

# Nutrition, Neuroinflammation and Cognition

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**Abstract:** Activation of microglia and astrocytes leads to the production of cytokines and other inflammatory mediators which may contribute to the apoptotic cell death of neurons observed in many neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Vulnerability of the central nervous system (CNS) to oxidative and inflammatory stress increases with age and has been postulated to be a leading contributing factor to the cognitive impairment and thereby development of neurodegenerative diseases. Suppression of microglial production of neurotoxic mediators may result in neuroprotection. This heightens the interest in the development of neuroinflammation-targeted therapeutics. Nutrition is involved in the pathogenesis of age-related cognitive decline and also neurodegenerative diseases. Certain nutrients facilitate human brain function with their immediate and long term effects. On the other hand, malnutrition influences the brain throughout life, with profound implications on cognitive decline and dementia. Several phytochemicals with potent antioxidant and anti-inflammatory activities, have been shown to repress microglial activation and exert neuroprotective effects. Thus this review highlights the role of foods, nutrients and phytochemicals in suppressing neuro-inflammation and also enhancing cognition.

**Keywords:** Microglia, Neuroinflammation, Neurodegenerative diseases, Malnutrition, Antioxidant, Nutrients, Phytochemicals.

## INTRODUCTION

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) are characterized by the chronic and progressive loss of neuronal functions, which in turn results in memory deficit, cognitive impairment and impaired neuromuscular coordination. According to the Global Burden of Disease estimates for the 2003 World Health Report, dementia contributed to 11.2% of years lived with disability in people aged 60 years and older which was more than the contribution of stroke (9.5%), musculoskeletal disorders (8.9%), cardiovascular disease (5.0%), and all forms of cancer (2.4%). Similarly, the disability weight for dementia, estimated by an international and multidisciplinary expert consensus, was higher than for almost any other health condition, apart from spinal-cord injury and terminal cancer [1]. It was estimated that 24.3 million people worldwide had dementia in 2005 which has increased to 35.6 million in 2010, with numbers expected to almost double every 20 years to 65.7 million in 2030 and 115.4 million in 2050. Even in countries with low and/or middle income 58% of people lived with dementia in 2010, with this proportion anticipated to rise to 63% in 2030 and 71% in 2050 [2].

The resident immune effector cells of central nervous system (CNS) i.e. microglia play a major role

in managing the brain homeostasis. They are the first responders against infectious, inflammatory and pathophysiological stimuli and react to these conditions by modulating their motility, phagocytic functions, shape of processes, and release of cytokines, chemokines, reactive oxygen species, prostaglandin metabolites and expression of innate and adaptive immune-function molecules [3, 4]. However, excessive production these substances may lead to neuroinflammation and neurodegeneration where as reduced production offers neuroprotection. Realisation of the importance of neuroprotection lead to the testing of plant products and their active components; screening of various pharmaceutical agents and development of novel synthetic compounds that selectively down regulate neuro inflammatory responses and finally resulted in the rapid discovery of neuroinflammation-targeted therapeutics [5].

Aging increases the vulnerability of the central nervous system (CNS) to oxidative and inflammatory stress. This is a leading contributing factor to the alarming rise in the incidence of Parkinson's and Alzheimer's diseases. Optimal brain function results from highly complex interactions between numerous genetic and environmental factors such as food intake, physical activity, age and stress [6]. Macronutrients especially essential fatty acids (EFA) and certain amino acids (e.g. choline, methionine) and micronutrients that are involved in DNA methylation (e.g. folate, vitamins B<sub>6</sub> and B<sub>12</sub> etc.) have both immediate and long-term effects on the epigenome influencing gene expression in the neurons of CNS. Moreover, energy contribution

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from each of the macronutrients was also found to influence neuronal functioning and thereby cognitive performance. Malnutrition is involved in the pathogenesis of age-related cognitive decline and neurodegenerative diseases. Plant foods consumed as part of a normal diet not only provide nutrients and energy, but also offer health benefits beyond basic nutritional functions [7].

