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Nutritional Regulation of Neuro-Inflammation: Mechanisms, Evidence, and Public Health Benefits

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Abstract

Neuro-inflammation is a major pathological feature that is responsible for a variety of neurologic and psychobiotic conditions like Parkinsosn's, Alzheimer's, multiple sclerosis, depression, and cognitive impairment. The growing body of research suggests that nutrition can significantly influence Neuro-inflammation processes through its effects on the regulation of the immune system, the generation of free radicals, the health of the metabolism, and signaling in the gut-brain axis. This review summarizes the present knowledge regarding the dietary management of Neuro-inflammation, especially focusing on the pathways of the mechanisms through which this occurs, the support of preclinical and clinical studies, and the implications for public health. An even wider range of dietary patterns and nutrients, among which are the omega-3 fatty acids, polyphenols, dietary fiber, vitamins, and minerals, are discussed regarding their impact on microglial activation, inflammatory cytokine production, and neuroprotective signaling pathways. The record further addresses the function of intestinal microbiota as player in the Neuro-inflammation reactions triggered by diet. The paper showcases the potential of artificial intelligence and machine learning in nutritional neuroscience with applications such as dietary pattern analysis, biomarker discovery, and customized nutrition methods. When looking at public health, food based interventions are seen as cost-effective, scalable ways to get rid of the Neuro-inflammation burden and keep the brain healthy at the level of the population. The review also points out the existing shortcomings, the areas of research that need to be filled, and the ethical considerations that are always there, and stresses the need for standardized biomarkers,

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longitudinal studies, and equal access to nutritious foods. In general, the combination of nutrition strategies and digital technologies in public health systems for the treatment of Neuro-inflammation and the improvement of neurological outcomes has great potential.

Abbreviation

AGEs	Advanced glycation end products
AI	Artificial Intelligence
ARE	Antioxidant response element
BBB	Blood–Brain Barrier
CNS	Central nervous system
CRP	C-reactive protein
DASH	Dietary Approaches to Stop Hypertension
DHA	Docosahexaenoic acid
EGCG	Epigallocatechin gallate
EPA	Eicosapentaenoic acid
GABA	Gamma aminobutyric acid
GPCRs	G-protein coupled receptors
HDAC	Histone deacetylase
HO-1	Heme oxygenase-1
IL-10	Interleukin 10
IL-6	Interleukin 6
LPS	Lipopolysaccharides
MAPK	Mitogen-activated protein kinase
MAPMPs	Microbial associated molecular patterns
ML	Machine Learning
MS	Multiple sclerosis
NK-KB	Nuclear factor kappa B
NMDA	N-methyl-D-aspartate
Nrf2	Nuclear factor erythroid 2–related factor 2
RCTs	Randomized Controlled Trial
RNA	Reactive nitrogen species
ROS	Reactive oxygen species
SCFAs	Short chain fatty acids
SOD	Superoxide dismutase
TLR4	Toll-like receptor 4
TNF-α	Tumor necrosis factor-α
ZO-1	Zona occludens-1

Introduction

Neuro-inflammation is defined as the central nervous system (CNS) response to injury and disease that involves immunological activation of microglia and astrocytes along with the release of inflammatory mediators like cytokines, chemokines, and reactive oxygen species (ROS).[1] While acute Neuro-inflammation responses are powerful and highly active, they are essential for protecting the host and facilitating tissue repair. The chronic or improperly regulated Neuro-inflammation is increasingly acknowledged as a crucial pathological factor contributing to numerous neurological and psychiatric conditions.[2] Abstaining from neuronal inflammation exposure, maintaining the type of synapses, and preventing the loss of neurons, the blood-brain barrier, and neurogenesis are all done by Neuro-inflammation.[3] Neuro-inflammation impedes

the brain's way of processing, which leads to clinical manifestation and cognitive decline in patients quicker than if they had not been exposed to Neuro-inflammation. Parkinson's disease, Alzheimer's disease, multiple sclerosis (MS), depression, and some other neuropsychiatric disorders are the major areas where the Neuro-inflammation pathways are shared and the Neuro-inflammation can be considered the unifying biological process across the diversity of brain disorders.[4] The global burden of the diseases related to Neuro-inflammation is enormous, and the situation gets worse with time.[5] As per the latest report, Alzheimer's alone accounts for nearly 60-70% of the estimated 55 million dementia patients worldwide.[6] Furthermore, Parkinson's disease, which has already affected more than 10 million people, has seen its incidence rate more than double in the last 30 years.[7] Up to 2.8 million people are suffering from multiple sclerosis, which is often the cause of long-term disability.[8] At the same time, neuropsychiatric disorders like depression are still affecting over 280 million people globally and are increasingly being recognized as a consequence of inflammatory and immune dysregulation.[9] The disorders, together, have a tremendous impact on the economy and society, and each year they account for billions of dollars spent in the healthcare sector and the demand for caregivers.[10] This issue of aging has not only made it inevitable but also urgent to uncover the risk factors that can be prevented and modified, which in turn will lessen the Neuro-inflammation processes. Nutrition has, in this respect, become one of the most likely candidates among the modifiable determinants of Neuro-inflammation and brain health. Food components affect Neuro-inflammation pathways via several mechanisms, such as controlling the inflammation throughout the body, oxidative stress, insulin sensitivity, and altering the composition of gut microbiota.[11] Diets that are rich in ultra-processed foods, sugar, and saturated fats not only worsen the inflammatory biomarkers but also increase the risk of cognitive decline. Conversely, diets abundant in nutrients, like the Mediterranean and plant based diets, have demonstrated contrasting outcomes, namely reducing Neuro-inflammation and improving cognitive function.[12] Moreover, specific nutrients such as omega-3 fatty acids, polyphenols, dietary fiber, vitamins, and minerals are recognized for their anti-inflammatory and neuroprotective properties in both experimental and clinical settings.[13,14] Diet based interventions are cost effective, culturally adaptable, and scalable to large populations. Consequently, they hold significant value for public health initiatives focused on disease prevention and health promotion. The critical analysis of nutrition's role in modulating Neuro-inflammation, drawing on data from mechanistic studies, preclinical models, and human research.[15] Additionally, the involvement of the gut-brain axis is examined along with the prospective use of artificial intelligence and machine learning in nutritional sciences. The synthesizing current evidence and pinpointing research gaps, this review intends to shed light on the public health importance of dietary approaches that are successful in reducing Neuro-inflammation and consequently improving neurological and psychiatric conditions at the population level.

