CHAPTER 18

# Role of Dietary Supplements in the Management of Brain Diseases

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## SUMMARY

Dietary supplements are an important part of the management of brain illnesses because they include vital nutrients that enhance cognitive function and overall brain health. The brain has a high metabolic rate, so it needs nourishment continuously to stay in its proper structural and functional state. Although a well-balanced diet is the best way to obtain essential nutrients, dietary supplements can be helpful add-ons, particularly when meeting certain nutritional needs can be difficult when relying solely on food. Omega-3 fatty acids are crucial for brain health because they maintain neurotransmission and contribute to the construction of cell membranes. They are frequently found in fish oil supplements. Vitamins that are antioxidants, like C and E, aid in preventing oxidative stress in the brain, which is linked to neurodegenerative illnesses like Alzheimer's. Vitamins B, which include B6, B9, and B12, are also involved in the production of neurotransmitters and the upkeep of myelin, the sheath that surrounds nerve fibers. Certain nutrient deficiencies are common in illnesses like Alzheimer's disease, and supplements like coenzyme Q10, vitamin D, and vitamin E have been found to slow down cognitive deterioration in these patients. Furthermore, synaptic plasticity and neuroprotection depend on minerals like zinc and magnesium. It is important to recall that dietary supplements should not be used as stand-alone treatments for brain disorders, though they can enhance brain health and complement a balanced diet.

## INTRODUCTION

Diet is regarded to be much richer than it used to be. People's misunderstanding of fundamental nutritional concepts has led to a substantial portion of the population eating a diet that is heavy in calories and fat but deficient in proteins, vitamins, and other minerals. This long-term scenario has resulted in the establishment of several degenerative illnesses. To address this worry, nutritional supplements were offered as a possible remedy (Jicha & Markesbery 2010; Hassan et al., 2020).

The products that are used to augment diet are defined as dietary supplements. These products consist of many dietary ingredients such as herbs, amino acids, fish oil, and metabolites. Remember that dietary supplements should not be used as a sole source of nutrients. It is true that these supplements provide many essential nutrients which can be difficult to find in some areas, but these supplements cannot replace a whole nutritious meal. It is important to note that these supplements should be labeled as dietary supplements and not marketed as regular food items. Dietary supplements come in different forms such as gel capsules, powder, or liquids. Dietary supplements have a long history. These have been in use since ancient times for better health. An example includes *Echinacea purpurea*, which was extensively used by the Great Plains Indians and is still an important component of the dietary product sold in America. This plant supports immune health (Nesheim, 1999). Dietary supplements have extensive health benefits. Athletes use supplements to support fast recovery between training sessions and to enhance their performance. Energy-providing bars, energy drinks, and protein supplements are used by sportsmen to increase the efficiency of their performance and to help in muscle growth. Another use of dietary supplements is relief in menopausal symptoms such as hot flashes. There is not much experimental evidence to support this use but still used by many

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women (Geller & Studee 2005). A well-balanced and nutritious diet plays a crucial role in maintaining a healthy brain, preventing brain aging, and reducing the risk of neurological disorders. Antioxidants, antidepressants, and anti-stress ingredients in dietary supplements help in the decline of neurodegenerative disorders like Parkinson's disease and Alzheimer's disease (Naureen et al., 2022).

## INTRODUCTION TO BRAIN DISEASES

Nowadays life has become so taxing, that it is not rare for people to be exposed to different neurological disorders. Our whole body is affected by defects in the brain. Human brain diseases are of two types which are neurodegenerative and neuropsychiatric disorders. Examples of brain diseases include dementia, Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis, schizophrenia, etc. Alzheimer's disease is a sort of dementia in which neurons of the cerebral cortex are affected. The symptoms of AD include loss of memory, less energy, language problems, and many more (Nejash). In Parkinson's disease, nerve cells and basal ganglia are affected. The symptoms of PD include tremors, shaking hands or fingers, rigid muscles, etc. (Naz & Siddique 2020). These brain disorders diminish the ability of humans to lead a normal life (Mohsin et al., 2022).