Several nutritional intervention trials have been conducted towards prevention and treatment of neuroinflammation. A study conducted by Yuliva *et al*, in 2004 [8] showed that an experimental diet composed of eicosapentaenoic acid (EPA, 20:5, n-3), docosahexaenoic acid (DHA, 22:6, n-3), zinc, curcumin, piperine, melatonin, choline and uridine attenuated cognitive and behavioral deficits, reduced hippocampal atrophy and peripheral immune activation in mouse model thus proving its therapeutic benefit in the prevention and treatment of neurodegenerative diseases. In another study, different food samples like lime zest, English breakfast tea, honey-brown mushroom, button mushroom, oyster mushroom, cinnamon and cloves inhibited NO production in N11 microglia [9].

## DISCUSSION

Dietary factors can affect multiple brain processes by regulating neurotransmitter pathways, synaptic transmission, membrane fluidity and signal-transduction pathways. A review conducted by Gomez-pinilla (2008) stated that dietary components can influence epigenetic events such as DNA methylation, transcriptional activation, translational control and posttranslational modifications that cause a potentially heritable phenotypic change and have potential for disease modulation. Thus the effects of diet on mental health can be transmitted across generations [10]. It is interesting to note that food components including nutrients and phytochemicals, whole foods as well as food combinations were found to exhibit neuro protective effects. The individual impact of each of these on neuroinflammation has been discussed below. Studies on the association between nutrients and cognitive functioning have examined both supplemental and dietary intake with dietary sources generally exhibiting stronger effects.

### Role of Dietary Energy and Macronutrients in Cognition

Caloric content of the diet has shown to affect cognition as the metabolic processes that are initiated

by the burning of fuels in mitochondria can modulate synaptic plasticity [10]. Moreover, individual macronutrients consumed within a meal differentially affect cognitive performance [11, 12]. Dietary pattern including high carbohydrate, low protein and low fat has been found to increase the risk of MCI or dementia in geriatric subjects [13]. Kaplan *et al*, in 2001 [11] examined the impact of macronutrients on cognition and reported that pure dietary protein, carbohydrate, and fat individually enhanced memory performance. Diets containing low carbohydrate and low fat have also shown to improve the cognitive abilities and enhance mood in overweight and obese participants [14].

### Carbohydrates

Glucose provides energy to the brain and is essential component for brain metabolism. Regulation of glycaemia improves the quality and duration of intellectual performance. Poor glycaemic control is associated with lower performances on tests of memory in all age groups of non diabetic as well as diabetic individuals. Scientific data demonstrated clear associations between elevated glycaemia which may be partly due to the effect of dietary and lifestyle factors; and relatively poor cognitive performance. Dietary fibre content in foods influences the speed at which the foods increase blood glucose level. Overall, presence of dietary fibre in the diet was shown to be associated with higher alertness ratings and ensures less perceived stress [15, 16]. Glycemic index and glycemic load are the concepts often used to understand the contribution of foods to blood glucose level. Gilseman *et al* (2009) opined that there is insufficient evidence to demonstrate a consistent directional effect of Glycemic Load on short-term cognitive performance [17]. But in a recent review, in spite of inconsistent results of various studies, it was concluded that a low Glycaemic index meal may favour cognition [18]. Future studies employing consistent methodologies to facilitate meaningful comparisons and interpretation of results would help to further establish the role of complex carbohydrates in cognition.

Very low carbohydrate consumption has been reported to provide neurocognitive benefit to older adults suffering from early memory decline, increased risk for neuro-degeneration and thereby increased risk of Alzheimer's disease. The mode of action was attributed to the dietary ketosis induced by carbohydrate restriction [19].

The effect of glucose and saccharin drink on cognition was compared in a review which included only one randomised control trial. Results showed a better cognitive performance among the participants on consumption of glucose drink than saccharin drink. However, since only one RCT was included, strong recommendation on the use of any particular form of carbohydrate for enhancing cognitive performance in older adults could not be made. Contradictorily, significant beneficial effects of oligosaccharide supplementation were found on memory performance and indicators of well-being [20]. However, more studies on various forms of carbohydrates are needed to find out complex nutritional interactions [20].

### Proteins

The nature and the quantities of cerebral proteins and neurotransmitters are influenced by the quality of dietary proteins. Amino acids like tryptophan, glutamine, glutathione and taurine contribute to cerebral function. Thus, the amino acid profile of the cerebral extracellular milieu is a function of the content and nature of dietary proteins. In fact, some indispensable amino acids present in dietary proteins help in the regulation of neurotransmitters and neuromodulators. Kwashiorkor which implies protein deficiency can severely affect the functioning of the brain [15].

