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REVIEW

Dietary supplements in neurological diseases and brain aging

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Keywords

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Summary

A healthy diet shapes a healthy mind. Diet quality has a strong association with brain health. Diet influences the onset and consequences of neurological diseases, and dietary factors may influence mental health at individual and population level. The link between unhealthy diet, impaired cognitive function and neurodegenerative diseases indicates that adopting a healthy diet would ultimately afford prevention and management of neurological diseases and brain aging. Neurodegenerative diseases are of multifactorial origin and result in progressive loss of neuronal function in the brain, leading to cognitive impairment and motoneuron disorders. The so-called Mediterranean diet (MedDiet) with its healthy ingredients rich in antioxidant, anti-inflammatory, immune, neuroprotective, antidepressant, antistress and senolytic activity plays an essential role in the prevention and management of neurological diseases and inhibits cognitive decline in neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases. The MedDiet also modulates the gut-brain axis by promoting a diversity of gut microbiota. In view of the importance of diet in neurological diseases management, this review focuses on the dietary components, natural compounds and medicinal plants that have proven beneficial in neurological diseases and for brain health. Among them, polyphenols, omega-3 fatty acids, B vitamins and several ayurvedic herbs have promising beneficial effects.

Introduction

Neurodegenerative diseases (NDs) involve a progressive loss of neuronal activity, resulting in impairment of cognitive function. They have genetic and epigenetic etiology and are increasing at an alarming rate. For instance, 17.2 million people worldwide are suffering from NDs such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disease (HD) and dementia [1, 2]. As the symptoms appear only when neurological degeneration has reached an advanced stage, the prevention of NDs and the search for new therapeutic agents is a challenge. Although the mechanisms of NDs are multifactorial and complex, they share common pathways, such as oxidative stress, inflammation, mitochondrial dysfunction and intracellular Ca^{2+} overload. In addition, cross talk between these multiple pathways often makes therapeutic intervention less effective.

The brain is highly sensitive to oxidative stress and increased reactive oxygen species produced during neuroinflammatory processes. As the antioxidant defence system has low activity in the brain, increased oxidative stress results in NDs and aging [3]. Genetic and epigenetic factors greatly influence the onset and development of these disorders, while nutrition and metabolism play a key role in the manifestation of epigenetic modifications of DNA in the central nervous system [4-5]. Bioactive ingredients in food and gut microbiota can greatly influence DNA methylation in the adult central nervous system, indicating a role of diet and dietary components in NDs [6]. The so-called Mediterranean diet (MedDiet) is currently regarded as the healthiest diet in the world. It includes daily intake of whole grains, vegetables, fruit, legumes, white meats, fish, nuts, olives and olive oil. Rich in antioxidants, fibre, vitamins, minerals, phytosterols, probiotics, omega-3, and omega-6 fatty acids, it promotes human health and wellbeing. The MedDiet has been associated with improvements in overall health, prevention of cancer, maintenance of a healthy cardiovascular system and metabolism, and with preventing, alleviating and slowing neurological disorders (Fig. 1).

Clinical studies on efficacy of MedDiet in major neurodegenerative disorders

Several studies have evaluated the efficacy of the MedDiet in prevention and management of neurodegenerative disorders (Tab. I). These studies inferred that following the MedDiet not only decreases the incidence of NDs but also improves overall cognitive function and hampers the onset and progress of decline caused by NDs and cerebral aging.

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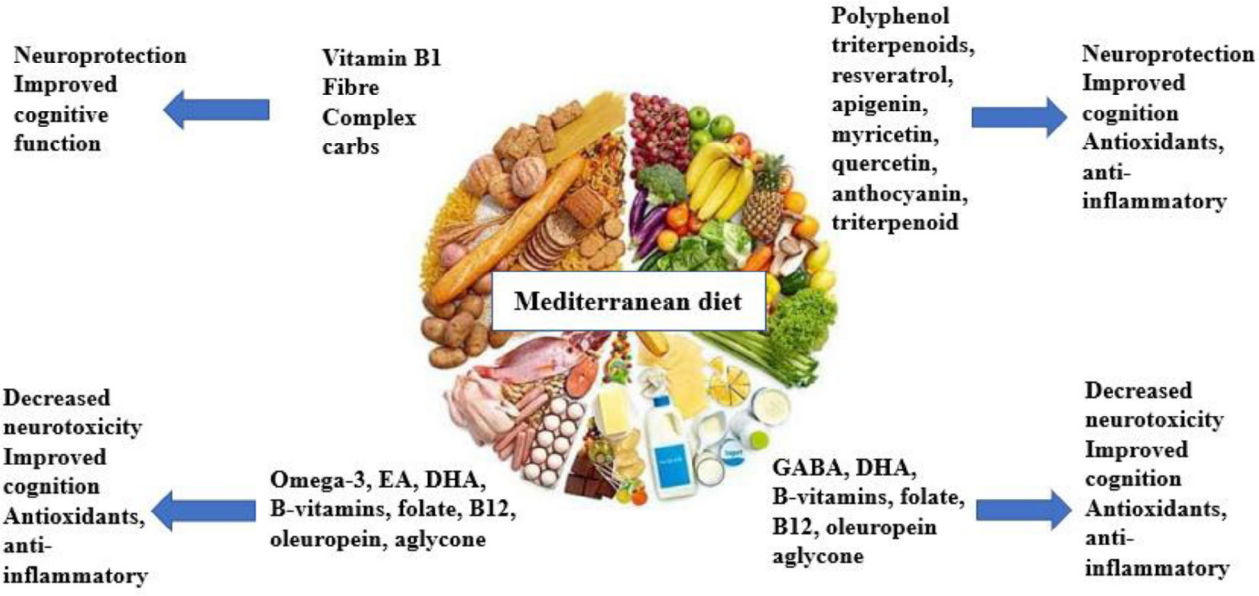
Fig. 1. Effects of dietary components of Mediterranean diet in neurodegenerative diseases and cerebral aging.



