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Review Article

Nutritional interventions for the prevention and treatment of neurological disorders such as anxiety, bipolar disorder, depression, epilepsy, multiple sclerosis, and schizophrenia

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Abstract

Neurological disorders are a significant cause of mortality and disability across the world. The current aging population and population expansion have seen an increase in the prevalence of neurological and psychiatric disorders such as anxiety, bipolar disorder, depression, epilepsy, multiple sclerosis and schizophrenia. These pose a significant societal burden, especially in low - and middle-income countries. Many neurological disorders have complex mechanisms and lack definitive cures; thus, improving our understanding of them is essential. The pathophysiology of neurological disorders often includes inflammation, mitochondrial dysfunction and oxidative stress. Oxidative stress processes, especially the generation of reactive oxygen species, are key mechanisms in the development of neurological disorders. Oxidative stress refers to an imbalance between the production of reactive oxygen species and antioxidants that can counteract them. Through their impacts on the pathophysiology of neurological disorders, nutrients with anti-inflammatory, neuroprotective and antioxidative properties have been suggested to prevent or mitigate these disorders. Certain vitamins, minerals, polyphenols and flavonoids may have therapeutic effects as adjuvant treatments for neurological disorders. Diet quality is also a risk factor for some neurological and psychiatric disorders and addressing nutritional deficiencies may alleviate symptoms. Therefore, optimizing nutritional intake may represent a potential treatment or prevention strategy. This review summarizes a selection of promising nutrients for the prevention and amelioration of neurological disorders to provide a summary for scientists, clinicians and patients, which may improve understanding of the potential benefits of nutrients in the treatment of neurological disorders.

More Information

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Introduction

Neurological disorders including anxiety, bipolar disorder (BD), depression, epilepsy, multiple sclerosis (MS), and schizophrenia are posing a significant societal burden due to their devastating effects, including life-long disability to the aging population. Recent evidence has shown that oxidative stress and neuro-inflammation play crucial roles in the onset of neurological disorders [1-3]. Despite the importance of oxygen for life and in biological processes such as transcription and signaling, oxygen can cause damage to biological molecules via the formation of reactive oxygen species (ROS) and free radicals including superoxide, hydroxyl radicals and hydrogen peroxide by univalent reduction [4-6]. Accumulation of ROS leads to oxidative stress (OS), due to an imbalance between the levels of oxidants and antioxidants within a cell [7]. This state can also be caused by deficits in the cell's antioxidant system [8,9]. Free radicals have at least one unpaired electron, which causes them to be highly reactive [10]. Oxygen free radicals are produced during cellular metabolism [7]. In metabolic reactions, some electrons prematurely leak, leading to the formation of superoxide (O_2•−) [11]. In conditions of OS, excess O_2•− causes iron to be released from iron-containing molecules, allowing the Fenton reaction to occur and produce highly reactive hydroxyl radicals (•OH) [12]. These can then produce other reactive radicals such as peroxyl radicals, the simplest of which is the perhydroxyl (or hydroperoxyl) radical, capable of peroxidating fatty acids [5]. Moreover,

O_2•− reacts rapidly with NO to form peroxynitrite, a reactive nitrogen species which can cause substantial damage within the cell [7,13].

ROS can cause great damage to lipids, proteins, nucleic acids and polysaccharides [14,15]. Within the central nervous system, neurons are particularly vulnerable to ROS damage because of their fatty acid content (which is susceptible to peroxidation), high metabolic rates and levels of transition metals, low antioxidant defenses, and low capacity for regeneration [12]. Neurons also have high energy requirements, meaning that the mitochondria produce high amounts of ROS while also being vulnerable to damage from ROS themselves [16]. Moreover, OS has been shown to cause mitochondrial fission [17]; exposure of cultured cerebellar granule neurons to H_2O_2 causes mitochondrial fragmentation to occur within one hour [18]. OS can cause changes in protein structure, which can in turn contribute to further oxidative damage [6]. Furthermore, ROS and other continuous OS can cause mitochondrial dysfunction, inhibit DNA damage repair and cause cellular injury, which together may accelerate aging and promote the onset of neurological disorders [19,20]. A vast body of evidence supports the role of ROS in neurological and several other diseases [21-24].