Neurological disorders affect a wide range of the human population. The most widespread neurological disorders include dementias such as AD affecting approximately 3 million people, migraine which affects the lives of approximately 69 million people (about twice the population of California), and about 8 million people (about half the population of New York) are affected by strokes. The brain diseases which are the major cause of death include dementia (about 259,000 deaths), and PD [30 000 deaths approximately (Feigin et al., 2021)].

### Etiological factors

The factors leading to neurological disorders may include trauma, accidents, neuronal defects, metals such as mercury, and many other environmental and hereditary factors. Here we will discuss the etiological factors of some of the main brain diseases:

**Alzheimer's disease:** The etiology of AD includes both genetic and non-genetic factors. Genetic factors play a major role in both early-onset (EOAD) and late-onset (LOAD) AD. Genetic factors are passed from generation to generation whereas non-genetic factors include various environmental factors. Non-genetic factors include exposure to pesticides, hypertension, diabetes, depression cancer, etc. (Jiang et al., 2013).

**Parkinson's disease:** The etiological factors leading to PD include head injury, neurotoxins, contaminated water, farming, metals, diet less in essential nutrients, smoking harmful toxins, etc. (Lai et al., 2002).

**Schizophrenia:** Prenatal exposure to infection is one of the main factors. Drug abuse is also thought to cause schizophrenia. Many individual factors may work together to cause this disease (Dean & Murray 2022).

### Pathogenesis

**Oxidative stress and neuro-inflammation:** Redox levels in the body are targeted by oxidative stress involving uncontrolled synthesis of damaging ROS or the functions of the protective antioxidant system are hindered. Oxidative stress happens when the levels of ROS increase the defense mechanisms of the antioxidant system. This causes damage to proteins, nucleic acids, and lipids, altering normal functions of the body and causing diseases such as NDs (Feigin et al., 2020).

**Mitochondrial dysfunction:** Mitochondrial dysfunction plays a very important role in Parkinson's disease, Alzheimer's disease, and Huntington's disease. Mitochondria dysfunctionality is involved in all these three diseases but with different mechanisms (Rey et al., 2022). In Alzheimer's disease, mitochondrial dysfunctionality leads to a decrease in the activity of Complex-I and cytochrome-c. In Parkinson's disease, mitochondrial dysfunction results in a decrease in regional blood flow and oxygen usage. Whereas in Huntigton's disease, activities of Complex I, III, and IV are compromised due to mitochondrial dysfunctionality, followed by the production of reactive oxygen species.

**Role of the gut-brain axis and microbiome in brain diseases:** The human body has many microorganisms which are known as human microbiota and their genome is known to be microbiome. Among them, the most discussed phylum with impressive roles is *Bacteroidetes* and *Firmicutes* (Nandwana et al., 2022)

Microbiota-gut-brain axis is referred to as two-way communication between the brain and the gut. The gut stimulates the brain and the brain and, in return sends the message to the gut via vagus and enteric nerves (neurological), immunological, endocrine, and hormonal stimulation. Microbiota seems to be showing effects on blood-brain barrier formation and growth, myelination, stability, and neurogenesis leading to brain diseases such as ASD, Alzheimer's, Parkinson's, and schizophrenia (Jelani et al., 2023). If any nutrients cause damage to microbiota, microbes show different pathways. For Example, oxidative stress, mitochondrial function, neuroinflammation, and disturbed epigenetic processes, which ultimately influence to genetic system of humans. For this reason, probiotics are given to maintain this

healthy relationship between the brain and the gut (Lagier et al., 2012).

**Role of coenzyme Q10**: Coenzyme Q10 is also known as vitamin Q10 (Bonakdar & Guarneri 2005). Human cells produce the endogenous enzyme cofactor ubiquinone. The majority of it is found in the mitochondria (Suksomboon et al., 2015). It is a member of the electron transport chain and takes part in aerobic cellular respiration, producing adenosine triphosphate as energy (ATP). Co-Q10's ability to function as an antioxidant or a pro-oxidant suggests that it also contributes significantly to the regulation of the cellular redox system under both pathological and physiological circumstances (Santos et al., 2009).