Animal studies and clinical trials have shown that the MedDiet has anti-inflammatory, antioxidant and free radical-scavenging properties that alleviate or mitigate neurotoxicity and neurodegeneration (Tab. II).

MedDiet and depression

Increasing evidence suggests that depression, the foremost global cause of disability, is a subtle neurological disorder [22, 23]. Besides other therapies, diet may be useful for improving overall mental health and relieving stress and anxiety. The MedDiet, rich in vitamins, minerals, antioxidants, healthy fats and proteins, reduces the risk of depression [24]. Research-based evidence suggests that dietary measures can be an adjunctive treatment for mental disorders. For instance, a healthy diet has been tested clinically in two different trials for its effects on symptoms and remission rates of depression, showing promising results [25, 26]. As many as 37 studies have reported a reduction in symptoms of depression in groups of persons on diets rich in polyphenols [27]. An observational study also revealed that following the MedDiet was crucial for reducing depressive outcomes in overweight patients with metabolic syndrome [28]. Vicinanza et al. (2020) reported a positive impact of the MedDiet on mental health in elderly patients with multimorbidity [29]. They also observed that the diet prevented symptoms of depression in these patients, promoting healthy aging. Yet another promising clinical study named PREDI-DEP is underway to assess the MedDiet supplemented with extra virgin olive oil or nuts for precluding relapse of unipolar depression [30]. Diet plays an important role in shaping behaviour and modulating mood (Tab. III). For instance, omega-3 essential fatty acid supplements alleviated symptoms of bipolar disorder in 30 patients [31].

Effect of natural compounds and medicinal plants on neurological disorders

Several medicinal plants and natural compounds have been deployed to prevent or alleviate neurological diseases and symptoms in vivo and in clinical trials. Here we discuss important natural compounds that can be obtained from dietary sources or nutritional supplements and that mediate various aspects of practical utility in the management of neurodegenerative disorders.

N-acetylcysteine (NAC) in neurological disorders

N-acetylcysteine (NAC) is a mucolytic thiol known for its ability to alleviate stress and mediate the impacts of toxicity, infections and inflammatory conditions by supporting the body's antioxidant and nitric oxide systems [37]. It crosses blood brain barrier (BBB) and is a precursor of l-cysteine and reduced glutathione GSH, as well as a source of sulfhydryl groups in cells. It scavenges free radicals and interacts with reactive oxygen species (ROS) [38]. It has a multifaceted mode of action, acting as a drug, a xenobiotic and a cytoprotectant. The effects of NAC on various neurological and neurodegenerative diseases are summarized in Table IV.

Effects of phospholipids on neurological conditions

The brain and nervous system have a more diverse lipid composition than the rest of the body, showing a pre-

Tab. I. Clinical studies demonstrating effect of MedDiet on ND progression.