Neuro-inflammation: Biological Basis

The immune response that occurs within the CNS as a result of damage, infection, neurodegeneration, or environmental and metabolic stresses is known as Neuro-inflammation. In contrast to peripheral inflammation, which is primarily mediated by immune cells that invade the site of inflammation, central nervous system inflammation is primarily mediated by resident glial cells, particularly microglia and astrocytes, which are capable of carrying out immune system functions.[15] Microglia are the main immune effector cells of the CNS and they respond very quickly to the pathological stimuli by transforming their morphology and releasing various mediators of inflammation. When activated, microglia release pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and also produce reactive oxygen and nitrogen species.[16] In the short term, the activation of microglia facilitates the neuronal protection, synaptic remodeling, and the clearance of debris, whereas when the activation is prolonged it results in chronic inflammation, synaptic dysfunction, and neuronal death.[17] Astrocytes, which are involved in the maintenance, support, and communication of neurons, are also very important in the inflammatory process occurring in the brain.[18] The activated astrocytes induce the inflammatory process by the release of cytokines, chemokines, and complement proteins and by controlling the permeability of the blood–brain barrier. Chronic neuro-inflammation arises from sustained activation of microglia and astrocytes, leading to prolonged release of

cytokines, chemokines, and reactive oxygen species. Persistent blood-brain barrier dysfunction, impaired resolution pathways, and continuous neuronal injury maintain region-specific inflammatory signaling and progressive neurodegeneration. Cytokines act as the messengers of Neuro-inflammation, linking immune responses and sometimes even increasing the intensity of inflammatory cascades if they are not properly regulated.[19] If the influence of the cytokines becomes too strong or lasts too long, then they will interfere with neuronal communication and eventually lead to the death of neurons as in neurodegeneration. The communication of microglia, astrocytes, and cytokines is the basis of Neuro-inflammation, thus, their interrelations highlight the central position of the latter in the development of both neurological and psychiatric disorders.[20]

Molecular Pathways Involved

Neuro-inflammation represents an intricate biological mechanism that involves the activation of the immune system, production of inflammatory signals, and cell death of neurons. Neuro-inflammation is regulated by nuclear factor kappa B (NF-κB) signalling, NLRP3 inflammasome, activation, and oxidative stress pathways are the three interconnected pathways that primarily control this mechanism.[21] NF-KB controls pro-inflammatory gene expression, NLRP3 mediates IL-1β release, and oxidative stress amplifies neural damage. Numerous triggers, including pro-inflammatory cytokines, microbial agents, and cellular stress, can activate the NF-κB pathway, which is the main regulator of inflammation in the nervous system.[22] When NF-B is exposed to such triggers, it first translocate to the nucleus, where it starts the production of genes that produce pro-inflammatory cytokines such as inducible nitric oxide synthase, IL-1β, IL-6, and tumor necrosis factor-alpha (TNFα).[23] Because NF-κB activation in microglia and astrocytes is persistent, it accelerates neurodegeneration and contributes to persistent Neuro-inflammation. Another inflammatory mechanism is the NLRP3 inflammasome, which operates as a protein complex in the cytosol, detecting signals of cellular distress like the malfunction of mitochondria, the loss of ions' balance, and accumulation of proteins.[24] Activation of the NLRP3 inflammasome results in the processing of IL-1β and IL-18 via caspase-1 and their subsequent release, which subsequently promotes the amplification of the inflammatory process and neuronal injury.[25] The producing large concentrations of reactive oxygen and nitrogen species that harm cellular constituents like lipids, proteins, and DNA, oxidative stress also plays a role in Neuro-inflammation.[26] Activating factors such as NF-κB and the NLRP3 inflammasome sustain the inflammatory signals in a cycle of oxidative stress caused by mitochondrial dysfunction and compromised antioxidant defenses.[27]

Link between Chronic Neuro-Inflammation and Neurodegeneration

Chronic Neuro-inflammation, which is a result of inflammation lasting for a long time, has been shown to accelerate the process of neurodegeneration since the immune pathways in the central nervous system being continually activated lead to the gradual dysfunction of neurons and their eventual deathA.[28] Prolonged Neuro-inflammation causes the persistent activation of microglia and astrocytes, which is accompanied by the continuous release of pro-inflammatory cytokines, chemokines, and reactive oxygen and nitrogen species.[29] Acute inflammatory responses support repair and homeostasis. Consequently, this inflammatory milieu decreases neuroplasticity, slows synaptic connection, and increases the vulnerability of neurons to the harmful effects of glutamate; ultimately, all of these processes lead to the gradual death of neurons. Raised levels of the inflammatory cytokines TNF-α, IL-1β, and IL-6 disrupt neurotransmitter balance and synaptic plasticity, both of which are essential for learning, memory, and cognition.[30] Chronic Neuro-inflammation also contributes to mitochondrial dysfunction and oxidative stress, both of which are major causes of cellular death accumulation. The ROS are produced as a result of chemotactic and inflammatory processes lead to neuronal deaths by affecting membranes, proteins, DNA, and so on, thereby hastening the neuron's aging and vulnerability. Among the other inflammatory pathways, NF-κB and NLRP3 inflammasome are the ones that mainly operate by forming a vicious cycle of inflammation and cellular injury in a manner conducive to their activation.[31] In neurodegenerative diseases, for instance, aggregated proteins in the form of amyloid-β in Alzheimer's disease and α-synuclein in Parkinson's disease not only trigger the activation of microglia but also, through the latter, reinforce the inflammatory responses and thus, the consequences, the destruction of neurons,

and so on.[32] On the down side, persistent Neuro-inflammation weakens the blood-brain barrier, allowing peripheral immune cells and inflammatory mediators to enter the brain and exacerbate pre-existing neurodegenerative processes. Long-term inflammation will cause neuronal death, synaptic loss, and eventually a steady reduction in function. The intimate connection between Neuro-inflammation and dementia indicates that inflammation is a factor that both facilitates and speeds up the disease.[33] Because long-term brain health is at risk, it is now crucial to recognize the significance of early therapies aimed at altering inflammatory pathways.