The potential for oxidative damage and abnormalities in energy metabolism might lead to the pathogenesis of neurodegenerative disorders. (Young et al., 2007). The effective antioxidant Co-Q10 protects against the possible negative effects of free radicals generated during oxidative phosphorylation in the inner mitochondrial membrane. Many neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, have been linked to oxidative stress, which is a significant contributor to the development of neurodegenerative diseases. It causes glutathione loss as well as oxidative DNA and protein damage (Beal, 1992). The central nervous system is vulnerable to oxidative stress, which may highlight the importance of Co-Q10 in this system. (Santos et al., 2009).

## ROLE OF NUTRITION IN BRAIN DISEASES

Nutrition has a significant lifetime impact on the brain, with implications for dementia and cognitive decline. Energy intake, physical activity, energy metabolism, and related changes in body composition, as well as micronutrients involved in DNA methylation, such as folate, vitamins B6 and B12, choline, and methionine, are some of the mechanisms by which nutrition plays a role in the pathogenesis of age-related cognitive decline. (Dauncey, 2014). The synthesis of mitochondrial energy is influenced by nutritional nutrients, which are also essential for antioxidant defense against the free radical byproducts of oxidative phosphorylation. The antioxidant defense system could be weakened by increased oxidative stress brought on by a poor diet. On the other hand, a diversified, well-balanced diet rich in fruits and vegetables or dietary supplements containing vitamins, minerals, alkaloids, caffeine, and omega-3 fatty acids may promote neuroprotection. (Seidl et al., 2014). The majority of studies show that dietary sources of brain-accessible antioxidants may provide a way to slow the onset and progression of the dementing disease (Mi et al., 2013). Dietary Supplements play a vital role in curing nutritional deficiencies associated with neurodegenerative disorders or to reverse metabolic abnormalities. Nutrition plays an antioxidant and neuroprotective role in the management of brain diseases. Recent investigations prove its strong relationship between nutrition neurodegenerative disorders.

## DIETARY SUPPLEMENTS AS A COMPLEMENTARY APPROACH TO MANAGING BRAIN DISEASES

Dietary supplements, according to the European Food Safety Authority (EFSA), are “concentrated sources of nutrients or other substances with a nutritional or physiological effect that are marketed in dose form. A wide range of nutrients and other ingredients might be present in food supplements, including, but not limited to, vitamins, minerals, amino acids, essential fatty acids, fiber, and various plants and herbal extracts” Food supplements.

Dietary supplements are frequently integrated with traditional drug therapies to improve patient health and alleviate the symptoms of chronic illnesses like cardiovascular disease, gastrointestinal disease, liver disease, and neurological disease. Recently great emphasis has been laid on the role that diet and dietary supplements can play a vital role in the prevention and management of neurodegenerative diseases. Dietary supplements contain vitamins, phytochemicals, and minerals that can be effective in preventing and reducing neurodegenerative disorders, these substances have the potential to combat some of the main pathophysiological processes that contribute to the onset of the disorder, including oxidative stress, neuro-inflammation, and production of free radicals (John et al., 2020)

### Vitamins

Vitamins are organic compounds that regulate normal physiological function in the body, but the body cannot produce them on its own. Therefore, they must be obtained from the diet in small quantities. Vitamins are micronutrients that are crucial for maintaining normal brain function. They play key roles in several biochemical processes that occur in the brain, including the synthesis of neurotransmitters, energy metabolism, regulation of oxidative stress, and enzymatic activity by acting as coenzymes (Liu et al., 2017). For example, B6, B9 (folate), Cobalamin (Vitamin B12) play a hand in the synthesis of neurotransmitters that are essential for focus, mood control, and memory and also dementia, cognitive decline, and mood problems have all been linked to low vitamin levels.