Neurological conditions	Description	Study type	Participants	Duration	Findings	Reference
Alzheimer's disease	Formation of widespread extracellular amyloid plaques and intraneuronal neurofibril tangles in the brain (Reitz and Mayeux, 2014), a major cause of dementia	Follow-up study	70 subjects with normal cognitive function, age 30-60 years	3	Not following MedDiet was correlated with progressive AD abnormalities	[7]
		Cohort studies	1393 normal and 482 with mild cognitive impairment, age 76.7-77.5 years	4.5	Following MedDiet reduced risk of cognitive impairment and AD	[8]
Dementia	Loss of cognitive function due to brain aging or neurodegenerative diseases	Longitudinal	1865 (41%M) patients with dementia, mean age 73 years	1.4	10% decrease in dementia on MedDiet. Cereals shown to have positive impact on mental performance	[9]
		Cross sectional	52 subjects with normal cognitive function	-	Low intake of rice and higher intake of milk and soybean reduced risk of dementia	[10]
Huntington's disease	a rare, hereditary condition that causes progressive neurodegeneration	Prospective	211 patients with expanded CAG repeats	3.4	Diet and high energy intake may delay onset	[11]
Parkinson's disease (PD)	Neuronal degeneration, dopaminergic loss. PD symptoms include tremors, motoneuron changes, cognitive decline, dementia and loss of muscle strength (Gratwicke et al., 2015)	Population-based cohort	1731 (41% male) PD-free individuals, age 65 and over	-	MedDiet lowered probability of prodromal PD in elderly people	[12]
Amyotrophic lateral sclerosis (ALS)	Degeneration of brainstem and spinal cord motoneurons resulting in progressive muscle atrophy, paralysis and respiratory failure (Oh et al., 2015)	Cross sectional baseline analysis	302 patients with a history of ALS symptoms of 18 months or less	-	Better function associated with antioxidants and with carotenes in fruit and vegetables	[13]
Multiple sclerosis	Demyelination of nerve fibres and myelin sheaths, affecting the optic nerves, brain and spinal cord	Survey	396	-	MedDiet reduces risk of relapses	[14]

dominance of phospholipids [45]. Phospholipids occur in varying concentrations in the brain, e.g. 31 nmol/mg phosphatidylcholine, 54 nmol/mg phosphatidylethanolamine, 8 nmol/mg phosphatidylserine and 5 nmol/mg of phosphatidylinositol [46]. Sphingomyelin levels in the hippocampus and prefrontal cortex are similar to those of phosphatidylethanolamine in adult male rats [47]. Phospholipids also occur in the membranes of organelles such as mitochondria, endoplasmic reticulum, Golgi apparatus, peroxisomes and lysosomes, which illustrates their importance in cells. Studies have revealed that phospholipid-enriched diets can modulate cognitive processes [48] and phospholipid supplementation has been shown to increase cognitive function in a polyunsaturated fatty acid-deficient mice model and to improve memory in piglets on permanent supplements [49].

Phosphatidylserine

Phosphatidylserine (PS) is an acidic phospholipid and a natural component of brain neuronal membranes and other biological membranes. It plays a pivotal role in normal neuronal function by determining neuronal membrane surface potential and the local ionic environment [50]. Phosphatidylserine is a brain-specific nutrient [51] and activates protein kinase C (PKC) in neural membranes. It is thought to decrease in the brain with aging, leading to cognitive decline and impairment as well as lower PKC

Tab. II. Antioxidant and anti-inflammatory nutrients of the Mediterranean diet used in animal and human studies.

MedDiet component	Nutrient	Study design	Study population	Proposed antioxidant activity	References
Extra virgin olive oil	Total polyphenol fraction of olive oil and hydroxytyrosol.	In vitro	Endothelial cells and murine myoblasts	Redox potential enhanced by increasing glutathione levels and free radical scavenging	[15,16]
	Hydroxytyrosol and tyrosol	Randomized	Male Wistar rats	Hydroxytyrosol and tyrosol activate GSH, reduce lipid peroxidation, restore glutathione balance in liver	[17]
	Extra virgin olive oil, oleuropein aglycone	Randomized	TgCRND8 mice	Inflammation and neurotoxicity reduced by induction of autophagy and recovery of lysosome system	[18]
Fish and dairy	B-vitamin folate (vitamin B9) and vitamin B12	Transverse	ALS patients	Less inflammatory damage and oxidation, improvement in myocytic atrophy	[19]
Citrus and green tea	Phytochemicals, triterpenoids, resveratrol	Randomized clinical	SOD1 (G93A) mice	Increased SIRT and AMPK resulting in enhanced survival of motor neurons Resveratrol treatment reduces activation of NF-kB pathway in LPS-activated microglia and stabilizes autophagic flux	[20]
Diet enriched with oily fish, seafood, dairy, nuts, vegetables, fruit and eggs	Docosahexaenoic acid (DHA)	Transverse	BV-2 murine microglial cells	Unsaturated fatty acid-based decrease in toxic effects of 7-ketocholesterol	[21]

Tab. III. Effect of dietary components and regimes on mood and psychological disorders.

Dietary components/ regimes	Effect on mood	Study type	Participants	Reference
Vitamin D	Improved mood	Double-blind placebo-controlled	44 healthy volunteers	[22]
Vitamins, minerals and essential fatty acids	Reduction in antisocial behaviour	Double-blind, placebo-controlled	231 young adult prisoners	[32]
Tryptophan depletion	Worsening of mood in seasonal affective disorder/winter type (SAD)	Randomized, balanced, double-blind crossover	11 SAD patients with recurrent episodes of winter depression	[33]
Folic acid therapy	Improved intellectual function	-	16 patients with impaired intellectual function	[34, 35]
Folic acid deficiency	Increased depression, impaired cognitive function, impaired abstract thinking	-	260 healthy subjects 60 to 94 years old	[36]
Omega 3 fatty acids	Improved short-term course of illness in bipolar disorder	Placebo controlled	30 patients with bipolar disorder	[23]
Traditional vs western diet	Traditional diet reduced odds in bipolar disorder	Epidemiological cohort study	23 women with bipolar disorder and 691 normal subjects	[31]

Tab. IV. Mechanism of action of NAC in different neurological disorders.