Nutrients can affect many aspects of physiology including monoaminergic activity, inflammation, mitochondrial activity, neuroprogression and oxidative stress [25-27]. Antioxidant treatments are emerging as promising strategies to slow the progression of neurological disorders [28,29]. Consumption of dietary antioxidants can ameliorate the oxidative damage caused by free radicals that are produced in states of inflammation, impaired antioxidant defense and mitochondrial abnormalities [30,31]. Accordingly, antioxidant-based treatments can delay or even reverse OS to protect against neurological disorders [32]. Nutrition is a key aspect in the development and progression of neurological diseases, and making dietary changes to include certain nutrients may prevent neurological decline [33,34]. Vitamins, omega-3 fatty acids, zinc and magnesium support brain function through their antioxidant and anti-inflammatory functions [35]. Additionally, polyphenols and flavonoids counteract oxidative stress, inflammation and apoptosis [36-40]. The present paper discusses nutrients with the potential to mitigate reactive OS in neurological disorders and provides a comprehensive overview of the benefits of nutrients in patients with neurological and psychiatric disorders. Improving our understanding of the influence of nutrients on the course of neurological disorders may enable the development of nutrients to mitigate symptoms and promote recovery.

Anxiety

Anxiety disorders are the most common mental illness [41-44]; they affect about one in five people globally and are among the most frequently diagnosed psychiatric disorders in youth [45,46]. About 31.1% of the population of the United States report having suffered from an anxiety disorder at some point in their life, with the prevalence of anxiety disorders among women being twice as high as among men [47]. Anxiety disorders can include psychological symptoms such as apprehension, compulsions, uneasiness, and panic attacks [48-50]. Other symptoms of anxiety include irritability, worry, restlessness, difficulties in sleep and concentration, headaches, nausea, stomachaches and palpitations [46,51,52]. Children who have anxiety disorders often report difficulties in academic settings, decreased self-confidence, and challenges with interpersonal relationships [46].

Anxiety and nutrients

Recent evidence suggests that anxiety is associated with vitamin C deficiency and that vitamin C supplementation may reduce symptoms [53-56]. A study using a rat model found that the administration of 80 mg/kg/day of vitamin C in drinking water for 83 days inhibited anxiety-like behavior [57]. Similarly, a placebo-controlled trial involving 42 high school students found that oral administration of 500 mg/day of vitamin C for 14 days increased plasma vitamin C levels and reduced self-reported anxiety [53]. Supplementation of vitamin E has also been found to significantly reduce anxiety among patients with type 2 diabetes [56] and magnesium reduces self-reported anxiety [58,59]. Three clinical trials have confirmed magnesium, in combination with other therapies (for example, one study administered 200 mg/day of magnesium and 50 mg/day of vitamin B6) to be effective in decreasing anxiety symptoms [60-62]. Patients with a magnesium deficiency have been reported to benefit from the administration of 125 mg – 300 mg of glycinate or magnesium taurine four times a day to attenuate symptoms of anxiety [63].

Omega-3 (ω3) fatty acids influence serotonergic and dopaminergic activity, which ameliorate anxiety and depression [64-69]. People with anxiety and depression have been found to have decreased ω3 PUFA levels in the blood and brain, as well as a lower ratio of ω3 to ω6 PUFAs [70-72]. A placebo-controlled study demonstrated that supplementation of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) over 12 weeks reduced the severity of symptoms of anxiety by 20% among medical students [73]. Additionally, a meta-analysis of 402 patients with major depressive disorder identified adjuvant ω3 PUFA as beneficial for managing anxiety and depression [74]. Another meta-analysis of 150,278 subjects found high fish intake to be associated with a 27% lower chance of developing depression [75]. Similarly, a cross-sectional study of 12,268 subjects reported a negative correlation between anxiety disorders and intake of ω3 PUFAs including DHA, EPA and docosapentaenoic acid [76]. Another study treated students who experienced anxiety around examinations with 90 mg or 360 mg of linoleic acid

daily and reported improved mood, focus and organization [77]. A 3 - months treatment with 2250 mg/day EPA and 500 mg/day DHA was found to alleviate anxiety and anger among 22 people with the substance-use disorder [78] and another study involving 52 heart attack survivors found 1 month of adjuvant therapy with 375 mg/day DHA and 465 mg/day EPA to decrease anxiety and depressive symptoms by 10% and 22%, respectively [79].