**Vitamin B2 (riboflavin):** An adequate intake of riboflavin or vitamin B2 is necessary to facilitate several enzymatic reactions involved in the macronutrient breakdown of proteins, lipids & carbohydrates termed as cellular metabolism happening within our bodies continuously. The proper functioning of these

enzyme systems requires participation from the co-facing compound riboflavin forming four proton intermediates' catalytic cascades initiating necessary biological operations required for optimal energy production& immune support. In addition to playing a role in the cellular metabolism of macronutrients, this essential micronutrient exerts potent antioxidant activities neutralizing reactive oxygen species that may cause deleterious effects like cell degeneration in the body (Liu et al., 2017). Vitamin B2 may be beneficial for elderly because of improvement in cognitive health. There is evidence that this vitamin may stimulate the brain's anti-oxidation structures, promote myelination, and increase mitochondrial function. Furthermore, by up regulating Nrf2 expression while simultaneously downregulating Keap1 expression in the brain tissue of transgenic mice models exposed to reactive oxygen species-induced damage associated with Alzheimer's disease pathogenesis; thus demonstrating its potential role as a neuroprotective tool against oxidative stress (Saedisomeolia & Ashoori 2018).

Riboflavin has been found to have therapeutic effects for the management of neuro-inflammatory illnesses and Parkinson's disease. It works by preventing the activation of protein nuclear factor-kappa B (NF-B). Because riboflavin stops NF-B from activating, less pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-alpha) and nitric oxide (NO) are produced. NF-B is essential for regulating immune responses and enhancing inflammatory responses in the body. The production and secretion of high-mobility group protein B1 (HMGB1) are also inhibited by riboflavin, in addition to NF-B activity. HMGB1 is a nuclear protein that is in charge of immune-related disease management. HMGB1 is released into the circulation, where it can induce inflammation and tissue damage by activating immune cells and promoting the production of pro-inflammatory cytokines. This could have a role in the failure of many organs. By preventing the development and release of HMGB1, riboflavin might lessen tissue damage and inflammation. It might therefore be a helpful therapeutic agent for the management of inflammatory illnesses. (Pinto & Cooper 2014).

**Pyridoxine (B6), folic acid (B9), and cobalamin (B12):** Alzheimer's disease is caused by high levels of homocysteine in the blood. Alzheimer's disease symptoms can be managed with vitamins B9, B6, and B12. Homocysteine decreases the ability of antioxidant enzymes to protect cells from damage caused by oxidative stress and also damages neurons by inducing oxidative stress. Vitamins B9, B12, and B6 can help regulate blood homocysteine levels because they contribute to the conversion of homocysteine into cysteine, reducing homocysteine levels could boost cognitive performance in patients having AD and also reduce the risk of acquiring AD. Parkinson's disease may benefit from the use of pyridoxine, as a cofactor for an enzyme involved in the generation of dopamine. Pyridoxine promotes the conversion of L-DOPA to dopamine in animal models of PD which is characterized by a deficiency of dopamine in the brain. It indicates that pyridoxine may aid in the management of Parkinson's disease (Jiang et al., 2017).

Deficiencies of vitamin B6, B9, and B12 in particular lead to a condition known as hyper-homocysteinemia which is increased homocysteine, and as a result of this, greater stress and inflammation is faced by the body, which could contribute to the development of schizophrenia. Studies have indicated that people, with schizophrenia, might experience a lack of B vitamins, including B6, folate, and particularly B12. Homocysteine accumulation disrupts the metabolism of glutathione, an antioxidant that keeps the redox state in check, which might result in oxidative stress. Free radical damage to the brain may be exacerbated by homocysteine accumulation and an absence of folate, which may cause calcium imbalance in the cytosol. Vitamin B supplements might treat schizophrenia by minimizing the oxidative stress that homocysteine leads to by dropping homocysteine levels (Krebs et al., 2009; Mitra et al., 2017).