Dietary Patterns and Neuro-Inflammation Risk

Western Diet and Pro-Inflammatory Effects

The Western diet has a strong pro-inflammatory effect and raises the risk of Neuro-inflammation and related illnesses since it is high in ultra-processed foods, refined carbohydrates, and saturated and trans fats. More precisely, in both peripheral immune cells and brain microglia, unsaturated fats and trans fats trigger innate immune signaling pathways like Toll-like receptor 4 (TLR4) and nuclear factor kappa B (NF-κB).[34] TNF-α, IL-1β, and IL-6 are examples of anti-inflammatory agents that can either penetrate or disrupt the blood-brain barrier, activating microglia and sustaining chronic Neuro-inflammation.[35] The high intake of refined sugars and simple carbohydrates leads to postprandial hyperglycemia oxidative stress and the production of advanced glycation end products (AGEs), which in turn trigger inflammatory signaling, as a result of insulin resistance.[36] Additionally, by reducing microbial diversity and encouraging the growth of pro-inflammatory bacterial strains, the Western diet negatively impacts the makeup of gut microbiota. Increased intestinal permeability brought on by the ensuing dysbiosis permits the release of bacterial endotoxins such lipopolysaccharides (LPS) into the bloodstream, where they trigger both the systemic and central immune responses.[37] The brain eventually loses its ability to signal, form synaptic connections, and produce new neural cells as it becomes accustomed to such dietary induced inflammatory stimuli. This accelerates the development of mood disorders, neurodegenerative diseases, and cognitive decline. Neuro-inflammation in fact, the Western diet through a complex interplay of immune activation, oxidative stress, and metabolic dysregulation, and gut-brain axis disruption, thus, dietary modulation being of great significance for brain health.[38]

Mediterranean, DASH, and Plant Based Diets as Anti-Inflammatory Models

The most debated and accepted anti-inflammatory diets that reduce the risk of Neuro-inflammation through different but interconnected mechanisms. The abundance and variety of fruits, vegetables, whole grains, legumes, nuts, and healthy fats mostly monounsaturated and polyunsaturated fatty acids, such as those found in olive oil and fatty fish as well as the restriction of ultra-processed foods, refined sugars, and saturated fats are common characteristics of these diets. The diet's high omega-3 fatty acid content prevents microglia activation and inhibits pro-inflammatory pathways by reducing their targets, such as TNF-α, which, along with IL-1β and IL-6, are continuously produced by activated immune cells and cause inflammation.[39] Because they can scavenge ROS and activate the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, which enhances the endogenous antioxidant defense, polyphenols and flavonoids are the main heroes in the fight against inflammation and oxidative stress that occurs in fruits, vegetables, and whole grains.[40] Additionally, consuming dietary fiber promotes the diversity of the gut microbiota, which in turn increases the production of short chain fatty acids (SCFAs), such as butyrate, acetate, and propionate, which fortify the intestinal barrier and reduce the amount of systemic endotoxin that may trigger a Neuro-inflammation reaction.[41] Moreover, the dietary patterns enhance insulin sensitivity, change lipid profiles, and diminish oxidative stress, all of which contribute to the reduction of central inflammatory signaling indirectly. Conclusively, the Mediterranean, DASH, and plant based diets positively affect the oxidative stress, immune activation, and gut-brain axis integrity simultaneously.[42] Thus, these diets have created a neuroprotective environment that diminishes chronic inflammation, supports synaptic function, and keeps cognitive health, thereby turning them into effective dietary models for the prevention or mitigation of Neuro-inflammation disorders.

Epidemiological Evidence Linking Diet Quality to Brain Health

Epidemiological studies have always shown that the quality of the diet is highly correlated to the brain

health and the incidence of Neuro-inflammation and neurodegenerative disease. Epidemiological studies link high quality such as the Mediterranean and DASH diets to better brain health. Greater intake of fruits, vegetables, whole grains and omega-3 fatty acids is associated with reduced cognitive decline, lower dementia risk, and improved neurological function across aging populations. Mechanisms of action, rich in nutrients and by their nature, anti-inflammatory diets like the Mediterranean, DASH, and plant based diets affect the brain through the modulation of systemic inflammation, oxidative stress, metabolic regulation, and signaling in the gut-brain axis.[43] The reduction of microglial activation, suppression of NF-κB signaling, and enhancement of antioxidant defenses through pathways such as Nrf2 are the main ways in which high intakes of omega-3 fatty acids, polyphenols, fiber, vitamins, and minerals, together with the reduction of Neuro-inflammation and the preservation of neurons.[44] For one thing, improved insulin sensitivity and lipid regulation lead to a further reduction of metabolic inflammation, while modulation of gut microbiota results in a greater production of short-chain fatty acids, which then reinforce the blood-brain barrier and inhibit Neuro-inflammation signaling. These mechanisms have been quantitatively supported by several large scale epidemiological studies. The Lyon Diet Heart Study stated that a Mediterranean diet led to a 35% risk reduction of cognitive decline and stroke during a 4-year follow-up.[45] The NU-AGE study, with a participation of over 1,200 elderly persons from different parts of Europe, reported that higher Mediterranean diet adherence was related to the presence of lower levels of inflammatory biomarkers, such as CRP and IL-6, and better cognitive performance.[46] The large scale observational data provided by the Nurses' Health Study pointed out that there was a significant relationship between good diet quality scores and the risk of developing depression and age related cognitive decline.[47] Western style diet populations showed higher rates of Alzheimer's disease, Parkinson's disease, and other diseases associated with aging of the nervous system, and these conditions were often connected to increased systemic inflammation and metabolic dysregulation.[48] All these epidemiological observations acted as a strong support to the mechanistic theory that diet quality has a direct impact on Neuro-inflammation pathways and thus brain health by establishing the nutrient dense, anti-inflammatory dietary patterns as the best ways to prevent not only at the individual level but also for public health overall.