Polyphenols can be beneficial in the management of anxiety through their influence on mechanisms including oxidative stress, inflammation, the adrenergic and serotonergic pathways and the HPA axis [80]. For example, researchers demonstrated the polyphenol quercetin administered at 300 mg/kg had activity against anxiety [81]. Polyphenol resveratrol has also been suggested to improve behavioral symptoms of anxiety and depression, as it has antiapoptotic, antioxidative and anti-inflammatory effects [82]. 50 mg - 100 mg of flavonoids given as supplements for at least 8 weeks may be effective against depression and anxiety [83]. Considerable evidence has posited that flavonoids scavenge ROS and decrease the formation of free radicals [84,85]. For instance, quercetin was found to prevent lipid peroxidation and damage to antioxidant enzymes, as well as reduce anxious behaviors in mice undergoing immobilization stress [86]. Table 1 shows the nutrients that may be beneficial for anxiety.

Table 1: Effective nutrients for neurological disorders Anxiety, Bipolar Disorder, Depression, Epilepsy, Multiple Sclerosis and Schizophrenia.

Neurological Disorder	Effective Nutrients	Sources
Anxiety	Vitamin C	[53-57]
	Magnesium	[58-63]
	Omega-3 PUFAs	[64-79]
	Polyphenols/Flavonoids	[80-86]
Bipolar Disorder	Vitamin D	[124-129]
	Omega-3 PUFAs	[130-140]
	Magnesium	[140,141]
Depression	Vitamin D	[170-175]
	Omega-3 PUFAs	[64,65,153-169]
	Magnesium	[176-183]
	Zinc	[74,184-187]
	Polyphenols/Flavonoids	[188-195]
Epilepsy	Vitamin B6	[211-218]
	Vitamin D	[213,219-224]
	Vitamin E	[213,225-228]
	Vitamin C	[229-231]
	Omega-3 PUFAs	[232-239]
	Magnesium	[240-243]
	Polyphenols/Flavonoids	[244-252]
Multiple Sclerosis	Vitamin A	[265-275]
	Vitamins B3, B12	[276-285]
	Vitamin D	[271,286-296]
	Omega-3 PUFAs	[297-306]
	Polyphenols/Flavonoids	[308-321]
Schizophrenia	Vitamins B6, B12, B9	[339-342]
	Vitamin C	[343-348]
	Vitamin E	[349,350]
	Vitamin D	[352-357]
	Omega-3 PUFAs	[350,358-365]
	Polyphenols/Flavonoids	[366-371]

Bipolar disorder

Bipolar Disorder (BD) is a debilitating psychiatric condition involving altered neural plasticity [87-93]. It is characterized by episodes of depression and mania or hypomania [94-101]. There are two major categories of bipolar disorder: type I (BD-I) and type II (BD-II) [102,103]. The former is diagnosed in patients who have had at least one manic episode, marked by heightened activity and grandiosity, after which they experience a depressive or hypomanic episode [104-107]. In contrast, BD-II involves hypomanic and depressive episodes without manic episodes [108,109]. Some patients with BD display progressive alterations in neuroanatomy such as decreasing cortical thickness, lateral ventricle enlargement, or decreasing hippocampal volume, which is correlated with BD progression [110-114]. Ultimately, BD is a complex illness influenced by a variety of genetic, environmental, and social factors with a pathophysiology including disrupted brain development; altered chronobiology and neuroplasticity; mitochondrial dysfunction; oxidative and nitrosative stress; endoplasmic reticulum stress; and defects in signaling involving apoptosis, neurotrophic factors, inflammation, calcium and neurotransmitters [115-122]. The parietal lobe-which plays an important role in memory, attention, and other cognitive functions-is also involved in BD development [109,123].

Bipolar disorder and nutrients

One study comprising 118 participants found that patients with BD were 470% more likely to be deficient in vitamin D than the general population [124]. In contrast, one cross-sectional study found plasma 25-hydroxy vitamin D levels to be higher in patients with BD who were in a state of decompensation than in healthy controls [125]. There is evidence to suggest that vitamin D supplements may reduce symptoms of depression and mania, although further research is required to determine clinically effective dosages [126-128]. Moreover, vitamin D has been reported to have anti-inflammatory activity [129].