Some genetic disorders cause alterations in the brain, due to abnormal changes in metabolism such as phenylketonuria, caused by abnormal metabolism of an essential amino acid, tryptophan. Hulsken *et al.*, (2013) in their review examined the effect of tryptophan intake on cognition and reported that intake of foods containing moderate to high tryptophan like chicken, soybeans, cereals, tuna, nuts and bananas help in improving cognitive abilities, whereas higher intake of those foods containing very low tryptophan like cereals, maize and milk formulas may lead to cognitive impairment. However enhancing available tryptophan in these foods may represent an efficient and cost-effective way of increasing mood and cognition [21].

### Fat

Different types of fatty acids influence cognition differently. Fatty acids like PUFA and MUFA may have a beneficial role whereas SFA may lead to neuroinflammation and thus impair cognition. Moreover, the source of fatty acids also plays an important role in cognition. A study conducted on adults

(39 to 65 years) concluded that consumption of low fat dairy products have beneficial effects on social functioning, stress and memory, while intake of whole fat dairy products, rich source of SFA may be associated with poorer psychological well-being. More dietary intervention trials are needed in order to understand the relationship if any between dairy consumption and cognitive and psychological health [22].

Essential polyunsaturated fatty acids (PUFA) are important class of nutritional lipids that are not synthesized in the body and thus must be obtained from the diet. They, especially the Omega-3 type polyunsaturated fatty acids play important roles in cell integrity, maintenance and development; and are key components of glial cell biomembranes. PUFAs deposit in the brain during the perinatal period depending on the dietary supply. They regulate both prostaglandin and pro-inflammatory cytokine production in the immune system and thus exhibit immunomodulatory properties. Omega 3 fatty acids are highly anti-inflammatory, while n-6 fatty acids are proinflammatory. The protective role of n-3 fatty acids in neurodegenerative diseases is often linked to aging [23] as the brain levels of PUFAs diminish with age. Moreover, the increasing exposure of the population to diets low in PUFAs may lead to increased production of inflammatory cytokines in the brain.

Consuming monounsaturated fatty acids and PUFAs have shown to slow cognitive decline in animals and in humans. Most studies have emphasized beneficial role of PUFAs found in fish and nuts on cognitive abilities in aged animals. Numerous studies have also shown that consuming diets deficient in  $\omega$  3 fatty acids will impair cognitive functioning [24]. But the role of PUFAs needs to be better characterized by multidisciplinary studies aimed at assessing the effects of these molecules at different levels, from the molecular level to that of the organism as a whole [25].

Among the PUFAs, DHA has been studied more extensively with regard to its role in neuroinflammation. DHA (docosahexaenoic acid) is one of the important constituents of membrane phospholipids of brain and thus necessary for normal neuronal function. High amounts of DHA are found in the nervous system, particularly in photoreceptors and synaptic membranes. DHA has been shown to reduce expression of tumor necrosis factor- $\alpha$ , interleukin-6, nitric oxide synthase, and cyclo-oxygenase-2, induced by interferon- $\gamma$ , and induced up regulation of heme oxygenase-1 (HO-1) in

BV-2 microglia. DHA has also been reported to reduce the amyloid production, accumulation, and downstream toxicity in aged Alzheimer mouse model. Therefore it can be used as a potential therapeutic agent in the treatment of Alzheimer's disease [26].

DHA administered for 12 weeks significantly improved the working memory errors and also enhanced the spatial cognition and learning ability [27]. Furthermore, DHA suppressed the high levels of lipid peroxide and reactive oxygen species in the cerebral cortex and the hippocampus of A $\beta$ -infused rats, suggesting that DHA increases anti-oxidative capacities. Therefore it can be concluded that DHA may act as a therapeutic agent for improving learning deficits in Alzheimer's disease [28]. Moreover, studies have also shown that dietary DHA supplementation enhances the supportive action of exercise on learning and memory capacity and synaptic plasticity [29, 30].

