. In the seventh step, neurotransmission is ultimately activated. Following these events, synaptic strength can either be positively or negatively charged at different time scales (Figure 1). All long-chain PUFA synaptic targets are closely associated due to the powerful effect membrane fluidity has on the performance of voltage-gated ion channels and transmembrane proteins. Endocannabinoids can activate ion channels through a receptor-independent mechanism. PUFAs from the diet can trigger long-term changes in neuronal excitability and network balance. Endocannabinoids (E-CB) are key players in meta-plasticity.[18, 19] Another emerging neurotransmission modulator includes oxylipins derived from various PUFAs, whose physiological roles are being studied in more detail.[20] In conclusion, PUFAs are crucial participants in meta-plasticity, showing that diet and life experiences can influence synaptic processes and, ultimately, brain stability.[21] Comparative studies in experimental and clinical trials show that long-chain PUFAs, particularly n-3 PUFAs, are beneficial in the treatment of brain diseases. Due to their significant effects on synaptic functioning, PUFAs are used commercially in pharmaceutical products to treat conditions related to synaptic malfunction, including neurodevelopmental and neurodegenerative diseases, neuropsychiatric disorders, and brain traumas such as strokes and epilepsy. The importance of PUFAs in synaptic mechanisms continues to grow.

Health Benefits of Fats in Human Neurodegenerative Diseases

Good fats provide several health benefits for both the body and brain. Healthy fats, such as omega-3 fatty acids (found in fatty fish), help maintain normal cholesterol levels. Consuming healthy fats also improves heart health and brain function. Foods rich in healthy fats, such as monounsaturated fatty acids, can aid in weight loss and fat reduction. This makes them an excellent dietary alternative for individuals who find it challenging to adhere to a high-carbohydrate, low-fat diet. Diets rich in healthy fats, particularly monounsaturated fatty acids, have been shown to improve markers of inflammation and blood clotting.[22] Healthy fats, like omega-3 fatty acids, play a crucial role in brain development, enhancing mood, and neurodegenerative processes.[23]

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Table 1: Food Sources of Omega-3 and Omega-6 Polyunsaturated Fatty Acids and Monounsaturated Fatty Acids.[26]

Omega-3 polyunsaturated fatty acids	Omega-6 polyunsaturated fatty acids	Monounsaturated fatty acids
Fatty fish, like herring salmon, sardines and tuna.	Fats and oils, Nuts and seeds, Meat and poultry, Vegetables,	Olive oil, Nuts, almonds, cashews, pecans and macadamias, Canola oil, Avocados, Nut butters, Olives, Peanut oil.
Nuts and seeds such as walnuts, chia seeds, and flaxseeds	Cereal and cereal based products.	
Plant oils like canola oil, soybean oil, and flaxseeds oil.		

Table 2: Articles and Findings Related to Neurological Diseases

SN	Title	Findings	References
	Attention Deficit Hyperactivity Disorder (ADHD)		
1.	Prenatal unhealthy diet, insulin-like growth factor-2 gene (IGF-2) methylation, and attention deficit hyperactivity disorder symptoms in youth with early-onset conduct problems.	Polyunsaturated fatty acids and different micronutrients plays important and therapeutic role in the prevention of ADHD.	38
2.	The treatment of attention deficit hyperactivity disorder has no proven long-term benefits but possible adverse effects	Various studies advocated that if maternal intake of DHA is greater or DHA level are increased than there is low birth risk of ADHD.	30
3.	The role of marine omega-3 in human neurodevelopment, including Autism Spectrum Disorders and Attention-Deficit/Hyperactivity Disorder – a review	In this review article's main finding is the low intake of DHA is causing severe risk factors for the children and intake of DHA may decreases the severity of the disease.	28, 40
4.	The role of environmental factors in etiology of attention-deficit hyperactivity disorder	There are various factors like social and environmental factors involve in the cause of ADHD but some external factor like tobacco, alcohol or other toxic compound administration during pregnancy and pre or post term delivery play a role in ADHD.	29
		Autism Spectrum Disorder (ASD)	
5.	Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses	From this review article it was concluded that some birth complications like trauma, ischemia and hypoxia, and some other pregnancy related complications like maternal diabetes, obesity risk, and also nutritional deficiency of folic acid, and omega-3 fatty acid are associated with ASD.	23, 40
6.	Neuro inflammation in Autism: Plausible Role of Maternal Inflammation, Dietary Omega-3, and Micro biota	This review article advocates that polyunsaturated fatty acids specifically omega-3 fatty acids provide best support for the neurological development of the fetus, so prenatal omega-3 PUFA are recommended.	24, 40
7.	Recalled Initiation and Duration of Maternal Breastfeeding Among Children with and Without ADHD in a Well Characterized Case–Control Sample	Neurological diseases occur in children due to inadequate intake of Polyunsaturated fatty acid. Inadequate administration of PUFAs (essential fatty acids) is observed in ASD, ADHD and schizophrenia patients.	21

