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Review Article

Exploring the Impact of Diet on Inflammation in Neurological Disorders: A Review

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ABSTRACT

Introduction: Neurological disorders pose significant challenges globally in terms of disability and mortality. Increasing evidence underscores the role of inflammatory processes and gut microbiome imbalances in these conditions, prompting exploration into dietary approaches like the Mediterranean, ketogenic diets, and DASH (Dietary Approaches to Stop Hypertension) for their potential benefits. With ongoing advancements in understanding neurodegenerative diseases like Alzheimer's, Parkinson's, Multiple sclerosis, Depression, and Schizophrenia, there is a heightened focus on finding more impactful interventions.
Methods: This review delves into the influence of diet and its components on inflammation linked to neurological diseases like Alzheimer's disease development and progression. Data from in vitro experiments, animal models, and various studies are integrated, providing a comprehensive analysis of effectiveness of nutritional interventions to combat neurodegenerative disorders. Systematic searches of reputable databases like PubMed and Google Scholar ensured the inclusion of up-to-date and reliable literature.
Key Findings: Data suggests that adopting a diet rich in anti-inflammatory elements such as minerals, vitamins, polyphenols, omega-3 fatty acids and probiotics from vegetables, fruits, spices, herbs, nuts, and legumes could foster a brain-friendly environment and reduce neurological disease risks.
Conclusion: Nutritional strategies hold promises as a non-invasive and effective approach to combatting these disorders.

Keywords: Neurological conditions, inflammation, anti-inflammatory diet, Nutrition intervention, psychological disorders, Degenerative brain disorders, Alzheimer's Disease

INTRODUCTION

Neurological disorders are commonly associated with the aging population. Among younger individuals, meningitis and epilepsy are the primary conditions treated, whereas neurodegenerative diseases like Alzheimer's and Parkinson's are more prevalent among the elderly. In Eastern Europe, strokes and migraines have the highest incidence according to Disability-Adjusted Life Year (DALY) rankings, followed by Alzheimer's, brain and nervous system tumours, drug-related headaches, epilepsy, and others [1-3]. Diseases affecting the CNS are significant health concerns, potentially leading to death or disability [4]. The development of neurological illnesses involves complex processes with various potential causes, including brain, spinal cord, or nerve injuries, as well as genetic, environmental, congenital, infectious, and lifestyle factors.

Some neurological conditions show gender differences in prevalence or outcomes, such as autism being more common in boys, depression in women, Parkinson's disease in men, and multiple sclerosis in women. Women tend to have a less favourable outcome in stroke cases, experiencing a more rapid decline in health status compared to men [5].

Role of free radicals in increasing the risk of neurological disorders

Free radicals, mainly generated by molecular oxygen, are thought to increase the risk of various health issues, including aging and neurological disorders [6]. The damage caused by free radicals to tissue biomolecules like lipids, proteins, and DNA is believed to significantly contribute to oxidative stress-related pathophysiology. Oxidative stress is identified as a key factor in CNS disorders at the cellular level. Neurodegenerative conditions such as Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, and stroke (brain ischemia/reperfusion injury) are closely linked to oxidative damage [6].

Influence of microbiota in mood and behaviour regulation:

Recent research indicates that dietary choices influence molecular processes governing energy metabolism and synaptic plasticity [7-10]. Nutrients affect factors such as microbiome composition, microbial metabolites, gastrointestinal signalling molecules, and neurotransmitters, suggesting that dietary patterns impact metabolic changes and inflammation development [7,8]. Studies suggest a connection between alterations in microbiota composition and psychiatric disorders like depression, anxiety, and schizophrenia, with the gut-brain axis playing a crucial role. The microbiota's influence extends to neurotransmitter levels like serotonin and dopamine, which are involved in mood and behaviour regulation. Some studies indicate that probiotics might offer benefits for depression, anxiety, and cognitive function [11-13].