Disease	Mechanism	References
Unverricht–Lundbor type SCD, tardive dyskinesia, myoclonus epilepsy	Antioxidant effect by scavenging free-radicals and enhancing glutathione	[39]
Multiple sclerosis	Scavenges free-radicals and inhibits TNF toxicity	[40]
Amyotrophic lateral sclerosis	Enhances glutathione peroxidase and free-radical scavenging	[41]
Parkinson's disease	Enhances glutathione and free-radical scavenging	[42]
Huntington's disease	Scavenges free radicals and prevents mitochondrial dysfunction	[40]
Alzheimer's disease	Boosts glutathione levels	[43]
Focal cerebral ischemia	Enhances glutathione levels, improves microcirculation and tissue oxygenation, inhibits NOS and regenerates endothelium-derived relaxing factor	[44]

Tab. V. Effect of phosphatidylserine on neurological conditions.

Neurological conditions	Subjects	Nutrients	Findings	References
Alzheimer's disease	Aged patients with AD and dementia	Soy lecithin-derived phosphatidylserine plus phosphatidic acid	Improved cognition, mood, and memory	[58]
Attention deficit hyperactivity disorder (ADHD)	Children with ADHD	Phosphatidylserine	Improved short-term auditory memory and ADHD symptoms	[59]
Premenstrual syndrome (PMS)	40 women age 18-45 years diagnosed with PMS	400 mg PS + 400 mg PA per day or a matching placebo	Significant reduction in PMS symptoms	[60]
Cognitive impairment	Elderly persons with impaired memory	100 mg/day phosphatidylserine enriched with docosahexaenoic acid (PS-DHA)	May improve or maintain cognitive status	[61]
Cognitive function improvement	Elderly persons with impaired memory without dementia	Phosphatidylserine enriched with docosahexaenoic acid (PS-DHA)	May improve cognitive performance	[62]
Acute cognitive effects	Healthy young volunteers	Ginkgo biloba extract with soy-derived PS	Significantly improved memory task speed and improved secondary memory	[63]
Cognition and cortical activity after mental stress	Healthy subjects doing cognitive tasks under induced stress in a test–re-test design	Phosphatidylserine supplementation	Continued supplementation significantly was connected with a more relaxed state compared to the controls	[64]
Age-related cognitive function	130 elderly persons with cognitive impairment	PS derived from soybean 300 mg/day	Safely improved cognitive function	[65]
	494 elderly persons with cognitive impairment	300 mg/day PS supplements	Improved cognitive function in 6 months	[66]

activity [52]. Phosphatidylserine functions equally well in adults, children and the elderly. For instance, in young healthy males it mitigates stress-induced activation of the hypothalamus-pituitary-adrenal axis [53]. Phosphatidylserine-omega 3 supplementation reduces attention deficit hyperactivity disorder (ADHD) symptoms in children [54]. This indicates that PS may prove beneficial in correcting disrupted neural function under various conditions. It also modulates several important enzymes and proteins, such as synapsin I, that maintain neural function [55]. Table V lists some of the studies depicting the role of PS in neurological conditions.

Phosphatidylcholine

Phosphatidylcholine (PC) is the major phospholipid component of cell membranes, lecithin, organ meats, nuts and spinach. Phosphatidylcholine supplements derived from egg yolk are well-absorbed in the gut and their levels can vary in different regions of the brain under different circumstances. For instance, PC and phosphatidylethanolamine levels increase in the whole brain of a stress-induced mouse model [56], while phosphatidylethanolamine and sphingomyelin levels decrease in the prefrontal cortex, and sphingomyelin in the hippocampus [47]. Likewise, an age-induced reduction in PC and phosphatidylethanolamine levels was detected by HPLC in the hippocampus and frontal cortex of elderly persons (89-92 years) [57].

Effects of Gamma-aminobutyric acid on brain and behaviour

Gamma-aminobutyric acid (GABA) is a non-protein amino acid found in high concentrations in different

Tab. VI. GABA and prevention of neurological disorders.