A transgenic model expressing an n-3 fatty acid desaturase which converts n-6 PUFAs into n-3 PUFAs was studied. Results confirmed the capacity of the transgene to produce n-3 PUFAs, thereby increasing the brain n-3: n-6 PUFA ratio. This helped in reducing the inflammatory processes in the brain although it was not as effective as dietary DHA supplementation. Overall, the results strongly suggested that dietary intervention with n-3 fatty acids particularly DHA constitutes a potent method to achieve neuro protective levels in the brain, particularly in the context of Parkinson's disease [31]. Another study conducted by Delpech *et al*, (2015) confirmed the above findings [32]. The results of their study not only provided insight into how n-3 PUFAs can influence microglia activity but also suggested a role for EPA and DPA in the prevention of spatial memory deficit linked to inflammation. Central n-3 PUFA increase observed in transgenic mice modulated the brain innate immune system activity, leading to the protection of animals against LPS-induced pro-inflammatory cytokine production and subsequent spatial memory alteration [32].

In addition to DHA, the monounsaturated fatty acid (MUFA) oleic acid was found to inhibit LPS-induced phosphorylation of Akt and p38 MAPK in an *in vitro* study. It was also seen that oleic acid suppressed the release of proinflammatory mediators NO and PGE2 as well as the expression of i-NOS and COX-2 in LPS-stimulated microglia. This anti-inflammatory effect of oleic acid is associated with blockade of ROS accumulation, p38, and Akt/IKK/NF- $\kappa$ B signaling pathways in LPS-stimulated BV2 microglia. This finding

suggests that oleic acid may provide a beneficial effect on the treatment of inflammatory brain damage induced by microglial activation, although further studies on animal model are necessary to know whether oleic acid shows similar anti-inflammatory effect *in vivo* too [33].

Long-term consumption of both refined and pomace olive oil changed the brain fatty acid composition in a mice model and exhibited positive effects on neuroinflammation and brain function. The effect has been attributed to the presence of oleic acid in these oils [34]. Thus these oils can be regarded as functional foods in neurodegenerative diseases. Older adults with moderate or intensive use of olive oil showed lesser cognitive deficit as compared to those who did not use olive oil, however the association needs to be confirmed further [35]. In order to establish a direct therapeutic benefit of oleic acid in neurodegeneration, it is necessary to conduct experimental research on persons suffering from neurodegenerative diseases.

Short chain fatty acids (SCFA) were also found to decrease the production of inflammatory molecules. For example, butyrate has decreased the production of pro-inflammatory mediators including TNF- $\alpha$ , NO and IL-6 in glial cells. It also improved the release of the anti-inflammatory cytokine IL-10 and inhibited the microglial activation in the ischemic brain of rats. Thus due to its potential to decrease neuroinflammation, butyrate could be regarded as neuroprotective fatty acid [36, 37].

### **Role Micronutrients in Cognition**

The water-soluble vitamins (B group and C), and minerals like calcium, magnesium and zinc are associated with cognitive performance. Marginal deficiencies of these micronutrients may negatively influence cognitive performance, especially in elderly and those adults who are exposed to occupational pressures along with a stressful lifestyle [38].

Vitamin B 12 deficiency has been associated with cognitive impairment. Its been postulated that low vitamin B<sub>12</sub> status may lead to neurotoxicity and deficiency of S-adenosylmethionine (SAM), and thus result in deficient methylation reactions in the central nervous system. Low levels of SAM have been found in the brain and cerebrospinal fluid of patients suffering from Alzheimer's disease [39]. Surprisingly, high folate intake was associated with cognitive decline in a population based study on older adults, though high intake of folate may cover up vitamin B<sub>12</sub> deficiency

with regard to haematological symptoms, but the neurological symptoms and neuropsychiatric changes would continue. The possible mechanism might be that both the vitamins perform similar function i.e. synthesis of Sadenosyl-methionine (SAM), which is the most important methyl-group donor of the brain [41]. In another study on older adults, it was seen that high homocysteine levels increased the risk of dementia. However the association between total homocysteine and dementia is independent of plasma folate, B<sub>12</sub> and antioxidant micronutrient status [40, 42].

Harrison (2012) reviewed several studies on Vitamin C and concluded that it can be protective against the oxidative damage that is involved in the pathology of Alzheimer's disease as well as cognitive decline associated with aging [43].