**Minerals**

Minerals are tiny amounts of trace elements that are often present in fish, meat, fruits, and vegetables. By acting as an essential cofactor to speed up enzyme reactions, they play an essential part in nutrition. Recent studies also suggest that several minerals may have antioxidant and anti-inflammatory properties that are important for brain health (Shah et al., 2023)

**Magnesium:** One of the necessary minerals found in a range of food sources is magnesium (Mg). It serves as a cofactor for various enzymes involved in the metabolism of carbohydrates and lipids, stabilizes protein, nucleic acid, and lipid membranes, and is crucial for hormonal and cellular signaling (Glasdam et al., 2016) In N-methyl-d-aspartate (NMDA) receptors, Mg inhibits the calcium channel, but low Mg levels may enhance excitotoxicity, resulting in neurotoxicity and neuronal cell death. As a result, magnesium insufficiency could result in altered glutaminergic neuronal function which is linked to neurological conditions like Parkinson's, epilepsy, and Alzheimer's disease (Olloquequi et al., 2018). Higher dietary Mg intake is linked to a decreased risk of MCI, suggesting that Mg intake or supplementation may have a neuroprotective impact (Glick & McMillan, 2016)

**Iron**: The mineral iron is extensively distributed in food sources and is also sold as a nutritional supplement. It is mostly recognized as a necessary component that transports oxygen for the production of hemoglobin. It is crucial for the CNS's production

of myelin, ATP and ADP synthesis, enzyme activity, and neurotransmitter cycling (Spence et al., 2020). The majority of animal research confirms the positive effects of iron reduction in AD or age-related cognitive decline. Following a 12-week course of treatment with the iron chelator deferiprone in their drinking water, rabbits with AD-related pathologies brought on by high-cholesterol diet feeding were able to drastically drop their systemic iron levels and decrease Aβ42 and Tau phosphorylation in the hippocampus (Prasanthi et al., 2012). The brain's microglia's transition from pro-inflammatory M1 to anti-inflammatory M2 activation may serve as a partial mediator of the neuroprotective effects of iron chelators (Prasanthi et al., 2012).

**Copper**: The brain stores the second-highest quantity of copper after the liver (Szerdahelyi & Kasa 1986). In the frontal cortex, caudate nucleus, temporal lobe, substantia nigra, striatum, and cerebellum, copper is broadly distributed, highlighting the possibility of a connection between low copper levels and the development of AD (Kardos et al., 2018). According to a study, mice with APP deletion had elevated Cu levels, but mice with APP23 had lower Cu levels when APP was overexpressed (Bayer et al., 2003). Cu levels in the brains of these AD mice were raised by treatment with Cu in drinking water, but A-peptide levels were shockingly and dramatically reduced. When Cu was added to APP-transfected cells, the result was similar (Qureshi, 2020; Shah et al., 2023)

**Alkaloids**

A group of organic compounds with at least one nitrogen atom in them are called alkaloids. The important mechanisms explain how alkaloids can be utilized in the management of Parkinsonism and Alzheimer's disease.

**Beta-carboline alkaloids:** Neuro-inflammation has a significant role in the etiology of neurodegenerative illnesses including Parkinson's and Alzheimer's. Interleukin 1 (IL-1) and Interleukin 6 (IL-6) are two pro-inflammatory mediators that can control the processes that lead to nerve injury through the development of amyloid beta aggregation and tau protein hyperphosphorylation. However, it has been found that alkaloids can hinder neuro-inflammation, potentially improving the condition (Kinney et al., 2018). Alkaloids such as harmalol and harmaline have been found to reduce the generation of oxidative stress in the brain (Lee, 2000). Moreover, Alkaloids increase the concentration of GABA and decrease the concentration of glutamate in the brain, which prevents the release of TNF which is what stops neuro-inflammation brought on by astrocytes and microglia (Sahoo et al., 2018). Moreover, alkaloids significantly downregulate the production of TNF-α in a concentration-dependent pattern (Deng et al., 2019).