Neurological conditions	Sources of GABA	Subjects	Effect on neurological conditions	Reference
Alzheimer's disease	Naturally produced by cerebral cortex	Thirty-eight AD risk participants, 14 with normal cognitive function, 11 with cognitive decline, 13 with impaired cognitive function	In high-AD risk participants GABA levels were associated with the dorsomedial-dorsoanterolateral prefrontal cortex	[71]
Menopausal depression, insomnia and autonomic disorder	GABA-enriched rice germ	Twenty menopausal patients	Improvement in sleep, somnipathy and depression	[72]
Depression	GABA-rich Monascus-fermented product	Depression animal model	Prevented depression	[73]
Sleep quality	GABA powder from lactic acid bacteria fermentation	32 Japanese volunteers	Prevented sleep disorders	[74]
Sleep latency and non-REM sleep	GABA (90.8%) and l-theanine (99.3%)	Pentobarbital-induced sleep in ICR mice	Decreased sleep latency and enhanced sleep duration	[75]
Stress	GABA from natural fermentation with lactic acid bacteria	8 stressed volunteers	Increased relaxation, reduced anxiety and raised immunity	[76]
Cognitive function	GABA-enriched product fermented with kimchi-derived lactic acid bacteria	50 mice	Improved long-term memory loss and increased neuronal proliferation	[77]
	GABA-enriched fermented *Laminaria japonica* product	40 elderly persons	Prevented cognitive impairment in the elderly	[78]

parts of the brain [67]. Foods such as germinated brown rice, soybean, green tea, cabbage, yogurt, kimchi and pickles are excellent sources of GABA. GABA is the main inhibitory neurotransmitter in the human cerebral cortex [68]. As a food supplement it is used to alleviate anxiety and improve sleep quality. Several studies have reported that GABA crosses the blood-brain barrier, albeit in small amounts [69]. GABA is a known antihypertensive, anti-inflammatory, antidiabetic, antimicrobial, antiallergic, hepatoprotective, renal protective and intestine protective agent [70], and it demonstrated effects on several neurological disorders (Tab. VI).

Melatonin in neurodegeneration

Melatonin, a neurohormone secreted by the epiphysis cerebri and extra pineal structures, has several important functions (chronobiotic, normothermal, immune-modulating, antioxidant, oncostatic, cryoprotective and anxiolytic) in the body [79]. Melatonin affects the gastrointestinal tract, cardiovascular system, reproductive system and metabolism, and regulates body weight. Acting as a chronobiotic, melatonin modifies the phase and amplitude of biological rhythms. It acts as a cytoprotective molecule in neurodegenerative disorders and aging by reversing inflammatory damage. It also prevents neurodegeneration in experimental models of Alzheimer's and Parkinson's disease. Melatonin supplementation has been recommended for the treatment of insomnia [80]. Table VII lists the effects of melatonin supplementation on various neurological conditions.

Omega-3 fatty acids

Omega-3 fatty acids are essential for a variety of physiological functions involved in neuroinflammation, neurotransmission and neurogenesis and therefore play a major role in brain development, performance and aging. The importance of omega-3 fatty acids is indicated by the fact that a deficiency leads to many neurological conditions such as depression, ADHD, schizophrenia, bipolar disorder, dementia and autism (Tab. VIII). Eicosapentaenoic (EA) and docosahexaenoic (DA) acid modulate inflammatory processes and maintain mental health, while a deficiency results in mental disorders (Tab. VIII). They also directly affect neuronal membrane fluidity and receptor function. Although omega-3 supplementation and enriched foods have long been studied for their vital role in neurological homeostasis, randomized clinical trials investigating their therapeutic potential have yielded inconclusive results, limiting their use in psychiatry. High-quality clinical trials are urgently needed to evaluate the effectiveness of omega-3 fatty acids in inhibiting and treating NDs.

Neurotropic B vitamins

Neurotropic B vitamins have crucial roles in the nervous system, not only as coenzymes. Their importance is in-

Tab. VII. Effects of melatonin supplementation on various neurological conditions.

Clinical condition	Melatonin dose	Findings	References
Parkinson's disease	0.25 and 1.25 mg/kg i.v.	Striking improvement in symptoms	[81]
Amyotrophic lateral sclerosis	60 mg/day oral for 13 months	Neuroprotective effects	[82]
	300 mg/day rectal for 2 years in 31 sporadic patients	Reduced oxidative damage	[83]
Muscular dystrophy	70 mg/day for 9 months	Mitigated hyperoxidative state of erythrocytes	[84]
Multiple sclerosis	50-300 mg/day oral for 4 years	Improved overall symptoms of progressive MS with long-term use	[85]
Migraine	3 mg/day for 4 months	Lower duration, frequency, and intensity of pain	[86]

Tab. VIII. Neurological implications of omega-3 fatty acids.