Patients with BD have been found to have altered levels of PUFAs [130-132]; an analysis of six studies involving a total of 118 patients with BD-I and 147 healthy controls found erythrocyte DHA and EPA levels to be decreased in patients with BD-I [131]. Supplementation with omega-3 PUFAs has been proposed to be beneficial for many diseases including dementia, cancer, hypertension, diabetes, arthritis, arteriosclerosis and autoimmune disease and evidence supporting the use of ω3 PUFAs in managing BD is particularly promising [133]. Omega-3 PUFAs may improve symptoms of BD by increasing levels of brain-derived neurotrophic factors [134]. Epidemiological and experimental studies have investigated the relationship between PUFA intake and the presence and severity of depression and several studies have reported similar benefits for patients with BD [135-137]. Administration of 1 g/day - 2 g/day of EPA has been found

to decrease depressive symptoms in patients with BD-I [138], while a placebo-controlled study reported administration of 1 g/day EPA and 1 g/day DHA for 52 weeks as a prophylactic and adjuvant therapy to be effective for patients with BD [139]. However, a randomized placebo-controlled trial involving 31 patients with BD in a euthymic state and 15 healthy controls found that 1250 mg/day DHA for 12 weeks improved cognitive performance in healthy controls only [140].

The findings relating to blood magnesium levels in patients with BD are varied, with one study reporting serum magnesium levels to be significantly higher than those of healthy controls during mania, depression and hypomania, but comparable during remission [141]. Therefore, serum magnesium could be a useful biomarker of acute BD episodes. Several studies have also observed altered serum levels of copper in patients with BD [142]; one study involving 133 patients with BD found elevated serum copper levels in patients with stage I BD compared with those in more advanced stages of BD [142]. Table 1 shows the nutrients that can be effective for bipolar disorder.

Depression

Depression is one of the most common psychiatric illnesses, affecting hundreds of millions of people globally [143-146] and over 17% of the population of the United States [147]. Major depressive disorder (MDD) accounts for 40% of psychiatric disorders in the United States and affects almost 350 million people around the world [148,149]. This condition is associated with a high level of morbidity and the increased risk of stroke, suicide, cardiac emergencies, hypertension and diabetes resulting in high mortality rates. Symptoms of MDD include apathy, anhedonia, changes in appetite and weight, psychomotor retardation/agitation, depressed mood, disrupted sleep, impaired cognition, guilt and recurrent suicidal ideation [148,150,151]. Depression creates an economic burden through loss in productivity, fatigue and mortality [152].

Depression and nutrients

Reduced brain levels of DHA due to deficiency in omega-3 PUFA are correlated with depressive behavior [153-160]. A meta-analysis of 255,076 subjects found consumption of 50 g/day of fish to reduce the risk of depression by 16%, 0.5 and 1.8 g/day of ω3 PUFAs to lower depression risk by 31% and 70%, respectively, and EPA and DHA to show a dose-response relationship [161]. Another meta-analysis of 14 studies found EPA, DHA and total ω3 PUFA levels to be lower in the blood of depressed patients compared with controls [65]. Post-mortem studies have revealed patients with MDD, BD, or those who had committed suicide to have decreased DHA levels in the prefrontal cortex [162]. Consuming fish less than once per week has been reported to increase the severity of depression [163,164], while EPA—but not DHA—purportedly mediates the benefits of ω3 supplements in patients with MDD [64,165,166], with considerable evidence of the benefit of 1–2 g/day ethyl-EPA for patients with MDD resistant to antidepressants [167,168]. Furthermore, EPA-rich supplements without DHA are more effective for MDD than supplements rich in DHA [169]. In the case of vitamin D deficiency, vitamin D receptors in the brain are less stimulated, which may contribute to depressive symptoms [170-174]. A meta-analysis of seven trials including 3,191 subjects did not find vitamin D supplementation to improve depressive symptoms, even though two studies of patients with MDD found vitamin D to moderately improve depressive symptoms [175].