Vitamin E bioavailability, metabolism and plasma levels have been studied in humans and in AD, particularly as  $\alpha$ -tocopherol. Alpha tocopherol is widely tested in randomized controlled trials in subjects with AD and MCI. Vitamin E can cross the blood brain barrier and lower lipid peroxidation and  $\beta$ -amyloid deposition. It also prevents neuronal damage in the brain by decreasing isoprostane levels [44]. Vitamin D deficiency in the body is linked to poor cognitive performance and increased risk of AD, however the mechanism is unclear and therefore further studies are required [45, 46].

In a meta-analysis, it was concluded that iron supplementation improved attention and concentration in adolescents and adult women irrespective of baseline level of iron status. Iron supplementation also improved IQ in women and children who were anaemic at baseline, but had no effect in other groups or on other cognitive domains [47]. However, results of a study conducted by McNeill *et al.* (2007) showed that daily consumption of multivitamin and multimineral supplements may not improve different domains of cognitive function in geriatric population [48].

### Role of Phytochemicals in Cognition

Polyphenols help in reduction of neuroinflammation *via* attenuation of the release of cytokines, such as interleukin-1 $\beta$  (IL-1  $\beta$ ) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and down regulation of the pro-inflammatory transcription factors such as Nuclear Factor (NF- $\kappa$ B) [49]. Natural polyphenols inhibit glutamate-induced activation of calpains, normalize the levels of phosphorylated Akt kinase and cytosolic Bax,

and regulate the nuclear translocation of NF- $\kappa$ B. Each of these effects contributes to the substantial reduction of apoptotic neuronal death induced by glutamate. Thus it seems that polyphenolic compounds may inhibit NF- $\kappa$ B activity leading to downregulation of iNOS gene transcription. These mechanisms together with NADPH oxidase inhibition finally result in significant reduction of neuronal death [50].

Several phytochemicals in foods with potent antioxidant and anti-inflammatory activities, such as resveratrol and curcumin, have been shown to repress microglial activation and exert neuroprotective effects in the central neuron system following injury [19, 51]. The anti-neuroinflammatory and anti-cognitive impairment effects of several phytochemicals are consolidated and tabulated in Table 1.

In a review studying association between polyphenols and cognition, it was concluded that consuming additional polyphenols in the diet certainly led to cognitive benefits, but the observed effects were small. Polyphenol consumption influenced declarative memory, particularly spatial memory with the effects depending on the source of polyphenol. Berry fruit juice consumption improved immediate verbal memory, whereas isoflavone based interventions led to significant improvements in delayed spatial memory and executive function. However, the methodological inconsistencies hampered comparison between studies. Thus there was lack of clear evidence for an association between cognitive performance and polyphenol dose response and duration of intervention. In conclusion, the findings do imply that polyphenol consumption has potential benefits on cognition both acutely and chronically [52].

Blueberry supplementation has been shown to effectively decrease the proinflammatory mediators both *in vitro* and *in vivo* experiments [53, 54]. Crude extract of blueberry decreased the production of inflammatory molecules in lipopolysaccharide (LPS) activated murine BV2 microglia [55] and the effect was attributed to the presence of polyphenols. Thus it was concluded that diet rich in polyphenols can alleviate the inflammation associated with neurodegenerative diseases [56].

Dietary supplementation with fruit or vegetable extracts high in antioxidants (e.g. blueberries, strawberries, walnuts, and Concord grape juice) has shown to improve behaviour and decrease the