Research findings from animal models of CNS impairment support the hypothesis that nutrients, whether obtained through whole foods or dietary supplements, can mitigate the effects of brain damage. Diet and exercise present a non-invasive and practical approach to aiding in the treatment of neurologic and cognitive diseases [4]. Nutraceuticals containing vitamins, minerals, amino acids, fatty acids, or plant extracts in supplement form have gained attention for their potential role in this regard [14]. Optimal sleep, hydration, and a balanced diet are crucial for maintaining mental effectiveness [6]. However, the consumption of ultra-processed foods, high in saturated fats and carbohydrates, has been steadily increasing worldwide. These foods often lack naturally occurring ingredients and are packed with preservatives, stabilizers, emulsifiers, and other additives aimed at extending shelf life and enhancing profitability, ultimately posing a negative impact on the body, especially the brain [7].

The constituents of ultra-processed foods are not nutritionally recommended for frequent and large consumption [18]. Artificial preservatives, including synthetic or semi-synthetic compounds like benzoates, sorbates, nitrites, nitrates of potassium or sodium, potassium sulphites, glutamates, and glycerides, are generally considered safe but may have negative effects on consumer health [9]. Predicting the long-term effects of these components, even when present in small concentrations, on the complex human body is challenging [8,9]. However, evidence suggests that excessive consumption of these compounds could be unhealthy and accelerate the onset of chronic diseases [7-9].

Simple sugars and saturated fatty acids have been linked to memory problems and damage to the hippocampus [15]. Studies on mice have demonstrated that exposure to high-fat diets or simple sugars from infancy can negatively affect hippocampus-dependent learning and memory functions, with these deficiencies sometimes persisting into adulthood despite nutritional intervention, independent of obesity and metabolic disturbance [15-16]. While malnutrition remains a significant issue in less developed countries, excessive caloric intake and lack of physical activity are major concerns in the Western world, leading to weight gain and associated health problems. To promote good health, it's essential to maintain a balanced diet rich in fruits, vegetables, whole grains, lean proteins, and healthy fats, along with regular physical activity. The brain relies on glucose as its primary fuel for processing and storing data, but an excessive intake of simple carbohydrates has been shown to negatively impact brain vessels [16]. Recent studies indicate that the high intake of simple carbohydrates and saturated fats in an ultra-processed diet alters the redox state, gut microbiota, and inflammatory response [17,18]. The functioning of the CNS depends on both internal and external factors. Internal factors, known as neurotrophic elements, regulate the survival, growth, and function of nerve tissue by activating various signalling pathways and receptors. External factors also play a crucial role in brain function. This review aims to explore in-depth the influence of diet, including its inflammatory properties, on the onset and/or progression of CNS disorders.

Mechanisms associated with diet and neurological disease development.

The relationship between diet and inflammation is closely linked to the development of neurological diseases like Alzheimer's, Parkinson's, multiple sclerosis, schizophrenia, bipolar disorder, and depression. Dietary factors serve as significant regulators of inflammation, with a diet rich in whole foods such as fruits, vegetables, whole grains, and lean proteins associated with reduced levels of inflammatory markers like C-reactive protein (CRP) and interleukin-6 (IL-6). Conversely, diets high in processed foods, saturated fats, refined carbohydrates, and red meat have been correlated with elevated inflammation levels and an increased risk of chronic diseases, including neurological disorders.

Inflammation promoting diet

An inflammation-promoting diet comprises foods that can stimulate an inflammatory response in the body. In recent decades, Westernized countries have witnessed a significant shift towards increased consumption of Western diets, which are associated with inflammation-promoting effects. An inflammation-promoting diet is characterized by high consumption of processed meals, convenience foods, snacks, sugary soft drinks, high-fat foods, and carbohydrates. Ultra-processed foods contain a plethora of additives like preservatives, stabilizers, emulsifiers, bulking agents, and flavourings, which are not recommended for frequent or excessive consumption from a nutritional standpoint. Saturated and trans fats found in animal products and processed foods can increase inflammation by stimulating the production of pro-inflammatory cytokines like IL-1, IL-6, and TNF-alpha, with studies linking high intake of these fats to an increased risk of Alzheimer's disease and cardiovascular diseases [12-13,19]. Conversely, diets low in fat but high in omega-3 fatty acids have shown to protect against cognitive decline [20]. Polyunsaturated fats, particularly omega-3s, exhibit anti-inflammatory properties and are associated with reduced risk of cardiovascular mortality. The balance between omega-6 and omega-3 fatty acids is crucial in modulating inflammation and preventing non-communicable diseases [21-25].