Nutrients Regulating Neuro-inflammation

Omega-3 Fatty Acids

The primary function of the omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is to regulate Neuro-inflammation.[49] This is accomplished primarily through cytokine suppression and microglial modulation, which are components of protecting nerve cells and thereby averting chronic neurodegenerative processes.[50] The immune cells in the central nervous system called microglial cells are extremely sensitive to inflammatory stimuli and simultaneously protect neurons and kill those.[51] When these immune cells transition from the active, aggressive, and pro-inflammatory state of M1 to the quiescent, non-aggressive, and anti-inflammatory state of M2, the omega-3 fatty acids have an impact on them by altering their phenotype.[52] Reduced production of pro-inflammatory mediators like TNF-α, IL-1β, and IL-6 and increased secretion of anti-inflammatory cytokines and neurotrophic factors which are critical for neuronal survival and synaptic function are two effects of this kind of anti-inflammatory activity through microglia.[53] At the molecular level, EPA and DHA prevent the transcription of pro-inflammatory genes in microglia and astrocytes by blocking inflammatory signaling pathways like NF-κB and MAPK.[54] In addition to that, these fatty acids act as precursors for SPMs which include resolving, protectins, and maresins, and these mediators are the ones who actively solving the inflammation, speeding up the clearance of the cellular debris, and shielding the neurons from oxidative stress-induced damage.[55] Omega-3 fatty acids have the ability to inhibit the chronic Neuro-inflammation rounds which eventually lead to synaptic dysfunction, neuronal death, and cognitive decline by modulating microglial activity and inhibiting cytokine overproduction. In a way, these mechanisms show that dietary omega-3 fatty acids, as well as their potential in the prevention and management of Neuro-inflammation and neurodegenerative disorders, have neuroprotective effects.[56]

Polyphenols and Antioxidants

Polyphenols and antioxidants, which are bioactive compounds, come in great numbers mainly from

fruits, vegetables, teas, cocoa, coffee, and spices like turmeric and rosemary.[57] They are, indeed, very important in the fight against Neuro-inflammation and the betterment of brain health. On a mechanistic level, the activities of these compounds are to mainly give rise to the antioxidant and anti-inflammatory signaling; thus, they are neuroprotective. Polyphenols contribute to antioxidant activities by scavenging ROS and reactive nitrogen species (RNS), which lowers oxidative stress, the primary cause of chronic Neuro-inflammation and microglial activation.[58] Polyphenols are able to maintain the integrity of neurons and the activity of synapses by preventing oxidative damage to lipids, proteins, and DNA. In addition to antioxidants, polyphenols have an indirect impact on the inflammatory pathways by altering the important players. That is, pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 are produced less frequently when nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling are inhibited in the cells of brain supporting tissues.[59] Some polyphenols, such as resveratrol, curcumin, and epigallocatechin gallate (EGCG), also activate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which strengthens the body's natural antioxidant defenses and increases the expression of detoxification enzymes.[60,61] Regarding the clinical and epidemiological research, they do show that polyphenols have neuroprotective properties. For example, increased consumption of flavonoids has been linked to improved memory in older adults, a decreased risk of Alzheimer's disease, and a slowdown in cognitive decline.[62] Polyphenol rich foods, such as blueberries, cocoa, and green tea, have been used in intervention studies to test participants' cognitive performance in conjunction with a reduction in circulating inflammatory markers. The mechanism of action of the antioxidant and polyphenol activity involved in the modulation of the Neuro-inflammation process and the prevention of brain health deterioration is the suppression of oxidative stress, the suppression of pro-inflammatory cytokines, and the modulation of signaling pathways (Table 1).

Table 1: sources of polyphenols and antioxidants, their bioactive compounds, and neuroprotective mechanisms

Food Source	Bioactive Compounds	Neuroprotective Mechanisms
Berries (blueberries, strawberries)	Anthocyanins, flavonoids, vitamin C	Reduce oxidative stress, inhibit NF-κB signaling, improve synaptic plasticity and memory[63,64]
Tea (green, black)	Catechins, epigallocatechin gallate (EGCG)	Antioxidant activity, microglial modulation, anti-inflammatory signaling.[65]
Cocoa / Dark Chocolate	Flavanols, epicatechin, procyanidins	Enhance cerebral blood flow, reduce ROS, suppress pro-inflammatory cytokines.[66]
Turmeric	Curcumin, demethoxycur-cumin	NF-κB inhibition, Nrf2 activation, cytokine suppression, anti-inflammatory effects.[67]
Olive Oil (extra virgin)	Oleuropein, hydroxytyrosol, polyphenols	Antioxidant and anti-inflammatory effects, improves lipid metabolism and neuronal protection.[68]

Mechanisms: Nrf2 activation, ROS Scavenging

Polyphenols and other dietary antioxidants mainly activate Nrf2 and scavenge ROS to regulate Neuro-inflammation, thus providing essential neuroprotective effects. ROS, which are typically generated in cellular metabolism or as a response of cellular stress, can accumulate under pathological conditions and cause oxidative damage to proteins, lipids, and DNA.[69] Excessive ROS causes pro-inflammatory cytokines to be released, activates microglia and astrocytes, and exacerbates neuronal dysfunction, synapse loss, and cognitive decline.[70]

Additionally, food based antioxidants such as those found in berries, tea, cocoa, turmeric, and olive oil are directly linked to the neutralization of ROS turn reduces oxidative stress and prevents oxidative death of neuronal cells.[71] Polyphenols stimulate the nuclear factor erythroid 2–related factor 2 (Nrf2) signaling pathway, a master regulator of cellular antioxidant defenses, in addition to directly scavenging ROS.[72] Superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), heme oxygenase-1 (HO-1), and other endogenous antioxidant and detoxifying enzymes are produced when Nrf2 is activated and travels to the nucleus, where it binds to the antioxidant response element (ARE) in the promoter regions of target genes.[73] Together, these enzymes increase the cells' resistance to oxidative stress, decrease Neuro-inflammation signals, and maintain the balance of neurons. Additionally, Nrf2 activation reduces pro-inflammatory cytokines including TNF-α and IL-6 by indirectly blocking the NF-κB pathway.[74] The dual action of ROS scavenging by and the Nrf2-mediated induction of antioxidant defenses is the reason why polyphenols and dietary antioxidants suppress chronic Neuro-inflammation, protect neurons from oxidative stress, and hence maintain cognitive function.[75] The above mentioned actions on a molecular level present a compelling rationale for including the foods rich in antioxidants in the diets intended to deter or lessen the effects of neurodegenerative and neuropsychiatric disorders.[76,77]