**Table 1: Anti-Neuroinflammatory and Anti-Cognitive Impairment Effects of Phytochemicals**

Sr. No	Phytochemical	Food sources	Experimental model	Effect	Reference
1.	Ferulic acid	Vegetables and maize bran	Mouse	Reversed the neuroinflammation and ameliorated memory loss	[70]
2.	Curcumin and Tetrahydrocurcumin, Aromatic (ar)-turmerone	Turmeric	Mouse	↓ production of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and MCP-1, ROS Inhibition of NF- $\kappa$ B, JNK, and p38 MAPK signaling pathways ↓ Transcription factors or co-activators of activator protein-1	[71, 72]
3.	Cinnamaldehyde	Cinnamon	LPS activated BV2 microglia	↓ production of nitric oxide (NO), IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ; attenuation of NF- $\kappa$ B activation	[73]
4.	Hydroxytyrosol	Olives	LPS activated BV2 microglia	↓ production of pro-inflammatory cytokines and oxidative molecules	[74, 75]
5.	Sesame lignans such as sesamin, episesamin, sesamol, sesamol, and g-tocopherol	Sesame seeds	LPS activated BV2 microglia	↓ NO production, iNOS mRNA and protein expression and other inflammatory molecules	[76]
6.	6-Shogaol, 6-Gingerol, 10-Gingerol	Ginger	Mouse	↓ production of nitric oxide, IL-1 $\beta$ , IL-6 and TNF- $\alpha$ as well as their mRNA levels, attenuation of NF- $\kappa$ B activation	[77]
7.	Chrysin and propolis	Honey, fruits, vegetables, and certain beverages	LPS activated BV2 microglia	↓ Production of NO, TNF- $\alpha$ , IL-1 $\beta$ , i-NOS and COX-2 and attenuation of JNK and NF- $\kappa$ B	[78]
8.	Luteolin	Celery and green peppers	Mouse, Microglia	↓ production of IL-1 $\beta$ , IL-6, TNF $\alpha$ , NO, and prostaglandin E2, i-NOS, COX-2, PGE2, NO, NF- $\kappa$ B	[59, 79, 80]
9.	Resveratrol	Grapes, blueberries, raspberries, and mulberries	LPS stimulated BV2 microglia Mouse	↓ Production of IL-1b Attenuating acute cognitive disorders	[81, 82]
10.	Quercetin	Fruits and Vegetables	LPS stimulated BV2 microglia	↓ Production of TNF- $\alpha$ , IL-1b, IL-6, i-NOS and mitochondrial superoxide radicals	[82]
11.	Isoflavones (Diazzein)	Soyabean, Tempeh	Mouse	↓ Production of IL-6, NO, ROS. Attenuation of p38 MAPK phosphorylation, and NF- $\kappa$ B activation	[83, 84]
12.	Catechins	Green tea	Rat	Improve the spatial cognition learning abilities, ↑ antioxidant activity	[85]
13.	Theaflavins	Black tea	-	↓ Neurotoxicity	[86]

oxidative stress caused due to aging. The beneficial effects of fruits and vegetable consumption also included enhancement of neuronal communication due to increased neuronal signalling and decreased stress signals that were induced by oxidative/inflammatory stressors (e.g. nuclear factor - $\kappa$ B) [57].

Berry fruit supplementation has also been effective in reversing age related cognitive decline in animal studies. The antioxidant-rich berries consumed in the

diet can positively influence learning and memory in the aged mice. This effect is thought to be due to the direct relationship of berry polyphenols with neurons and thus reducing the impact of stress-related cellular signals and increasing the capacity of neurons to maintain proper functioning during aging [58].

Several studies have demonstrated that flavonoids significantly inhibited the activation of NF- $\kappa$ B and MAPK pathways in activated microglia and thus

attenuated the production of inflammatory molecules [59]. Foods rich in three specific flavonoid sub-groups, the flavanols, flavanones and anthocyanins possess the greatest potential to act on the cognitive processes. Age-dependent deterioration in memory and cognition can be reversed by the consumption of flavonoid-rich berries, apples and citrus fruits throughout life. They also protect vulnerable neurons and influence the cognitive performance [60]. The effects of flavonoid-rich foods on improvement of age-related cognitive and motor decline have been shown with blueberries, concord grapes, strawberries, and polyphenols from red wine [61].

The flavanols, catechin and epigallocatechin gallate (EGCG), are able to attenuate microglia and/or astrocyte mediated inflammation. These include iNOS and cyclooxygenase (COX-2) expression, cytokine release, NO production and NADPH oxidase activation. All these effects are linked to the ability to modulate directly various protein and lipid kinase signalling pathways. These include, for example, the inhibition of tyrosine kinase, protein kinase C and mitogen activated protein kinase (MAPK) signaling cascades. The latter cascades involve p38 or ERK1/2 which regulate both iNOS and the expression of the cytokine tumour

necrosis factor-alpha (TNF- $\alpha$ ) in activated glial cells [62, 63, 64].