Refined carbohydrates, such as white bread and sugary drinks, cause rapid spikes in blood sugar levels, leading to increased insulin release and potentially contributing to insulin resistance and inflammation [15]. Consuming high glycaemic index foods frequently correlates with elevated levels of inflammatory markers like CRP, TNF-α, IL-

1β, and IL-6, while dietary fibre intake has the opposite effect [17,18,26]. Additionally, an inflammation-promoting diet tends to be low in antioxidant-rich fruits and vegetables, which play a vital role in neutralizing free radicals and reducing inflammation. A diet lacking in these foods can lead to increased oxidative stress and inflammation, negatively impacting physical and mental health [16].

Anti-inflammatory components of diet

The impact of dietary components on human neurological function has been a subject of interest for researchers for decades, with growing evidence suggesting certain components have beneficial effects on the onset and progression of neurological disorders [7,27]. Here, we highlight dietary components with high anti-inflammatory and antioxidant activity:

- **High Fruits and Vegetables intake linked to lower inflammatory markers:**

Consuming a diet rich in fruits and vegetables is associated with lower levels of inflammatory indicators. These foods are abundant in bioactive substances like polyphenols, antioxidant vitamins, minerals, and fibre, inversely correlating with inflammation and oxidative stress. Research shows that adult consumption of fruits and vegetables is negatively correlated with pro-inflammatory cytokines and reactive oxygen species. It's recommended to consume five portions of fruits and vegetables daily to lower these markers [28].

- **Spices and herbs shown positive influence on health**

Herbs and spices, due to their high biological activity, complement various cuisines and offer positive health impacts [29,30].

Their antioxidant and anti-inflammatory effects are attributed to compounds like terpenes, phenolic acids, and flavonoids [31].

Curcumin and garlic stand out for their potent anti-inflammatory effects. Curcumin, found in turmeric, regulates various biological targets involved in inflammation, while garlic possesses multiple beneficial properties, including anti-inflammatory and antioxidant effects. Compounds like allicin, diallyl sulphide, diallyl disulfide, diallyl trisulfide, quercetin, and kaempferol in garlic exhibit strong anti-inflammatory effects and may be beneficial in inflammatory bowel disease treatment [31].

These dietary components offer promising avenues for mitigating inflammation and oxidative stress, potentially impacting the development and progression of various neurological disorders [32].

- **Zingiber Officinale**

Terpenes and phenolic compounds, particularly gingerols, are common physiologically active substances found in ginger, known for their anti-inflammatory, antioxidant, and analgesic properties [33]. Studies in rats have shown that high doses of ginger significantly reduce serum levels of PGE (2) and TXB (2), with a higher dose also resulting in a significant reduction in serum cholesterol levels. These findings suggest that ginger may have cholesterol-lowering, antithrombotic, and anti-inflammatory effects [33]. Initially, it was thought that ginger's anti-inflammatory effects were due to its inhibition of key enzymes involved in arachidonate metabolism, such as cyclooxygenase (COX) and 5-lipoxygenase (LOX). However, further research has revealed that ginger also downregulates the expression of pro-inflammatory genes [33].

Recent studies suggest that ginger preparations may positively impact COVID-19-related lung inflammation due to their anti-inflammatory and immunomodulatory properties [34,35].