Impairment in neurogenesis could lead to various neurodegenerative disorders and neurogenesis can be defined as the process of creating new neurons in the hippocampus's subgranular zone and subventricular zone. Adult neurogenesis issues may result in the onset of Alzheimer's disease, Parkinson's disease, and Huntington's disease (Winner & Winkler 2015). Impairment in adult neurogenesis has been demonstrated in vivo studies to be a potential early symptom of AD prior to the development of neurotoxic neurofibrillary tangles and A plaques (Moreno-Jiménez et al., 2019). Additionally, An in vitro study demonstrated that β-carboline alkaloids could induce neurogenesis in adults relieving the symptoms of AD and PD. These alkaloids have the potential to influence the differentiation of neuronal cells by inhibiting the enzyme monoamine oxidase (Morales-García et al., 2017).

**Isoquinoline alkaloids:** A peptide known as amyloid beta is produced when the enzyme (secretase) degrades the amyloid precursor protein. It seems that A has a role in the onset of Alzheimer's disease. due to its proclivity to aggregate into neurotoxic A plaques, which can cause abnormal synaptic and neuronal activity, cognitive impairment, and progressive memory loss (Martorana et al., 2010). Therefore, halting the aggregation of A may aid in slowing AD's progression.

Alkaloids such as nitidine and other isoquinoline alkaloids such as berberine chloride, have been shown to inhibit oligomerization of Aβ in vitro (Martorana et al., 2010). Berberine chloride has anti-cholinesterase activity and can reduce Amyloid-beta aggregation by preventing A-from forming. In vivo research has revealed that (Liew et al., 2015) can significantly decrease secretase activity in an AD brain, and the symptoms of AD can be significantly improved. Moreover, it has been demonstrated to boost secretase activity (Fawver et al., 2012).

Tau protein is another important factor and impairment in this protein can lead to severe neurodegenerative disorders. Hyper-phosphorylation, caused by glycogen synthase kinase-3, in the tau protein, leads to the development of neurofibrillary tangles and neuronal apoptosis which causes neurodegeneration. Nitidine inhibits GSK-3 activity due to its antioxidant property and increases protein phosphatase 2A, which lowers the hyperphosphorylation of tau (Liew et al., 2015). More research is required to determine the precise mechanisms by which nitidine reduces tau hyperphosphorylation (Patil et al., 2020).

**Phenolic compounds**

Phenolic compounds are biologically active organic compounds significantly found in many plants. It has been stated that plant-derived dietary phenolic compounds may

improve some disease conditions and assist to health. Emerging cases of evidence indicate that phenolic compounds are interconnected with neurodegenerative diseases, including alzheimer's disease, brain aging, parkinson's disorder, epilepsy as well as ischemic stroke (Shi et al., 2022).

**Anthocyanins:** Anthocyanins are among the class of innate occurring polyphenols magnificently present in vegetables and fruits, which imparts an important role in the treatment as well as prevention of various pathological diseases, due to which their utilization is increasing around the globe (Wallace & Giusti 2015). Anthocyanins manifest a prominent part of neuroprotection, majorly due to their well-observed anti-inflammatory along with antioxidant properties (Wallace & Giusti 2015). Anthocyanins have become recognized as dietary neuroprotective medicines for brain illnesses because in vitro and in vivo research suggests that they can greatly reduce the chronic inflammation in such pathological circumstances (Shabab et al., 2017). Anthocyanins are distinctively observed to prevent the LPS-induced activation of NF-κB, PI3K/Akt and MAPKs signaling pathways along with the reduction of various mediators, including nitric oxide, prostaglandin E2, TNF-α, and interleukin (IL)-1β (Shabab et al., 2017).