In a population-based study, it was concluded that intake of flavonoid-rich food, including chocolate, wine, and tea, is associated with better performance across several cognitive abilities and that the associations are dose dependent. However, the mechanisms were unknown and therefore further studies are required [65].

A study showed that Hesperidin, nobiletin, and tangeretin individually were not effective for reducing neuroinflammation, however in combination, they significantly reduced LPS-induced proinflammatory cytokine expression. Overall, tangerine peel possesses potent anti-neuroinflammatory capacity, which was attributed to the collective effect of hesperidin, nobiletin, and tangeretin [66]. The flavanones naringenin and hesperetin and the flavanols catechin and epicatechin, also inhibited LPS induced TNF- $\alpha$  production and attenuated ERK, JNK, MAPKs, NF- $\kappa$ B activation in LPS stimulated BV2 microglia. Apart from these, naringenin also inhibited LPS induced iNOS expression and nitric oxide production in glial cells [67, 68].

**Table 2: Anti-Neuroinflammatory and Anti-Cognitive Impairment Effects of Whole Foods and Food Products**

Sr. No.	Food	Bioactive Component	Experimental model	Effect	Reference
1.	Spinach	-	Rats	↑ production of TNF $\alpha$ and IL-1 $\beta$ in the cerebellum of old rats was reversed by intake of spinach rich diet for 6 weeks	[87]
2.	Bitter melon	Extract	Microglial cells	↓ high fat diet associated neuroinflammation And ↓ oxidative stress	[88]
3.	Mulberry leaves		Animal model	↓ microgliosis and astrogliosis, ↓ release of nitric oxide from microglia and cytokine release from activated astrocytes	[89]
4.	Cinnamon	sodium benzoate	mouse microglia and astrocytes	↓ Production of iNOS, TNF- $\alpha$ and IL-1 $\beta$ and surface markers (CD11b, CD11c, and CD68)	[90]
5.	Spirulina	-	Microglial cells (BV2 cell line)	↓ Production of iNOS, COX-2, TNF- $\alpha$ , and IL-6	[91]
6.	English walnuts		Microglial cells (BV2 cell line)	↓ Production of TNF $\alpha$ and iNOS	[92]
7.	Aged garlic extract		Rat model	diminished the neurological alterations (61.6%), the infarct area (54.8%) and the histological damage (37.7%) induced by cerebral ischemia, ↓ TNF $\alpha$ and COX-2 protein levels	[93]
8.	Broccoli	Sulforaphane	Mouse	↓ age-elevated cytochrome b-245 $\beta$ , an oxidative stressmarker, and ↓ glial activation markers	[94]
9.	Energy drinks containing caffeine, taurine and glucose		Humans	Enhanced executive control and working memory, and reduced simple and choice reaction time, enhanced object working memory and enhanced orienting attention.	[95]

Several other foods and food products like traditional herbs, certain fruits and vegetables, spices, nuts and nutraceutical products (energy drinks) have shown to be potent anti-neuroinflammatory agents and thus also help to improve cognitive abilities (Refer to Table 2). Ginseng extract and total saponins reduced LPS-induced expression of MMP-9, oxidative and proinflammatory cytokines in microglial cells. Similar effects were also observed in the mouse brain stimulated with LPS. Ginsenosides are easily absorbed into the body and thus they have been used to treat various diseases. The strong inhibition of microglial activation by ginsenosides may provide potential therapeutic strategies for neurodegenerative diseases such as Alzheimer's disease. Further research on the effects and molecular mechanisms of purified ginsenosides, is essential [69].

## CONCLUSION

Thus, from the above discussion it is evident that neurodegeneration is yet another inflammatory disease affecting the cognitive performance and thereby the quality of life. The increasing incidence of the same is indeed a serious cause of global concern, necessitating identification and implementation of preventive and therapeutic measures.

Nutritional therapy of neurodegeneration includes a healing system consisting of the nutrients, bioactive chemicals present in functional foods and nutraceuticals. Regular dietary consumption of EFA, micronutrients and phytochemicals would help in preventing cognitive impairment and thereby protect population from neurodegenerative diseases as evident from extensive scientific research. Besides offering preventive benefits in cognitive impairment, good nutrition could also enhance cognitive performance.

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