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		Epilepsy	
9.	The Epidemiology of Epilepsy	In epilepsy, uncontrollable convulsions occurs. This disease affecting both sexes but prevalence rate is higher in men than in women. Some studies reported that in half of the cases, there is long term seizure remission.	18
10.	Omega-3 Fatty Acids and Epilepsy	According to this data, omega-3 fatty acid have a beneficial role in the management of epilepsy (convulsions) when used along with Antiepileptic drugs.	6
11.	The effect of omega-3 fatty acids on clinical and paraclinical features of intractable epileptic patients: a triple blind randomized clinical trial	In this research, omega-3 fatty acids supplements (DHA 120 mg and EPA 180 mg) and placebo capsules were administered to the patients twice daily for 16 weeks. Results showed a decrease in the duration and frequency of convulsions, TNF-alpha and IL-6 concentrations were also reduced in the supplement group.	32
12.	Mechanisms of action of medium-chain triglyceride ketogenic diet in neurological and metabolic disorders	Ketogenic diet is a diet with high amount of fats. A ketogenic dietary pattern significantly decreased seizure. High fats intake generates ketones which provides more energy to the brain than glucose. This results in increased adenosine level in the cells which is beneficial for convulsion control.	36
		Dementia	
13.	Epidemiology and Pathophysiology of Dementia-Related Psychosis	Ninety percent of people are affected with different types of dementia. They present with various symptoms such as depression, agitation, and aggression. There are multifactorial mechanisms behind DRP, these include social, environmental, psychological, and neurological factors.	20
14.	The emerging role of omega-3 fatty acids as a therapeutic option in neuropsychiatric disorders	There are various studies (epidemiological and experimental) that advocate that omega-3 fatty acids intake is helpful and beneficial in various psychiatric and neurological diseases.	35
15.	Significance of long chain polyunsaturated fatty acids in human health	Omega-3 fatty acids such as EPA and DHA are very useful for nervous system protection and related diseases like dementia. DHA is more efficient as a neuroprotective then EPA	37
		Alzheimer's Disease	
16.	Role of cholesterol and sphingolipids in brain development and neurological diseases.	This study showed that a decreased plasma level of DHA is related to the cognitive decline associated with aging. The most affected areas of the brain are the cortex and hippocampus which are mainly responsible for memory and learning. Many experimental and epidemiological studies showed that the hazard of Alzheimer disease can be reduced with high consumption of DHA.	16
17.	Inhibition of sphingomyelin synthase-1 ameliorates alzheimer-like pathology in APP/PS1 transgenic mice through promoting lysosomal degradation of BACE1	In mammalian brain, DHA (omega-3) fatty acid is present in abundant amount; its level can be altered by diet, aging of brain membrane. The neuronal membrane fluidity increased by the incorporation of omega-3 PUFA in neuronal membranes which improves the neurotransmission signaling in the brain.	7
18.	Omega-3 Polyunsaturated Fatty Acids and Oxylipins in Neuroinflammation and Management of Alzheimer Disease	Alzheimer's disease is a neurodegenerative disease. Current knowledge of the pathology showed that AD is caused by progressive loss of synapses and neurons. Neuroinflammation and cognitive decline can be reduced by consumption of DHA, EPA and oxylipins. EPA positively	33