Depressed adults have lower levels of serum magnesium [176-179]. One study reported inadequate dietary magnesium to be associated with depression and reduced magnesium levels in serum and cerebrospinal fluid have been reported to be associated with depressive symptoms and suicidal behavior [180]. In rodent models, consumption of magnesium was effective for decreasing depression-like behavior as adjuvant therapy [181,182] while a trial of elderly patients with depression and magnesium deficiency found supplementation with 450 mg/day magnesium over 12 weeks to effectively decrease depressive symptoms at a level comparable with imipramine [183]. Zinc is required for the maximal function of many cellular processes, and zinc deficiencies can cause neurological disorders and depressive symptoms such as irritability, altered mood, and impaired cognition. Zinc can cross the blood-brain barrier and the blood-cerebrospinal fluid barrier [184]; once in the brain, zinc becomes concentrated in the neocortex, hippocampus and amygdala [185,186]. A systematic review of trials using zinc supplements identified the potential therapeutic value of zinc, either as a monotherapy or adjunctive to antidepressant medications for the treatment of depression [187]. A meta-analysis including three randomized control trials (RCTs) found that adjunctive supplementation with 25 mg/day zinc over 6 weeks - 12 weeks improved symptoms of MDD [74].

Polyphenols and flavonoids have been suggested to be beneficial in preventing diseases induced by OS, including depression [188-191]. In a study of 10,752 women with a 10-year follow-up, flavanone, flavanol and flavone intake were negatively associated with the risk of developing depression [192]. A double-blind randomized placebo-controlled study of 74 subjects found supplementation of green tea extract for 5 weeks resulted in the prevention of depressive symptoms [193]. In another study, researchers found that administration of the nonflavonoid phenol curcumin for 6 weeks at 1000 mg/day decreased the severity of the major depressive disorder in patients without suicidal ideation or other psychiatric disorders [194]. Additionally, a Gingko Biloba polyphenol extract containing the flavonoids quercetin and kaemferol has been found to have antidepressant activity in mice [195]. Table 1 shows the nutrients that can be effective for depression.

Epilepsy

Epilepsy is a chronic neurological disorder characterized by the presence of seizures [196-201] and affecting an estimated 50 million people globally [202-205]. Approximately 2.4 million - 4.6 million people are diagnosed with epilepsy every year [206], one-third of which do not respond to medications and continue to have seizures over their lifetime [207-209]. This burden has a significant societal impact and over half of the cases are idiopathic, with the cause of the disease unknown [210].

Epilepsy and nutrients

Adjunctive multivitamin therapy (100 mg vitamin B6, 5 mg vitamin B9, 1000 IU vitamin D, 400 IU vitamin E, and 100 mg Q10) has been shown to be effective for patients with drug-resistant focal epilepsy [211]; with a reported decrease in mean seizure frequency from 9 to 2 per month and 63% of subjects reporting a ≥ 50% reduction in seizure frequency at the 6-month follow-up [209]. However, although some studies of patients with epilepsy have identified a therapeutic benefit of vitamin B6 supplementation in terms of improved clinical outcomes, this is not the case for every patient [212-218]. Multiple studies have identified vitamin D deficiencies among pediatric and adult patients with epilepsy [219-222]. In one clinical trial involving 23 patients with epilepsy administered 4,000 IU/day of vitamin D3 was for 4 weeks followed by 16,000 IU/day for 4 weeks to one group and a placebo followed by 8,000 IU/day of vitamin D3 to another. The first group experienced a 67% – 71% reduction in mean seizure frequency [213]. Similarly, vitamin D3 supplementation has been shown to decrease seizure frequency by as much as 40% among patients with drug-resistant epilepsy and vitamin D3 deficiency [223]. Studies using animal models of epilepsy have found vitamin D to have anticonvulsive effects and knocking out the vitamin D receptor significantly increases seizure frequency in mouse models of epilepsy [224]. Another study of 648 children with epilepsy found improved seizure control with vitamin D supplementation [222].

Vitamin E has been found to reduce the peroxidation of lipids and proteins while preventing ROS accumulation in animal models of epilepsy [225,226]. In line with this, the administration of 400 IU/day of vitamin E over 3 months to patients with epilepsy has been shown to reduce seizure frequency by almost 60% compared with placebo treatment [213]. Clinical trials have also supported the long-term use of adjunctive vitamin E for patients with intractable epilepsy [227,228]. Studies found that patients with epilepsy have decreased serum levels of Vitamin C [229]. Animal studies also have suggested vitamin C to be beneficial for seizure control through the reduction of OS in the context of epilepsy [230,231].