Rosemary (Rosmarinus officinalis L.), native to the Mediterranean region, is known for its antimicrobial essential oil and is recognized in traditional medicine for its antioxidant and anti-inflammatory properties. Extracts and compounds derived from rosemary have demonstrated significant anti-inflammatory effects, attributed to compounds like carnosol, betulinic acid, and ursolic acid. These substances inhibit the release of proinflammatory mediators like NOx, IL-1, and TNF-1α while reducing leukocyte activation at the site of inflammation. Rosemary's anti-inflammatory properties make it a potential treatment for skin conditions like eczema [36-38].

Oily marine fish is a rich source of omega-3 fatty acids, particularly EPA and DHA, which possess anti-inflammatory, antiarrhythmic, anti-hypertensive, and anti-aggregating properties. These fatty acids also lower blood triglyceride levels, reducing the risk of cardiovascular incidents [27]. Seaweed and α-linolenic acid, a precursor to EPA, are additional sources of omega-3 acids that can be obtained from the diet [27].

- **Soybeans and Legumes**

Legume seeds, including soybeans, are high in fibre and vegetable protein. Soy isoflavones have demonstrated anti-atherosclerotic, antioxidant, antiproliferative, and anti-amyloidogenic properties, providing health benefits in preventing various diseases such as heart disease, obesity, cancer, diabetes, and osteoporosis [39,40].

Substituting some animal protein with vegetarian protein, especially in patients with chronic inflammatory diseases, is recommended [27,41]. Additionally, metabolites generated in the gut after consuming soy products may lower the risk of developing dementia [42].

- **Vegetable oils with unsaturated fatty acids**

Olive oil, have various health benefits. Olive oil contains monounsaturated fatty acids that modify anti-inflammatory pathways, reducing inflammation. Its composition, including high levels of oleic acid, vitamin E, and polyphenols, makes it resistant to oxidative changes and effective in minimizing cholesterol absorption [43]. Extra virgin olive oil is associated with a reduced risk of chronic degenerative diseases like cardiovascular disease, type 2 diabetes, and cancer due to its antioxidant, anti-inflammatory, and immunomodulatory properties [23,43].

Gamma-linolenic acid, an anti-inflammatory fatty acid from the n-6 family, can be added to the diet to treat disorders with severe inflammation. Evening primrose oil, borage oil, or blackcurrant seed oil are alternative sources of this compound. These dietary components offer promising avenues for combating inflammation and improving overall health [44].

- **Seeds and Nuts**

Incorporating nuts and seeds into snacks or meals can support the anti-inflammatory effects of the diet due to their rich content of nutrients such as dietary fibre, phytonutrients, vitamins, minerals, and essential fatty acids. High consumption of pumpkin seeds, pistachios, walnuts, and almonds is advised for their high antioxidant content [28]. These nuts contain active compounds that enhance the body's endogenous antioxidant defence and regulate the cellular redox state. Several studies have indicated that nuts, including almonds, hazelnuts, and walnuts, contain micronutrients and phytochemicals that can impact various pathways involved in Alzheimer's disease, such as amyloid genesis, tau phosphorylation, oxidative stress, and cholinergic pathways [45,46].

- **Tea**

Tea, both black and green, contributes significantly to reducing inflammation in the diet. Green tea extract, high in phenolic compounds, exhibits antioxidant capacity and inhibits LDL-cholesterol oxidation, making it a partial substitute for water in quenching thirst while lowering disease progression [30].

- **Coffee**

Research suggests that caffeine found in coffee, tea, and chocolate may have a protective effect against Alzheimer’s disease by reducing inflammation and protecting brain cells from damage. Studies have shown that caffeine intake is associated with a lower risk of developing Alzheimer’s disease in older adults [46-48].

- **Red wine**

Moderate consumption of red wine, particularly red dry wine, has been associated with a reduced risk of dementia and cognitive decline due to its polyphenol content, especially resveratrol [49-50]. Resveratrol supplementation can enhance cognition alongside cerebrovascular function, but it should be consumed in moderation (no more than 1 glass per day) and is not additionally advised for the prevention of cardiovascular disorders in non-drinkers [28].