Neurological condition/function	Subjects	Study type	Supplements/ doses	Findings	Reference
Anxiety and inflammation	68 medical students under low-stress such as exams	Placebo-controlled, double-blind 12-week RCT	n-3 (2.5 g/day, 2085 mg eicosapentaenoic acid and 348 mg docosahexaenoic acid) or placebo	14% decrease in lipopolysaccharide-stimulated interleukin 6 production and 20% reduction in anxiety symptoms; lowered n-6:n-3 ratio and anxiety	[87]
Dementia	5386 patients without dementia	Prospective evaluation of incidence of dementia	Fatty-acid-rich fish	Fish intake decreased dementia	[88]
Cognitive function	867 elderly persons	Observational epidemiological	Oily fish containing long-chain PUFA	Fish consumption was positively associated with delayed unadjusted recall in CVLT	[89]
Parkinson's disease	31 patients with major depression	Double-blind, placebo-controlled	Fish oil (containing omega-3 fatty acids) or mineral oil capsules for 3 months	Omega-3 enriched fish oil improved depression	[90]
Alzheimer's disease and vascular dementia	49 controls, 25 AD and 15 VD	Cross-sectional	Excess intake of n-6 polyunsaturated fatty acids	AD and VD associated with higher intake of n-6 animal fats	[91]

dicated by the fact that their deficiency leads to various NDs such as depression, beriberi, Wernicke's encephalopathy, seizures, subacute combined degeneration of the spinal cord and peripheral neuropathy [92, 93]. Synergistic interaction of vitamins B1, B6 and B12 has been reported to improve neuropathic pain, motor control and nociception (Tab. IX) [94].

S-adenosyl methionine (SAMe)

S-adenosyl methionine (SAMe) is a major methyl donor that influences central nervous system function via cell transmethylation pathways, including but not limited to DNA methylation. It is a strong antidepressant with impacts in mouse models of amyotrophic lateral sclerosis, epilepsy and Alzheimer's disease [100]. SAMe supplementation alters brain bioenergetics and is an effective treatment for depression (Tab. X) [101, 102].

Tryptophan

Essential amino acid tryptophan (TRP) is involved in various physiological processes including immunity, neuronal function and gut homeostasis. Its metabolism in humans takes place via the kynurenine and serotonin pathways and produces niacin, serotonin and melatonin. In addition, to endogenous TRP, the gut microbiota also produces specific TRP metabolites that indirectly influence host physiology. An alteration in TRP metabolites results in neurological and psychiatric disorders. Tryptophan supplementation has been used to treat a number neuropsychological disorders in various clinical trials (Tab. XI) and has been found to improve serotonin and tryptophan deficiency, thus alleviating the severity of symptoms in depression, schizophrenia and bipolar disorder.

Magnesium

Magnesium is an important mineral for homeostasis in the human body. It plays an essential role in neuroprotection, neuromuscular conduction and nerve transmission. It is a mineral of intense interest due to its capacity to protect the nervous system against ecotoxicity, thus im-

Tab. IX. Sources and neurological implications of vitamins B1, B6 and B12.

Vitamin	Sources	Coenzyme for	Deficiency symptoms	Implications in nervous system	Reference
B1 (thiamine)	Fish, beans, lentils, cereals, yogurt, sunflower seeds, cereals	Pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, transketolase	Beriberi, polyneuritis	Energy supply to nerve cells for synthesis of nucleic acids, neurotransmitters, and myelin	[95, 96, 97]
B6 (pyridoxine)	Salmon, tuna, beef liver, chicken, leafy greens, orange, banana, papaya, cantaloupe	Cystathionine-beta-synthase/lyase, serine-hydroxymethyl transferase, aromatic L-amino acid decarboxylase	Cognitive impairment, depression, premature aging of neurons	Metabolism of DNA/RNA, amino acids and neurotransmitters	[98]
B12 (cobalamin)	Dairy products, fish, poultry, eggs, meat	Methionine synthase, methylmalonyl CoA mutase	Cognitive impairment, impaired neurotransmitter production, polyneuritis, subacute combined spinal cord sclerosis	Metabolism of nucleic acids, fatty acids, amino acids, neurotransmitters, myelin	[99]

Tab. X. Neurological implications of S-adenosyl methionine (SAMe).

Neurological conditions	Study Design	Subjects	Dose	Findings	Reference
Abstinence from smoking	Three-arm, randomized, blind, placebo-controlled, dose-ranging clinical trial	120 adults	Oral SAMe 800 or 1600 mg/day or matched placebo for 8 weeks	SAMe holds little promise for the treatment of tobacco dependence	[103]
Parkinson's disease	Open label clinical trial	13 patients with depression	800 to 3600 mg/day for 10 weeks	SAMe is a well-tolerated, safe and effective alternative to antidepressants	[104]
Depression	Double blind randomised controlled trial	49 patients with depression	800 mg/day SAMe monotherapy versus placebo	Depression improved	[105]

Tab. XI. Clinical trials evaluating efficacy of tryptophan in neuropsychological disorders.