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		affects mood disorders, and DHA maintains the normal structure of the brain.	
		Parkinson's Disease	
19.	Role of cholesterol and sphingolipids in brain development and neurological diseases.	One-third of Parkinson's disease patients are dealing with depression, they also experience tremor, behavioral and postural issues. In the advanced stages of the disease, dementia is seen in the patients. A drop in fatty acid concentration is also seen in neurodegenerative problems like Parkinson's disorder.	16
20.	Significance of long chain polyunsaturated fatty acids in human health.	In Parkinson disease, the n-3 PUFAs showed neuroprotective effect. Both EPA and DHA were used in the treatment of cognitive disorder, and they positively improved brain health. PUFAs play a beneficial role in reducing the symptoms of the disease, such as lowering anxiety, improving mood and cognitive functions.	37
21.	Contribution of cholesterol and oxysterols to the pathophysiology of Parkinson's disease.	In this study, DHA was used to treat or lower the signs and symptoms of Parkinson's disease. 75% of patients were treated with DHA and EPA (DHA 800 mg/day and EPA 290 mg/day) for 6 months.	27

Liver fat can also be reduced by the consumption of polyunsaturated fatty acids. Sleep-related issues and brain functions may improve with the intake of essential fatty acids.[24] Both omega-3 and omega-6 fatty acids increase eicosanoids in the skin, which contribute to inflammatory response and promote healthy skin. In individuals with diabetes or insulin resistance, healthy fats help regulate glucose levels and maintain healthy blood sugar levels.[25]