- **Dark chocolate**

Dark chocolate, rich in cocoa flavanols, possesses anti-inflammatory and antioxidant properties that positively impact cognitive function and neuroplasticity [28]. Cocoa and cocoa products have been shown to have a positive impact on human cognition, particularly in elderly populations and patients at risk [28,30].

Diet and microbiome and its effect on neurological disease development and its outcome

The composition and amounts of the diet significantly impact the structure and function of the human microbiota, with recent research indicating that the gut microbiome can influence the development and outcomes of neurological diseases [16,51]. A healthy gut microbiome is crucial for maintaining overall health by positively affecting metabolic and immunological functions [52]. Often referred to as "the second brain" due to its resemblance to brain cells, the gut microbiota plays a critical role in regulating overall brain function through various pathways, including immune, endocrine, and vagal routes, influencing hormones, neurotransmitters, cytokines, and short-chain fatty acids [53-55].

Preclinical investigations suggest that administering probiotics can reduce both peripheral and central inflammation, as well as mitigate oxidative stress by altering levels of specific markers. In conditions like Multiple sclerosis (MS), Alzheimer’s disease (AD), and Parkinson’s disease (PD), alterations in the gut microbiome composition have been observed, characterized by shifts in beneficial and pro-inflammatory bacteria. High-fat diets have been shown to exacerbate symptoms and disease progression in animal models and humans with these neurological conditions [56,57].

A healthy diet rich in fiber and beneficial nutrients can promote a diverse and stable gut microbiome, potentially reducing the risk of neurological diseases. Conversely, a high-fat diet leading to dysbiosis and inflammation may increase the risk of these conditions and worsen their outcomes. In depression, dietary factors such as high-fat diets or low fibre intake have been linked to dysbiosis and inflammation, exacerbating depressive symptoms. Conversely, a diet rich in plant-based foods and whole grains has been associated with a more diverse and stable gut microbiome, potentially reducing the risk of depression and improving outcomes [58].

Furthermore, probiotics have shown promise in improving depressive symptoms and cognitive function in preclinical studies, highlighting the potential of targeting the gut microbiome for mental health interventions [59]

Significance of adopting an anti-inflammatory diet for the prevention and treatment of neural degenerative disorders

Alzheimer's disease

Alzheimer's disease (AD) remains a significant global challenge despite extensive efforts to prevent and treat it, with projections estimating 100 million AD patients worldwide by 2050[59]. This complex neurodegenerative disease is characterized by irreversible behavioural changes and has multiple risk factors, including age, gender, cardiovascular health, alcohol consumption, social engagement, sleep quality, and conditions such as depression and Down syndrome [60]. Individuals with Down syndrome are at a higher risk of developing AD, often exhibiting symptoms earlier than the general population. Engaging in mentally and socially stimulating activities has been linked with a decreased risk of AD [61].

While aging increases the likelihood of developing AD, it is not an inevitable aspect of aging. Women represent a majority of AD patients, and hormonal differences, particularly the effects of oestrogen and testosterone, may play a role in sex differences in neurological diseases. Oestrogen has shown neuroprotective effects, while testosterone may have neurotoxic effects, though the impact of these hormones varies depending on the disease and life stage [62-64].

The pathology of AD involves neurodegeneration, including extra neuronal neuritic plaques and neuronal death due to excessive production of amyloid β (Aβ) peptide. Protein phosphatase 2A (PP2A), a tau protein phosphatase, is involved in the regulation of tau protein phosphorylation. Dysregulation of PP2A can lead to the formation of neurofibrillary tangles, contributing to AD pathology [59]. Adopting an anti-inflammatory diet may play a significant role in the prevention and treatment of AD by addressing inflammation, oxidative stress, and other factors implicated in the disease's progression.