Dietary Fiber and Prebiotics

The fermentation products, or microbial metabolites, of the gut bacteria that act on the dietary fibers and prebiotics are SCFAs such butyrate, acetate, and propionate. They are the foremost players in the modulation of immune responses and Neuro-inflammation through several pathways that unite gut health with brain function. The increasing the production of tight junction proteins, which reduces gut permeability and stops bacterial endotoxins like LPS from entering the circulation, SCFAs contribute to the maintenance of the intestinal barrier.[78] As a result, there is less systemic inflammation, which is the main cause of Neuro-inflammation processes in the brain. The interacting with G-protein coupled receptors (GPCRs) including GPR41 and GPR43, which are present on macrophages, dendritic cells, and T cells, SCFAs directly affect immune cells.[79] Through these receptors, SCFAs increase the production of anti-inflammatory cytokines like interleukin-10 (IL-10) and Treg differentiation while reducing the production of pro-inflammatory cytokines like IL-6 and TNF-α.[80] In the CNS, SCFAs can alter the state of microglial activation, changing them from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype and thus decreasing Neuro-inflammation and making it harder for neurons to suffer from oxidative and inflammatory damage.[81] Experimental studies using animals as models have shown that the supplementation of butyrate leads to a decrease in Neuro-inflammation markers, an increase in synaptic plasticity, and a positive impact on cognitive performance. Similarly, human research showed that people on high fiber diets, which are a source of SCFA, experience less inflammation in the body and better cognitive functioning.[82] Taken together, the short-chain fatty acids are seen as important players in the gut-brain communication, connecting dietary habits to immune control, and thus providing protection to the nervous system, which makes their use in treating chronic Neuro-inflammation and preserving brain health over a long period of time very interesting from the therapeutic point of view.

Role of SCFAs in Maintaining Blood–Brain Barrier Integrity

Short-chain fatty acids, including butyrate, acetate, and propionate, are crucial for maintaining the blood brain barrier (BBB), which is necessary to prevent Neuro-inflammation and hence maintain brain function. Tight junction proteins, astrocytic end feet, pericytes, and endothelial cells are the main cell types that make up the BBB, a selective barrier that regulates the flow of chemicals and immune cells into the CNS.[83] The BBB, usually damaged by inflammation in the body, oxidative stress or imbalance of gut microbes, permits the entry of pro-inflammatory cytokines that are normally present in the blood along with bacterial by products LPS into the CNS, where they can start the process of microglial activation and chronic Neuro-inflammation.[84] SCFAs, in different ways, do their part to maintain the integrity of the BBB. Among them, butyrate is the one that competes as a histone deacetylase (HDAC) inhibitor, thereby augmenting the expression of tight junction proteins like claudin-5, occludin, and zona occludens-1 (ZO-1) in the endothelial cells, which ultimately fortifies the intercellular junctions and curtails the

permeability issue.[85] The SCFAs also possess the capability to counteract the inflammatory process, as they can activate G-protein coupled receptors (GPR41 and GPR43) on the endothelial and immune cells, suppressing the cytokine production that is mediated through the NF-κB pathway and reducing the signaling of the systemic inflammation that might invade the BBB.[86] Apart from that, the role of SCFAs in promoting the antioxidant defenses of the body by upregulating the Nrf2-mediated pathways of the endothelial cells is of great importance since it means the cells will not suffer oxidative stress-induced damage. The benefits of SCFA supplementation in terms of tight junctions integrity, Neuro-inflammation markers reduction, cognitive decline protection due to inflammation or aging have been well-documented in animal studies.[87] Research conducted on human subjects supports the notion that diets rich in fiber, which lead to the production of SCFAs are linked to reduced systemic inflammation and better cognitive performance. SCFAs together play an indispensable role as mediators in the process connecting gut microbiota activity to the maintenance of the BBB thus offering a mechanistic underpinning for dietary habits such as preventing Neuro-inflammation and maintaining long-term brain health that are targeted at these areas.

Vitamins and Minerals

Vitamin D is a vitamin that is soluble in fat and has an important function in controlling Neuro-inflammation through modulation. It activates microglia and reduces the synthesis of pro-inflammatory cytokines including IL-6 and TNF-α while simultaneously promoting the production of anti-inflammatory IL-10.[88] Vitamin D also supports neuronal survival and synaptic plasticity by coordinating neurotrophic factors and calcium transmission in the brain. Numerous cognitive deficits, depression, and even neurodegenerative illnesses have been linked to vitamin D insufficiency. The correct metabolism of homocysteine requires the B-complex vitamins, which include folate, B6, and B12. Increased blood homocysteine levels are associated with oxidative stress, endothelial dysfunction, and nervous system inflammation.[89] Sufficient B vitamin intake results in lowered homocysteine levels, thus protecting the central nervous system against oxidative damage and clearing the way for anti-inflammatory signalling.[90] These vitamins are also involved in the production of neurotransmitters and the maintenance of myelin which are important for cognitive function and the health of the neurons.[91] Magnesium is a mineral that plays a major role in regulating the activity of NMDA receptors which are important for synaptic plasticity and memory.[92] When magnesium is deficient, neurons may become excessively excited leading to the release of more ROS and increased inflammatory reactions. Magnesium's anti-inflammatory actions involve the inhibition of NF-κB pathway and the lowering of pro-inflammatory cytokines in the area.[93] Zinc is a trace element that the body requires in small amounts but it plays a significant role in modulating the immune response, neuronal activity, and protection against oxidative stress. Zinc is a microglial activator, stabilizes neuronal membranes, and is a part of the neurotransmitter signaling proces.[94] Along with zinc deficiency comes increased oxidative stress, poor neurogenesis, and a higher likelihood of Neuro-inflammation disorders.