Protocatechuic acid (PA), a crucial element of anthocyanins, is also observed as a neuroprotective agent, due to its antioxidant as well as anti-inflammatory properties (Wang et al., 2015). PA also prohibit the TLR4-mediated NF-κB and MAPKs pathways, which also cause inhibition of JNK signaling pathway, by downregulating some pro-inflammatory markers like TNF-α and IL-1β (Wang et al., 2015). Alzheimer's disease is a prevalent neurological condition characterized by amyloid-beta peptide buildup and tau protein hyperphosphorylation in the brain, resulting in cognitive impairment and memory loss (Heneka et al., 2015). *In vitro* study revealed that anthocyanins rich in blueberry can suppress p44/42 MAPK pathway in microglia, which ultimately cause the depletion of microglial inflammation and inhibition of Aβ aggregation. The antioxidant nature of phenolic compounds presents an alternative approach to improve cognitive deficiency by readily crossing the blood-brain barrier (Heneka et al., 2015). In this way, naturally occurring anthocyanins have been suggested to exhibit neuroprotective effects against AD due to its anti-inflammatory and antioxidant effects. Parkinson's disease is a chronic neurodegenerative condition marked by movement dysfunction and dopaminergic neuron loss. Chronic neurological inflammation is most probable to play a role in the pathophysiology of PD among the different pathways driving its development. In the context of PD, anthocyanins have been observed to suppress the neuroinflammatory response by the inhibition of JNK, ERK and NF-κB signaling pathways and prevent the overproduction of TNF-α, IL-1β, and IL-6 (Jung & Kim 2018). Anthocyanins rich in berries exhibit improved motor performances and cause a surge in hippocampal neurogenesis (Jung & Kim 2018). This implies that the anti-neuroinflammatory properties of anthocyanins may contribute to improve the PD symptoms.

**Flavonoids**

A flavonoid, Kaempferol, present in fruits and vegetables, also has neuroprotective actions in all diseases addressed above, prominently due to its anti-inflammatory and antioxidant effects (Silva dos Santos et al., 2021). It presents neuroprotective actions through the regulation of several signaling pathways such as NF-kB, p38, MAPK, serine/threonine kinase, and β-catenin, resulting in an overall anti-inflammatory action (Silva et al., 2021).

Quercetin is another biflavonoid, present in vegetables, fruits and grains (Suganthy et al., 2016). Quercetin manifests anti-inflammatory response by inhibiting the expression of TNF-α via modulating NF-kB, inducing the paraoxonase 2 pathway. Quercetin's anti-neuroinflammatory properties limit the progression of neurodegenerative conditions including Alzheimer's, Parkinson's, ischemic stroke, and multiple sclerosis (Suganthy et al., 2016).

Another flavonoid, myricetin, widely found in many natural plants has a therapeutic value in many neurological diseases, and also exerts antidepressant and antipsychotic-like effects (Song et al., 2021). Myricetin being an iron chelating agent can decrease brain's ion content by inhibiting the expression of transferrin receptors along with reduction of lipid peroxidation, thereby reversing the cognitive dysfunction and treats Alzheimer's disease.

**Caffeine**

Caffeine is an effective psychostimulant agent used around the globe for the coverage of neurodegenerative diseases. One of the basic contributors in the pathogenesis of Alzheimer's disease is elevated oxidative stress. Caffeine affects the expression of Nrf-2 and TLR-4-induced glial cells, which in turn influences the clinical manifestations of AD. Along with, caffeine suppresses the expression of the A2A receptors, regulates some inflammatory mediators like p-JNK, NF-kB, apoptotic markers (cytochrome C, and caspase-3) and prevents neurodegeneration (Ikram et al., 2020). Caffeine has also received considerable attention in the management of Parkinson's disease by reducing the expression of GABA and enhanced the strength in MPTP by activating PI3K/Akt signaling pathways (Prediger, 2010). In case of neuroinflammation associated with PD, anti-neuroinflammatory effects of caffeine are attained mainly by suppressing the adenosine A2A receptors (Prediger, 2010).

Hence, caffeine is reviewed as a strong candidate to restore the symptoms associated with AD and PD.