Neurological conditions	Study Design	Treatment	Findings	Reference
Depression	Human pilot clinical trial	Tryptophan	Replenished serotonin deficiency	[106]
Schizophrenia	Open baseline-controlled trial	Tryptophan	Improved impaired serotonin synthesis	[107]
Bipolar disorder	Clinical trial	L-tryptophan	Alleviated tryptophan deficiency	[108]

proving many neurological disorders. Table XII shows some selective studies of magnesium in NDs.

Polyphenols

Polyphenols are important nutrients abundant in spices and foods. They have antioxidant, anti-inflammatory and senolytic activities; they inhibit oxytosis, modulate the gut microbiome and promote protein aggregation and stability. They also maintain GSH levels and neurotrophic signalling pathways [113]. They show promise for preventing neurodegenerative diseases such as dementia, PD, HD, ALS, stroke, TBI, diabetes, cardiovascular diseases, liver disease and cancers. In addition, polyphenols control symptoms of depression. For instance, the antioxidant potential of polyphenols could possibly improve depression symptoms in women [114]. However, the effect of polyphenols in disease prevention and treatment depends on adequate dietary consumption. Fresh fruit and vegetables contain plenty of polyphenols that offer a variety of neurological benefits (Tab. XII). Polyphenol supplements, such as Pycnogenol® (a procyanidin) obtained from French maritime pine bark by Horphag Research (Geneva, Switzerland), have shown promising antioxidant and anti-inflammatory properties in various in vitro, animal and/or human models [115], besides improving endothelial function and showing beneficial effects in ADHD [116]. Another important commercially available polyphenol is silymarin, extract-

Tab. XII. Neurological implications of magnesium.

Neurological conditions	Study Design/type	Subjects	Treatment/ supplementation/ assessment	Findings	Reference
Risk of dementia	Prospective cohort Hisayama Study, Japan	1081 Japanese without dementia, age > 60 years, 17-year follow-up	Dietary intake of potassium, calcium, magnesium	Higher self-reported dietary potassium, calcium and magnesium intake reduces risk of dementia	[109]
Alzheimer's disease	Comprehensive geriatric assessment	101 geriatric patients with slight to moderate cognitive impairment	Assessment of Mg levels in blood samples	Mg ion levels were directly related to cognitive function	[110]
Parkinson's disease	Case control study	249 patients with PD for < 6 years and 368 controls	Dietary intake	Higher intake of magnesium, iron and zinc associated with lower risk of PD	[111]
Cerebral ischemia	Intravenous magnesium efficacy in stroke (IMAGES) trial	2589	A bolus dose of 16 mmol of MgSO4 was infused over 15 min and then a maintenance dose of 65 mmol MgSO4 was given over 24 h	Highly beneficial in early-treated patients	[112]

Tab. XIII. Dietary sources and neurological benefits of polyphenols.

Class of polyphenols	Biologically active compound	Dietary source	Neurological benefits	References
Non flavonoids	Curcumin	Turmeric	Significant reduction in severity of depression and improved cognitive function in elderly AD patients	[121, 122, 123, 124]
	Resveratrol	Grapes	Improved cognitive function, reduced oxidative stress and neuroinflammation, and neuroprotection in AD patients	[125, 126]
Anthocyanins	Cyanidin petunidin	Berries strawberries tea	Improved cognitive function and reduced risk of dementia	[127]
Flavones	Apigenin kaempferol myricetin quercetin	Apple skin, broccoli, fruit peel, lettuce, olives and onions	Quercetin reduces risk of AD and regulates microglial activity, neuroinflammation, oxidative stress and neural injury	[128, 129]
Flavonones	Fisetin hesperitin	Citrus fruit and peel	Fisetin slows loss of cognitive function and maintains brain health in dementia models	[113]

ed from milk thistle and sold with various brand names. It is commonly known as flavonolignans and is a mixture of eight stereoisomers: taxofolin, silybin A and B, isosilybin A and B, silychristin, isosilychristin and silydianin [117].

Silymarin shows neuroprotective mechanisms in AD, PD and cerebral ischemia including mediation of antioxidant mechanisms, regulation of kinases in cell signalling pathways, anti-inflammatory properties, neurotropic effects, modulation of neurotransmitters and inhibition of apoptosis [118, 119]. Silymarin also controls production of amyloid-β by inhibiting β-amyloid precursor protein and cholinesterase activity, thus inhibiting the onset of AD [120]. Its low cost, bioavailability and safety make silymarin a natural drug of choice for neuroprotection and hepatoprotection [119, 120].

Ayurvedic herbs in the treatment of neurodegenerative diseases

Ayurvedic medicine has been practised in the Asian subcontinent since ancient times. Many herbs and medicinal plants have been explored for their antioxidant, anti-inflammatory, antidiabetic, anticancer and cytoprotective properties. Medicinal plants such as *Withania somnifera* (ashwagandha), *Baccopa monnieri*, *Acorus calamus* and *Hypericum perforatum* have been shown to prevent or alleviate neurological diseases and symptoms (Tab. XIV).