Fish oil has also been observed to prevent seizures in patients with epilepsy as well in an open-label study [232-234]. However, the evidence of the anticonvulsive effects of fish oil and ω3 PUFAs is mixed with some RCTs reporting consumption of 0.6 g/day - 2 g/day fish oil to reduce the length and occurrence of seizures [235-237], but some non-randomized studies failed to identify any anticonvulsive activity [238]. Studies using animal models have indicated that ω3 fatty acids may control seizures, but their efficacy as a therapy against seizures remains to be established. Given the safety of fish oil at < 4 g/day, supplementation in conjunction with conventional medications could be a beneficial approach to control seizures [239]. Deficiencies in magnesium have also been suggested to cause seizures, and patients with epilepsy have been reported to have lower magnesium levels than healthy controls [240-242]. Additionally, severe epilepsy is associated with lower levels of magnesium than mild/moderate epilepsy [243].

Polyphenols and flavonoids may also be neuroprotective in epilepsy [244,245]. Polyphenols have been studied in animal models of seizures and epilepsy [246-249]. In one study, 15 mg/kg/d resveratrol for 10 days prevented neuron death and epilepsy onset in a rat model [247]. In another study, 30 mg/kg resveratrol per hour for 3 hours followed by administration twice a day for 3 days decreased OS and neuroinflammation in a rat model, while preventing abnormal neurogenesis [248]. Rats treated with 25 mg/kg and 50 mg/kg of the polyphenol epigallocatechin gallate (EGCG) were protected against kindling, an animal model of epilepsy. Moreover, EGCG prevented OS and cognitive decline [249]. Preclinical studies have recently indicated curcumin may be beneficial in epilepsy while being well-tolerated [250,251]. In zebrafish models of epilepsy-induced with pentylenetetrazol, curcumin was found to be similar to valproate in its ability to prevent tonic-clonic seizures [252]. Table 1 shows the nutrients that can be effective for epilepsy.

Multiple sclerosis

Multiple sclerosis (MS) is a chronic disease involving demyelination of the central nervous system [253-257]. The condition is an inflammatory and neurodegenerative disorder, with multifactorial causes including genetic and environmental factors [258-261]. Patients with MS struggle with cognitive function, respiration and malnutrition [262,263]; and the development of pain, vision impairments, fatigue and abnormal motor function is frequently seen in MS [264].

Multiple sclerosis and nutrients

In vivo and in vitro studies have identified potential benefits of vitamin A for the treatment of MS [265-268], and patients have been reported to have lower serum levels of the vitamin [269-271]. Vitamin A has antioxidant and anti-inflammatory properties [272] and administration has been shown to enhance astrocyte activity, attenuate the immune response and reverse demyelination in patients with MS

[273-275]. Vitamin B12 is an immunomodulator and serves as a cofactor in myelin synthesis and deficiencies are linked to MS [276-278]; patients with relapsing-remitting MS have been found to have reduced plasma levels of folate and vitamin B12, despite elevated concentrations of homocysteine [279-281]. Folate and vitamin B12 regulate MS by increasing the uptake of homocysteine, which is essential for myelin synthesis [282,283]. Additionally, vitamin B3 can promote remyelination, which may provide benefits for patients with MS [284]. Although one study has reported that high doses of thiamine improve fatigue in patients with MS [285], additional clinical trials are required to find the most effective regimen for vitamin B in the treatment of MS.

Many studies have observed an association between vitamin D levels and the development of MS [286-289] and the rates of MS development tend to be higher in areas where environmental vitamin D is less available [290]. Vitamin D has been reported to regulate inflammation in MS; consequently, higher intake may delay the progression of MS [271,291]. Vitamin D deficiency is an established risk factor for MS and targeting vitamin D levels could also represent an approach to control symptoms and progression of the disease [291-294]. Furthermore, MS is accompanied by a high risk of osteoporosis, for which prophylactic calcium and vitamin D are often considered during the initial stages of the illness [295,296].

Polyunsaturated fatty acids are suggested to be beneficial for MS patients [297-300]. Long-chain ω3 PUFAs including DHA and EPA may regulate cellular metabolism and inflammation in MS [301,302] and dietary intake of long-chain PUFAs can overcome the effects of low sun exposure, to reduce the risk of developing MS [303]. A low-fat diet supplemented with ω-3 fatty acids has been shown to lower fatigue by up to 60% and reduce the occurrence of relapse among patients with MS while reducing the severity of disability [304-306]. Similar results have been observed with dietary supplementation of vitamins A and E [307]. Although several studies have reported reduced levels of vitamin C in patients with MS, the potential benefits of the antioxidants vitamins C and E have not been widely investigated as therapies for MS.