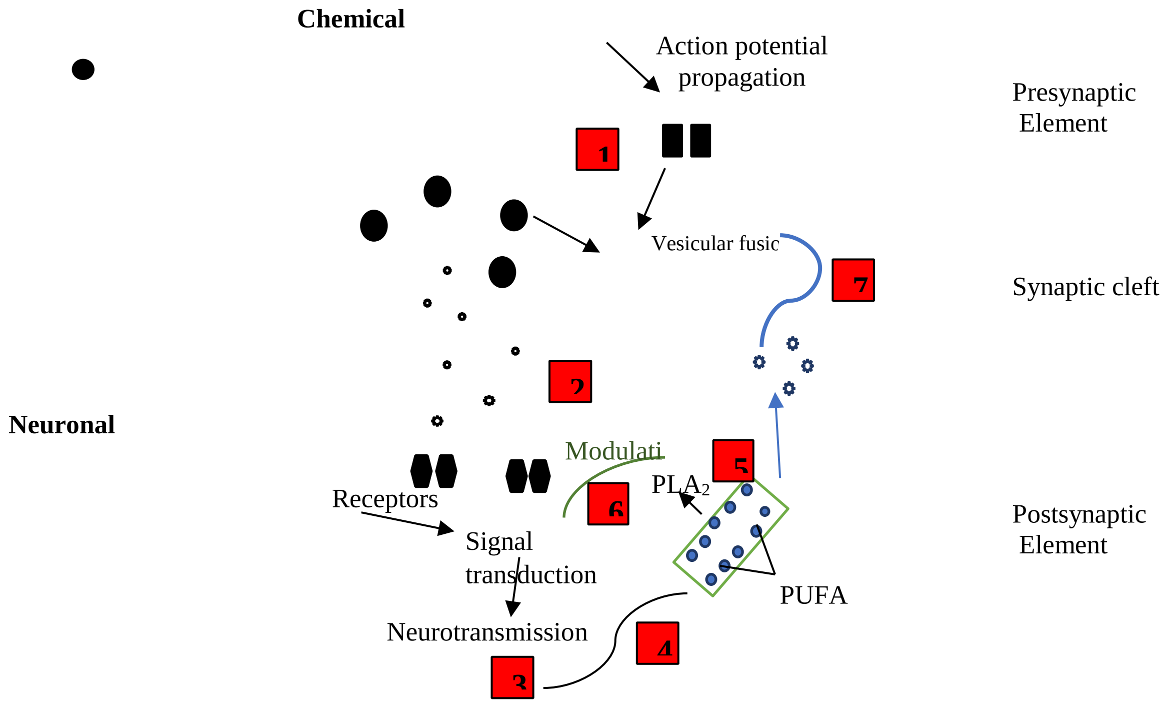

Figure 1: Role of PUFA's and its Derivatives in Neurotransmission

Importance of PUFAs in the Neurological Development of the Foetus

The development of the human brain begins in the third trimester of pregnancy, during which the foetal brain starts to accumulate DHA. This process continues postnatally, relying on breastmilk.[27, 28] Omega-3 fatty acids are vital dietary nutrients, providing the 22-carbon, six double-bond fatty acid known as DHA, which is essential for the growth and function of nervous tissue. Insufficient consumption of ω-3 PUFAs reduces DHA and increases ω-6 PUFA levels in the brain.[28, 29] In humans, the ability to convert ALA to DHA is extremely limited, especially in foetuses, who depend heavily on the maternal transmission of DHA via the placenta.[30, 31] This transmission is influenced by the mother's DHA production and the release of DHA from adipose tissue. Additionally, desaturase enzymes are responsible for converting alpha-linolenic acid (ALA) into DHA and linoleic acid (LA) into arachidonic

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acid, the second most important PUFA for brain development.[28, 32] Low levels of DHA may impair neural development, particularly in pre-term infants who miss out on maternal DHA supplies during the third trimester.[33, 34] Reduced DHA in the developing brain can lead to deficits in neurogenesis, neurotransmitter metabolism, and altered learning and visual functions in animals.[35] The DHA status of newborns and breastfed infants is dependent on maternal DHA intake, which varies widely. Epidemiological studies have linked low maternal DHA levels with a higher risk of impaired foetal neural development.[36, 37] Research suggests that increased maternal DHA intake reduces the risk of poor infant and child vision and neurological development. Therefore, there is substantial evidence to conclude that maternal FA nutrition is crucial for providing DHA to the infant both before and after birth, with both short- and long-term implications for neurological function.[38] Considering the role of ω-3 FAs in brain formation and development, improving omega-3 and omega-6 PUFA intake during pregnancy, lactation, and in the diet provided to neonates and infants on formula is important.[31, 39]

Conclusion

Polyunsaturated fatty acids and their derivatives play a vital role in maintaining a healthy brain and in foetal neurodevelopment during pregnancy. Adequate amounts of docosahexaenoic acid (DHA) are essential for synaptic mechanisms, a crucial step in the structural and functional development of the nervous system. Fats are also required for axonal regeneration after nerve injury. Focusing on the metabolism of polyunsaturated fatty acids in the body can help address many nerve injuries. Research shows that improving fat transport and increasing efficacy in treating neurodevelopmental disorders can provide immunity and inhibit further disease progression. DHA, a critical component of cell membranes, plays a beneficial role in the lifecycle of cells. This review has uncovered several hidden mechanisms of polyunsaturated fatty acid and DHA metabolism in relation to brain health and physiology, although further detailed research is necessary to fully understand these mechanisms. Additionally, the relationship between abnormal DHA and PUFA metabolism and neurodegenerative diseases (NDD) is discussed. More studies are required to improve the therapeutic applications of polyunsaturated fatty acids and their derivatives, specifically targeting agents that depend on them. Reducing total fat intake to 30% or less of total calories—particularly saturated fatty acid intake, which should be less than 10% of calories—and limiting cholesterol intake to less than 300 milligrams per day are recommended. Reducing the intake of unhealthy fats by replacing them with healthier options such as fish, skinless poultry, lean meat, and skim dairy products, as well as increasing the consumption of fruits, vegetables, cereals, and legumes, while avoiding egg yolks, fats, oils, and fried foods, is advised. This review suggests that consuming a diet rich in anti-inflammatory and antioxidant components such as nuts, fruits, vegetables, and spices, combined with lower caloric intake, can ultimately reduce age-related cognitive decline and the risk of developing neurodegenerative disorders.

Conflict of Interest

The authors declare no conflict of interest.

Author's Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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