Roles in Immune Balance and Neurotransmission

Essential vitamins and minerals, such as zinc, magnesium, vitamin D, and B-complex vitamins, have an indirect impact on brain health through neurotransmission, which affects Neuro-inflammation processes and overall brain health. The generating pro-inflammatory cytokines like TNF-α and IL-6 and encouraging the release of anti-inflammatory mediators like IL-10, vitamin D is considered an immunomodulatory because it controls the activity of microglia and astrocytes in the central nervous system.[95] Vitamin D inhibits the activation of signaling that results in neuronal death and synaptic loss through this immune balancing function. The metabolism of homocysteine depends on the B-complex vitamins, particularly B6, B12, and folate. High levels of homocysteine can cause oxidative stress and trigger inflammatory cascades that affect neurotransmitter synthesis negatively.[96] Adequate supply of B-vitamins results in lower homocysteine levels and thus, less oxidative and inflammatory stress, and at the same time supports the creation of serotonin, dopamine, and GABA, which are very important for the control of mood, learning, and the adaptability of synapses.[97] Magnesium is a factor that plays a role in both immunity and the nervous system through the regulation of NMDA receptor activity, which ultimately leads to the decrease of excitotoxicity and the suppression of NF-κB–mediated inflammation.[98] Zinc plays a

similar role as it influences both immune and neural function by regulating the activation of microglia, stabilizing the membranes of neurons, and being a part of the process of synaptic signaling. One of the micronutrients that is crucial for the operation of neurotransmitter receptors and the activity of enzymes that are critical for memory and learning is zinc.[99] These micronutrients together keep a very fine line between pro and anti-inflammatory signaling, facilitate neurotransmitter production and receptor function, and safeguard neuronal health. They thus offer the needed nutritional support to reduce Neuro-inflammation, retain cognitive function, and enhance brain longevity through the mentioned mechanisms.

Gut–Brain Axis and Neuro-inflammation

In the gastrointestinal system and throughout the body, including the brain (CNS), the gut microbiota plays a crucial role in controlling immunological signaling, which in turn influences Neuro-inflammation. Microbial associated molecular patterns (MAMPs), metabolites, and SCFAs, which include butyrate, acetate, and propionate, are some of the ways that the human immune system and the gut microbiome which is made up of billions of microorganisms communicate.[100] The binding to G-protein coupled receptors on dendritic cells, macrophages, and T cells, SCFAs affect immune cell function. This results in the growth of regulatory T cells (Tregs) and an increase in the release of anti-inflammatory cytokines like IL-10.[101] The immune modulation that occurs aids in keeping the inflammatory response balanced and preventing the harmful activation of tissues, including those of the neurons, that could eventually lead to death. The regulating the state of the intestinal barrier, the gut microbiota also influences immunological signals throughout the body. Good bacteria encourage the production of tight junction proteins, which reduces intestinal permeability and limits the amount of bacterial endotoxins, such as LPS that can enter the circulation.[102] Neuro-inflammation occurs when LPS enters the bloodstream and binds to the TLR4 on peripheral immune cells. This triggers the NF-κB signaling pathway, which releases pro-inflammatory cytokines that can penetrate the blood-brain barrier and activate microglia. These regulatory processes are upset by an imbalance of the gut microbiota, which is characterized by decreased microbial diversity or the predominance of pathogenic bacteria. The resulting in increased systemic inflammation and exaggerated CNS immune responses. Results from experimental studies indicate that re-establishment of microbial balance with the help of prebiotics, probiotics, or fiber supplementation not only increases but also further distributes SCFA, invigorates anti-inflammatory signaling, and lessens microglial activation.[103] Consequently, the gut microbiota serves as an indispensable intermediary for immune signaling, connecting the dietary and microbial inputs to the control of central Neuro-inflammation processes and the maintenance of brain health.

Probiotics, Fermented Foods, and Symbiotic

Probiotics, fermented foods, and the use of symbiotic are some of the dietary approaches that alter the gut microbiota composition so that it will be able to regulate the immune system and fight Neuro-inflammation. In addition to strengthening the gut barrier and producing related metabolites like SCFAs which are crucial in the medical field, probiotics are live microorganisms like Lactobacillus and Bifidobacterium that are regarded as health compounds because they can create the same environment as the killed bacteria.[104] The differentiating regulatory T cells (Tregs) and increasing the secretion of anti-inflammatory cytokines like IL-10 while simultaneously reducing the production of inflammatory cytokines like tumor necrosis factor-α (TNF-α) and IL-6, they reduce inflammation throughout the body.[105] Additionally, probiotics interact with the brain's microglia, modulating their activity and reducing the signals of the chronic inflammatory process. Fermented products such as yogurt, milk, and vegetables are supplying the gut with the naturally present probiotics and at the same time providing the bioactive substances such as peptides, vitamins, and polyphenols. They also support diversity of microorganisms in gut functioning of intestinal barrier, and the production of SCFAs that not only serve as nutrients for the gut bacteria but also as one of the factors that protect brain from diseases and possibility of Neuro-inflammation being caused.[106] Additionally, they aid in boosting the synthesis of relaxing neurotransmitters like serotonin and gamma aminobutyric acid (GABA), which makes the person more at ease and more resilient to stress. Probiotics and prebiotics combine to form synbiotics, which offer helpful microbes and the growth promoting substrates they need. Compared to probiotics or

prebiotics alone, symbiotic therapies produce more SCFAs, promote anti-inflammatory signaling, and restore microbial balance. Supplementing with synbiotics can improve the immune system, reduce symptoms of systemic inflammation, and speed up gut healing, according to both human and animal research.