Bacopa monnieri

Bacopa monnieri is a traditional Indian ayurvedic medicinal plant belonging to the family *Scrophulariaceae*. This memory enhancer, known as Brahmi, has been used

Tab. XIV. Neuroprotective properties and therapeutic potential of selected medicinal plants.

Medicinal plants	Active ingredients	Neuroprotective properties	Therapeutic potential	Reference
Bacopa monnieri (L.) Wettest (folk name: brahmi)	Bacopasides III–V, bacosides A and B, bacosaponins A, B and C	Antioxidant, antistress, anti-inflammatory, anti-microbial and smooth muscle relaxant. Improves memory	Neuroprotection in AD and bipolar disorder, improves intelligence and memory	[130, 133, 134]
Withania somnifera (L.) Dunal (folk name: ashwaganda)	Ashwagandhine, withanolides, withasomniferin, withasomniferols and withanone	Memory enhancer and anti-stress agent with effects on locomotor function and neural growth	Inhibits oxidative stress, improves cholinergic function and mitochondrial respiration in rotenone-induced Parkinsonism in *Drosophila melanogaster*	[131]
Acorus calamus (folk name: sweet flag, sway or muskrat root)	145 compounds α-asarone, β-asarone, eugenol, isoeugenol, 44 sesquiterpenes including lactones, monoterpenes (C-10), triterpenoid saponins	Antioxidant, anti-depressant, anti-inflammatory, anticonvulsant, neuroprotective, antianxiety, cytoprotective, immunomodulatory	Neuroprotection and anti-inflammatory agent in AD and PD	[132, 135]
Hypericum perforatum (Folk name: St John's wort)	Quercetin, hyperoside, quercitrin, rutin, hypericin, kaempferol, hyperforin	Antidepressive, antioxidant, neuroprotective	Restoration and improvement of microglial viability, inhibits amyloid-β toxicity in AD and brain malondialdehyde in PD	[47]

traditionally for more than 3000 years to treat various neurological disorders, to enhance digestion and to improve learning, cognitive function and concentration. It helps restore cognitive deficit and enhances mental and brain function. This nootropic plant promotes repair of damaged neurons, neuronal synthesis and synaptic activity. Recent studies show that it contains surplus bioactive phytochemical compounds with synergistic properties that are useful in the management of ND [130].

Withania somnifera

Withania somnifera or ashwagandha is another traditional Indian medicinal plant that promotes long life, youthful vigour and good intellectual powers. It is used traditionally in the treatment of neurodegenerative diseases, general frailty, nervous exhaustion and insomnia. It has anti-inflammatory, anti-tumour, antioxidant, immunomodulatory and anti-neuropsychiatric effects [131].

Acorus calamus

Acorus calamus or vacha is a traditional Indian ayurvedic medicinal plant. Its rhizomes are used to treat insomnia, melancholy, memory loss, hysteria, depression and mental disorders. Almost all parts of the plant have proven beneficial in the treatment of neurological, gastrointestinal, kidney, respiratory, liver, and metabolic disorders. Its action is anticonvulsant, anti-depressant, anti-hypersensitive, anti-inflammatory, cardioprotective, immunomodulatory and anti-obesity [132].

Hypericum perforatum

Hypericum perforatum or St. John's wort is a perennial plant. It is used in traditional medicine to treat external and internal disorders such as minor burns, anxiety and mild to moderate depression. It is also a herbal remedy for neurological disorders such as mental aliments, hypersensitivity, neuralgia, spinal convulsion, hydrophobia, spastic paralysis, spinal irritation, coxalgia and menopausal neurosis [47].

Conclusion

Oxidative stress and neuroinflammation are key factors in the onset and progression of neurodegenerative diseases. A diet rich in biologically active compounds with antioxidative and anti-inflammatory properties affords significant neuroprotection. Many recent studies have attempted to evaluate and recommend the Mediterranean diet and its ingredients with neuroprotective, oxidative stress mitigating and anti-inflammatory properties that impede the progression, delay the onset and reduce the severity of neurodegeneration in neurological disorders such as AD, PD, HD, MS, ALS and natural age-related brain aging. Several natural compounds, minerals and medicinal plants have been tested in clinical trials and animal studies and some, such as PLs, GABA, NAC, omega-3 fatty acids, magnesium, curcumin, resveratrol, *Hypericum perforatum, Acorous calamus* and *Bacopa monnieri,* have proven beneficial, safe and economical in the treatment of NDs. However, their effects are dose-dependent and must be administered in a precise manner. These potentially beneficial dietary components need to be evaluated in large clinical trials to assess their wider application across patients of different ethnic origin.

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Conflicts of interest statement

Authors declare no conflict of interest.

Author's contributions

MB: study conception, editing and critical revision of the manuscript; KD, MCM, Paola C, PM, Pietro C: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript.

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