Polyphenols may be beneficial in preventing and treating MS [308,309]. Compounds in this family including curcumin, resveratrol, apple flavonoid-enriched fraction, catechins, quercetin, extra virgin olive oil and white grape extract have been found to decrease the presence of OS and inflammatory cytokines in MS while influencing neural stem cells [310,311]. In a mouse model of MS, orally-administered resveratrol decreased neuronal damage [312]. 3 weeks of 250 mg/kg/d resveratrol administration showed benefit as an adjunctive therapy for MS. Effects of this treatment included decreasing OS, lowering NF-κB signaling, improving mitochondrial function and increasing motor coordination [313]. Additionally, prior studies have found that flavonoids reduced the extent of demyelination in MS, consistent with their possible therapeutic use [314,315]. In one study, patients with MS treated with grape seed capsules had improvements in quality of life, as well as in physical and mental functioning [316]. Preliminary data from an RCT indicates *G. Biloba* extract may decrease cognitive dysfunction associated with MS [317]. Surveys of Australian and American patients indicate *G. Biloba* is the most commonly used herbal supplement among MS patients [318,319]. Curcumin may also have protective effects in MS patients [320]. This may be the case particularly due to its ability to limit pro-inflammatory cytokine secretion [321]. Table 1 shows the nutrients that can be effective for multiple sclerosis.

Schizophrenia

Schizophrenia is a severe psychiatric disorder that causes cognitive, functional, and emotional disability [322-325]. Schizophrenia is often associated with frequent relapses and the condition is marked by anatomical changes in the brain including decreased brain volume, shrinking gray and white matter and increased volumes of the third and lateral ventricles [326,327]. Post-mortem analyses have identified abnormalities in regions including the prefrontal cortical areas, amygdala, basal ganglia, corpus collosum, superior temporal gyrus and medial temporal lobe in patients with schizophrenia [328,329]. Positive and negative symptoms have been reported (delusions, hallucinations and flat affect, social withdrawal, respectively) and cognitive impairment such as difficulty sustaining attention, memory problems, or executive dysfunction, may be present, even in the prodrome phase before the onset of active schizophrenia [330-333]. These cognitive deficits may manifest from a young age, diminishing patients' ability to participate in society and the workforce and creating difficulties with self-care [334,335]. Patients with schizophrenia often develop other psychiatric conditions including depression, anxiety, substance abuse, suicidality and obsessive behavior, which exacerbate the wide-reaching societal burden of the condition [336].

Schizophrenia and nutrients

Meta-analyses have revealed that patients with schizophrenia are more likely to be deficient in folate than healthy controls [337,338] and numerous trials have investigated the benefits of supplemental vitamin B6, folate, and folic acid with vitamin B12 or vitamins B6 and B12 [339]. A meta-analysis of seven RCTs comprising 297 patients found that vitamin B supplementation improved symptoms, while supplementation with 25 mg/day vitamin B6, 400 μg/day vitamin B12 and 2 mg/day folic acid over 3 months reduced total Positive and Negative Symptom Scale (PANSS) scores in patients with schizophrenia with elevated homocysteine [340]. However, vitamin B supplements have been shown to be most effective at alleviating symptoms during the early stages of schizophrenia [341,342].

The antioxidants vitamin C and vitamin E have been widely investigated for schizophrenia, as patients with schizophrenia have lower plasma levels of these vitamins than healthy controls [343-345]. Additionally, levels of superoxide dismutase (SOD), an antioxidant marker have been reported to be lower in patients with schizophrenia [346]. A placebo-controlled double-blind study of 40 patients with schizophrenia investigating the use of adjunctive vitamin C for 8 weeks alongside atypical antipsychotics found that vitamin C reversed the elevated serum MDA [347] and decreased plasma ascorbic acid, which is associated with schizophrenia, and improved the Brief Psychiatric Rating Scale (BPRS) scores more than the placebo [347]. Similarly, supplementation with vitamin C, vitamin E, or ω3 fatty acids has been found to reduce both BPRS and PANSS scores in patients with schizophrenia [348]. Vitamin C, either alone or in combination with vitamin E, has also been shown to be useful for decreasing dyskinesia scores and improving BPRS scores [347], while daily short-term and long-term treatment with 600 IU/day - 1600 IU/day vitamin E alone has not been found to change BPRS score [349]. Some early studies have suggested vitamin E may be beneficial in managing and preventing the progression of tardive dyskinesia, which may arise following the long-term use of antipsychotics [350]. However, a meta-analysis of 11 RCTs failed to find evidence of this effect [351].