Research suggests that Alzheimer's disease (AD) patients exhibit lower levels of brain insulin signalling and fewer brain insulin receptors, leading to brain insulin resistance [65,61]. Positron emission tomography (PET) data indicates a deficiency in cerebral glucose metabolism of 20–25%, along with a reduced number of mitochondria in neurons. These neurons also show diminished citric acid cycle and respiratory chain activity, resulting in decreased energy production [65].

Studies have investigated the effect of diet on AD treatment, with a focus on ketone bodies as a cellular energy source [65]. A randomized crossover trial assessed the impact of the ketogenic diet on AD patients' condition, demonstrating improvements in activities of daily living, quality of life, and cognitive function. Additionally, a study evaluated the influence of the Mediterranean diet enriched with coconut oil on AD patients, reporting improvements in cognitive abilities, memory, and inflammatory markers.

Furthermore, research on the Modified Atkins Diet (MAD) and a ketogenic diet showed beneficial effects on cognitive function and inflammatory markers in patients with AD, suggesting the potential of dietary interventions in managing the disease [66]. These findings underscore the importance of diet in AD treatment and support the exploration of dietary strategies to mitigate cognitive decline and inflammation associated with the disease.

Research findings suggest that adherence to the Mediterranean diet is associated with improved cognitive performance, reduced risk of cognitive decline and impairment, and a lower incidence of Alzheimer’s disease (AD). In a study by Hoscheidt et al., the impact of the Mediterranean and Western diets on AD biomarkers was evaluated in patients with mild cognitive impairment. Surprisingly, the Mediterranean diet increased CSF amyloid Beta (AB) levels in healthy individuals, while the Western diet decreased them. Conversely, in patients with impaired cognitive functions, the Mediterranean diet decreased AB levels, and the Western diet increased them.

Furthermore, studies have examined the effects of omega-3 supplementation alone and in combination with lipoic acid (LA) on oxidative stress and cognitive function in

AD patients [66]. While omega-3 supplementation alone did not significantly impact oxidative stress or cognitive function, the combination of omega-3 and LA slowed cognitive and functional decline over 12 months.

Additionally, research by Sun et al. explored the relationship between malnutrition and hyperhomocysteinemia in AD patients and the effect of diet intervention with betaine [61,67]. Malnutrition was prevalent in AD patients and associated with high levels of homocysteine. Betaine supplementation improved cognitive function, decreased phosphorylated Tau protein levels, inhibited A-Beta accumulation, and reduced proinflammatory cytokine levels in AD patients [61].

These findings underscore the significant impact of diet on the treatment of AD and highlight the potential of dietary interventions, such as the Mediterranean diet and supplementation with omega-3 and betaine, in managing the disease and improving cognitive function [68].

MATERIALS & METHODS

Data from in vitro experiments, animal models, and various studies are integrated, providing a comprehensive analysis of effectiveness of nutritional interventions to combat neurodegenerative disorders. Systematic searches of reputable databases like PubMed and Google Scholar ensured the inclusion of up-to-date and reliable literature.

RESULT

Evidence suggests that specific dietary patterns, such as the Mediterranean diet, are associated with a lower risk of cognitive decline in Alzheimer's disease and slower disease progression in Parkinson's disease. Additionally, diets like the ketogenic diet have shown promise in managing symptoms of multiple sclerosis and Alzheimer's disease. Furthermore, maintaining a diverse and healthy gut microbiome through proper nutrition can support neurological health by promoting neurotransmitter production, regulating inflammation, and preserving the integrity of the blood-brain barrier.

CONCLUSION

The conclusions drawn from the presented data highlight the significant impact of dietary choices on neurological health. Adopting a healthy diet rich in antioxidants and anti-inflammatory compounds can play a crucial role in combating various neurological disorders by restoring metabolic balance, reducing oxidative stress, and modifying inflammatory pathways.

Overall, the data underscores the importance of prioritizing a healthy diet and gut microbiome to actively support neurological health and reduce the risk of developing neurological diseases. However, further research is needed to fully understand the intricate mechanisms underlying the effects of dietary patterns on neurological disorders and to develop more targeted and effective dietary interventions.

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