Evidence from Preclinical and Clinical Studies

Animal Model Findings and Mechanistic Insights

Animal models have been crucial in revealing the mechanism by which dietary interventions, comprising probiotics, prebiotics, synbiotics, and fiber-rich diets, among others, modulate Neuro-inflammation and ratify brain health. Probiotic strains like *Lactobacillus rhamnosus*, *Bifidobacterium longum*, and *Lactobacillus plantarum* were among those that, in rodent therapy, led to gut microbiota restoration, SCFA production increase, and gut barrier strengthening.[107] According to the evidence, SCFAs, especially butyrate, are the primary anti-inflammatory agents. They work by promoting T-regulatory cell differentiation and the production of anti-inflammatory cytokines like IL-10, while they inhibit the synthesis of pro-inflammatory cytokines like IL-6, IL-1β, and TNF-α.[108] Research conducted at the mechanistic level suggests that the gut–brain axis connects the metabolic products of bacteria to the central nervous system. The activation of microglia, which reprograms M1 pro-inflammatory cells into M2 anti-inflammatory ones, is one of the mechanisms regulating the activity of SCFAs. This reduces oxidative stress and, as a result, protects neurons against malfunction and apoptosis. Besides, the protective effects of probiotics and synbiotics have been shown to be due to inhibiting the NF-κB pathway, which leads to reduced levels of ROS, while at the same time, the Nrf2-mediated antioxidant pathways are activated in both peripheral and central tissues.[109] Animal studies reinforce the hypothesis that dysbiosis induced by diet, e.g., high fat or low fiber diets, enhances Neuro-inflammation, makes blood–brain barrier less permeable, and accelerates cognitive decline. The application of prebiotics, probiotics, and polyphenol-rich foods not only restores but also enriches microbial diversity, improves BBB integrity, reduces microglia activation, and accordingly enhances cognitive and emotional output.[110] The evidence gained from the studies indicates a direct connection between the control of Neuro-inflammation and the modulation of the gut microbiota, hence emphasizing the possible use of dietary methods as a way to treat, prevent or lessen the impact of brain inflammation and the subsequent degeneration of nerve cells.

Table 2: The strengths, limitations, and inconsistencies in the evidence for dietary modulation of Neuro-inflammation

Aspect	Strengths	Limitations	Inconsistencies
Preclinical Evidence	Controlled experimental conditions; mechanistic insights; reproducible effects on microglia and cytokines	Animal models may not fully replicate human gut microbiota or CNS complexity	Strain specific effects vary; differences in dosage, duration, and model species.[113]
Observational Studies	Large cohorts; long-term dietary patterns; associations with cognitive outcomes and inflammation	Cannot establish causality; self-reported dietary data prone to bias	Conflicting results for some nutrients or foods due to population, age, or diet variability.[114]
Interventional Studies	RCTs provide causal evidence; measurable effects on inflammatory markers, cognition, and mood	Small sample sizes; short intervention periods; heterogeneity in probiotic strains or dosages	Some trials report minimal or no effect; differences in baseline microbiota may influence outcomes.[115]

Mechanistic Insights	Identifies molecular pathways (SCFAs, NF-κB, Nrf2, cytokines) linking diet to Neuro-inflammation	Translational gap between molecular mechanisms and clinical efficacy	Not all pathways are consistently validated in humans; interactions between nutrients may confound effects.[116]
Dietary Patterns (Mediterranean, DASH, Plant-based)	Broad health benefits; synergistic effects of multiple nutrients; reproducible epidemiological associations	Difficult to isolate effects of individual components; adherence variability	Some studies show limited effects in specific populations or age groups.[117]

Human Observational and Interventional Studies

Clinical and laboratory based research has consistently demonstrated the interrelationship of diet, gut microbiota, and Neuro-inflammation, with the potential of probiotics, fermented foods, symbiotic, and fiber rich diets to promote brain health. The diets of the people who participated in the studies were monitored in detail, and it was found that those consuming large amounts of fruits, vegetables, and whole grains, as well as fermented foods, had more diverse gut microbiota, lower levels of inflammation in the body, and better cognition. For example, large-scale cohort studies such as the Mediterranean diet reduced the risk of cognitive decline, reduced plasma levels of pro-inflammatory cytokines like TNF-α and IL-6, and improved memory and executive function in older adults.[111] The Western style diet, which is high in refined sugar and saturated fats, alters gut flora, increases intestinal permeability, upregulates systemic inflammation, and raises the risk of neurodegenerative disorders. Additionally, studies on probiotics and nutritional strategies have used microorganisms as their subjects. Randomized controlled trials have shown that probiotic supplements containing strains of *Lactobacillus rhamnosus* and *Bifidobacterium longum* reduce blood levels of inflammatory markers, improve people's cognitive abilities, and lessen the intensity of symptoms of anxiety and depression.[112] Fermented foods like yogurt and kefir have been associated with improved mood, more diverse gut microbes, and higher production of SCFA (Table 2).

Role of Artificial Intelligence and Machine Learning

Artificial Intelligence (AI) and Machine Learning (ML) are among the main drivers of research on nutritional modulation of Neuro-inflammation, as they allow the analysis of complex, high dimensional datasets that were hardly interpretable through traditional statistical means. Especially in dietary pattern analysis, the AI and ML algorithms are capable of pinpointing very delicate links between the intake of certain food items and the levels of inflammatory biomarkers across wide population groups, which in turn reveals the prediction of Neuro-inflammation risk based on these relationships.[118] The predictive models obtained through these methods enable the researchers to assess each individual's likeliness to Neuro-inflammation by taking dietary, lifestyle, and demographic factors into account, thus assisting in the implementation of personalized nutritional strategies. Moreover, AI speeds up the integration of multi-omics datasets, which include genomics, metabolomics, proteomics, and gut microbiome profiles, so that the pathways both at the molecular and microbial levels can be intricately mapped to discover the connections between diet and Neuro-inflammation repercussions.[119] Analyses of this sort constitute a big help in the process of determining biomarkers for the early diagnosis, continuous monitoring, and therapeutic targeting of Neuro-inflammation stages. Machine learning techniques contribute to the personalized nutrition further by providing clients with individualized dietary recommendations based on genetic, metabolic, and microbiome profiles that can maximize the anti-inflammatory and neuroprotective effects.[120] On a large scale, AI-based models play a significant role in precision public health through the method of detecting high risk populations and creating research based treatment plans to lessen the impact of Neuro-inflammation diseases. Nevertheless, there are still hurdles to be crossed like the firewall of interpretability, reproducibility, and data quality that sometimes raises concerns of ethics such as

privacy and bias. Meeting these issues head on is a major step that needs to be taken to certify the trustworthy and responsible use of AI/ML in nutritional neuroscience.