## SCIENTIFIC DATA ON USE OF DIETARY SUPPLEMENTS FOR MANAGING BRAIN DISEASES

Various scientific evidence supports the role of dietary supplements in managing brain diseases such as Parkinson's, Alzheimer's, epilepsy, and schizophrenia. Based on current scientific data, several nutritional supplements such as vitamins, minerals, alkaloids and fatty acids play their role in managing brain diseases due to their anti-oxidant and neuroprotective effects.

The results of an experiment conducted on female mice having Parkinson's disease showed that co-administration of vitamin D in a dose of 1mcg/ml x 1ml/kg per day and 0.1 ml of vitamin B12 three times a week played a neuroprotective role. This role was attributed to reduced necrosis and apoptosis in cerebellar neurons. Furthermore, there was a reduction in Bax (pro-apoptotic) gene expression along with an increase in Bcl-2 (anti-apoptotic) gene expression. (Khosravi et al., 2023)

An experiment illustrates that anthocyanin administered i.p in a dose of 30mg/kg acts as a neuroprotectant in a mouse model of Alzheimer's disease. This neuroprotective role is attributed to activation of the glycogen synthase kinase-3 (GSK3β) along with phosphatidylinositol-3 kinase (PI3K) pathways. Furthermore, anthocyanin also increased the expression of protein kinase B (Akt) along with nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which suppresses neurodegeneration and apoptotic caspases. Thus improving symptoms of AD (Ali et al., 2018).

Researchers have suggested the neuroprotective effect of omega-3 Poly-unsaturated fatty acids (PUFA) on an *in-vivo* model with cerebral ischemia related to PUFA-induced block of glutamatergic transmission, together with activation of the $K^+$ channel. (Lauritzen et al., 2000) An experiment was conducted on epileptic albino rats to investigate the anti-convulsant effect of essential fatty acids. A preparation consisting of both omega 3 and omega 6 fatty acids was administered in a dose of 40mg/kg i.p for three weeks. Omega 3 fatty acid shows an anti-convulsant effect on epileptic albino rats by preventing activation of epileptic focus by strong recurrent stimuli, thereby decreasing seizure threshold. Furthermore, it acts as a membrane stabilizer and also prevents abnormal discharges in the brain, consequently proving its neuroprotective function in epilepsy (Yehuda et al., 1994).

Deficit Hyperactivity Disorder (ADHD), 0.3g/L of caffeine was administered in male and female spontaneous hyperactive rats (SHR). It was found that SHRs from both sexes showed upregulation in the levels of brain-derived neurotrophic factor (BDNF), phospho-CREB along with truncated and phospho-TrkB receptors in the hippocampus. Moreover, caffeine regulated BDNF in males as well as truncated TrkB receptors in both sexes. (França et al., 2018; Nunes et al., 2018)

A recent study demonstrated that oleanolic acid a plant-derived terpenoid improves schizophrenia-like symptoms in mice induced by administration of MK-801. (Park et al., 2014) Its single administration blocked MK-801-induced hyper-locomotion and improved pre-pulse inhibition. Additionally, oleanolic also regulated the level of phosphorylation of Akt along with GSK-3β, in the frontal cortex. These findings suggest a neuroprotective role of oleanolic acid in schizophrenia. (Mony et al., 2022)

## CONCLUSION

Conventional treatment of neurodegenerative diseases primarily consists of medication, perhaps which is the frontline treatment. Side effects often result during pharmacotherapy in patients who respond to it, which can be discomforting and intolerable. Further pharmacological intervention is necessary to address the aforementioned side effects, which ultimately lead to discontinuation of treatment. The use of dietary supplements in managing brain diseases has received a bulk of empirical attention in recent years. Dietary supplements such as vitamins, minerals, alkaloids, phenolic compounds, etc., play anti-oxidant, and neuroprotective roles in managing various brain diseases. As a supplementary component to medical treatment, dietary supplements present a potential avenue for patient care with minimal risk of adverse effects. A balanced diet and the use of food supplements based on neuroprotective, anti-inflammatory and anti-oxidant properties can successfully act as a complement to normal medical treatments. Various scientific evidence supports the role of dietary supplements in managing brain diseases.

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