Vitamin D is involved in neuroprotection and nervous system development, and patients with schizophrenia are often deficient in this vitamin [352-354]. A study of 424 patients with schizophrenia and 424 controls found low neonatal blood levels of 25(OH)D3 to be associated with an increased risk of schizophrenia [355]. Similarly, another study comprising 20 patients with schizophrenia and 20 healthy controls found that lower 25(OH)D3 levels were associated with greater deficits in cognition and symptom severity in patients who had recently developed schizophrenia [356]. A placebo-controlled study involving 60 patients with chronic schizophrenia found that a 12 - weeks treatment of daily probiotics and 50,000 IU of vitamin D3 given every 2 weeks improved total PANSS scores, as well as scores on the PANSS general psychopathology scale [357].

Deficiencies in PUFAs can be associated with cognitive deficits and psychosis, which may be indicative of increased OS in schizophrenia [358,359]. Post-mortem studies have found lower levels of PUFAs, including DHA and arachidonic acid, in the brains of patients with schizophrenia [359], who also often have deficiencies and altered PUFA metabolism in erythrocyte membranes [350,360]. Multiple RCTs showed supplemental ω3 fatty acids to significantly improve symptoms of schizophrenia [350,361] possibly due to the antioxidative effects of these molecules [362,363]. One study reported that ω3 fatty acid supplements alleviated symptoms of tardive dyskinesia and schizophrenia [350]. Likewise, a combination of vitamin C, vitamin E and ω3 fatty acids given over 4 months has been shown to improve both positive and negative symptoms and erythrocyte SOD levels in patients with chronic schizophrenia [364]. An RCT of 71 patients with schizophrenia found that when ω3 PUFAs were administered over 26 weeks, the severity of schizophrenia symptoms decreased [365]. Another study evaluated supplemental vitamin C (1000 mg/day), vitamin E (400 IU twice/day) and ω3 fatty acids (1000 mg twice/day) as an add-on therapy to haloperidol and found that, over the 4 - month treatment period, the BPRS, Barnes Akathisia Rating Scale, Scale for the Assessment of Negative Symptoms and Simpson Angus Scale scores decreased [364].

As antioxidant, anti-inflammatory and antiapoptotic compounds, polyphenols provide neuroprotection against schizophrenia [366]. Quercetin, as a free radical scavenger, may be able to alleviate schizophrenia symptoms [367]. The compounds scopoletin and rutin have inhibitory activity against the D2 receptor, which may allow them to have less positive symptoms in schizophrenia [368]. Preclinical evidence points to the possible benefit of using EGCG in schizophrenia [369]. In a double-blind study, researchers found 240 mg/d of *G. Biloba* extract administered for 12 weeks on 157 patients significantly improved symptoms of tardive dyskinesia compared to placebo [370]. Moreover, curcumin may be beneficial in mitigating the adverse effects of treatment with neuroleptics in patients with schizophrenia [370,371]. Table 1 shows the nutrients that can be effective for schizophrenia.

Conclusion

Neurological disorders including anxiety, BD, depression, epilepsy, MS and schizophrenia have attracted considerable research interest due to their sometimes devastating effects, including life-long disability. These disorders arise from pathophysiological changes including mitochondrial dysfunction, neuroinflammation and OS. There is evidence that nutrients may improve these pathophysiological processes. Similarly, inadequate nutrition and deficiencies may contribute to the pathology of neurological disorders, presenting another obstacle to recovery. Nutritional consumption influences the functioning of the brain and the intake of certain nutrients may prevent pathology of the central nervous system. The findings presented here suggest that improving nutritional status is likely to be an important aspect of both treatment and prevention. Knowing how nutrients can affect cognition may inform strategies to protect and improve neuronal function through modifications to diet and mass nutrition. Greater awareness of how various nutrients affect the development of neurological diseases will facilitate the development of specialized diets and nutritional supplements for their treatment, symptom relief and recovery.

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Author contributions

The authors declare that all authors listed have made a substantial, equal, direct and intellectual contribution to the work and approved the paper for publication

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