Public Health Implications

The implementation of nutrition based strategies for Neuro-inflammation reduction is a good opportunity for public health as it is a highly effective and wide ranging method to prevent mental decline, metabolically induced and neurodegenerative diseases in people.[121] The encouraging the intake of foods filled with anti-inflammatory nutrients like omega-3 fatty acids, polyphenols, fiber, vitamins, and minerals, public health can apply the mechanism of Neuro-inflammation to tackle the problem and thus lower the incidence of neurological and psychiatric disorders.[122] Such a population based dietary shift, for instance the adoption of Mediterranean, DASH or plant based diets, can be supported by school nutrition programs, workplace wellness initiatives, community educational outreach, and widespread media campaigns, thus guaranteeing a broad reach and a lasting impact. The economic aspects of dietary interventions are so striking, given that raising people's nutritional standards can prevent or postpone the emergence of chronic Neuro-inflammation conditions that need costly medical treatment or healthcare management.[123] The extensive application of this strategy is possible since nutrient dense foods are widely available and infrastructure for public health nutrition is well established, but it is necessary to modify this approach according to the local food systems and cultural preferences for the compliance of the people. The incorporation of Neuro-inflammation focused suggestions into the national dietary guidelines and health policies can further legitimize these approaches, thus, leading the doctors, dietitians, and the government to put the brain healthy diets as a part of their war against health issues.[124] The problem of health inequalities must be taken into account, as often the lower socioeconomic status, the remoteness of the area, and the disparities in the food systems are the reasons for lack of access to healthy foods.

Limitations and Research Gaps

There is an increasing volume of proof that nutrition has a positive effect on Neuro-inflammation modulation, however, there are still several limitations and research gaps that hold back the effective interventions to be facilitated by the findings. Many studies are methodologically restricted by small sample sizes, short intervention durations, and the unevenness in dietary assessment tools, which leads to the decrease in the reproducibility and generalizability of results.[125] Observational studies are able to provide valuable associations but cannot establish causality between specific dietary patterns or nutrients and Neuro-inflammation outcomes thus making it hard to draw definitive conclusions. Even in randomized controlled trials, compliance with dietary interventions over a long period of time is very difficult to monitor thus bringing in variability that may obscure the effects noticed.[126] The lack of standardized Neuro-inflammation biomarkers is another major limitation. Presently, research involves a mixture of peripheral inflammatory markers, neuroimaging outcomes, and cognitive assessments, which differ from study to study and make the comparison of studies more difficult. Without any acknowledged and broadly used biomarkers, it is hard to measure the nutrition interventions' impact or even create specific dietary recommendations. What's more, genetic, microbiome composition, metabolism, and lifestyle factors differences among individuals result in differing responses to dietary interventions thus indicating the need for tailored approaches.[127] Researchers in the future need to pay attention to studies that are larger, last longer, and are mechanism based, to be done with the integration of multi-omics, neuroimaging, and standardized biomarker assessment to better understand the causal pathways linking diet and Neuro-inflammation.

Discussion

This review highlights the central role of nutrition in modulating neuro-inflammation and its broad implications for brain health, neurodegenerative diseases, and public health. Evidence from mechanistic, preclinical, epidemiological, and clinical studies consistently demonstrates that dietary patterns rich in anti-inflammatory nutrients such as omega-3 fatty acids, polyphenols, dietary fiber, vitamins, and minerals can regulate immune signaling, oxidative stress, gut microbiota composition, and blood–brain barrier integrity, thereby reducing chronic Neuro-inflammation. In contrast, Western dietary patterns exacerbate inflammatory pathways, disrupt gut–brain

communication, and accelerate neurodegenerative processes. The gut–brain axis emerges as a central mediator linking diet to neural health, with short-chain fatty acids, microbial metabolites, and immune signaling acting as modulators of microglial activity and neuroimmune balance. Furthermore, growing evidence supports the role of probiotics, prebiotics, and synbiotics in restoring microbial homeostasis and attenuating inflammatory signaling. Advances in artificial intelligence and machine learning further strengthen this field by enabling personalized nutrition strategies, biomarker discovery, and predictive modeling of disease risk. Despite strong evidence, challenges remain, including variability in study design, limited long-term clinical trials, and the absence of standardized biomarkers for Neuro-inflammation. Addressing these gaps through integrative, longitudinal, and systems based research will be essential. Overall, nutrition based interventions represent a cost-effective, scalable, and accessible strategy to mitigate Neuro-inflammation, support cognitive resilience, and improve public health outcomes, reinforcing the need to integrate dietary approaches into preventive and therapeutic frameworks for neurological and psychiatric disorders.

Conclusion

Nutrition is fundamental in controlling the level of Neuro-inflammation, thus giving people a chance to take care of their brains without the use of drugs and at the same time prevent the occurrence of neurodegenerative and psychiatric disorders. A large spectrum of anti-inflammatory nutrients is able to regulate the whole process and do it by different ways such as through very good interaction with the immune system and even as far as the blood brain barrier. The role of gut–brain axis is very crucial since it allows communication between gut microbiota and their metabolites, especially short-chain fatty acids, with immune and Neuro-inflammation processes. Gut health can be improved by the consumption of prebiotics, probiotics, fermented foods, and symbiotic which can lead to a cascading effect of anti-inflammatory responses in both peripheral and central systems. Research evidence comes mainly from preclinical models, epidemiological studies, and human interventions are all supporting dietary strategies as a means of reducing Neuro-inflammation and improving cognition and mental health. The development of AI and machine learning has made it possible to handle complex dietary, microbiome, and multi-omics data, thereby allowing predictive modeling, discovery of biomarkers, and personalization of nutrition interventions. On a population scale, public health policies and nutrition recommendations that include dietary advice focused on Neuro-inflammation would be very effective strategies to reduce the impact of these disorders, because they are accessible to everyone at a low cost. Nevertheless, the issues with methodology, differences in study designs, absence of uniform biomarkers, and problems with adherence in the long run all point to the necessity of conducting more rigorous research.

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