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Targeting neuroinflammation with nutraceuticals: A potential avenue for managing cognitive decline in dementia

Nabilah Syazwani Muzaparshah[1]
Gurmeet Kaur Surindar Singh[1]
Nurul Aqmar Mohamad Nor Hazalin[1,2+]

[1]*Department of Pharmacology and Life Sciences, Faculty of Pharmacy, Universiti Teknologi MARA, (UiTM), 42300 Bandar Puncak Alam, Selangor, Malaysia.*
[1]*Email: nabilahsyazwani12@gmail.com*
[1]*Email: gurmeet9952@uitm.edu.my*
[2]*Integrative Pharmacogenomics Institute (iPROMISE), Level 7, FF3, Universiti Teknologi MARA (UiTM), 42300 Bandar Puncak Alam, Selangor, Malaysia.*
[1,2]*Email: nurulaqmar@uitm.edu.my*

(+ Corresponding author)

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ABSTRACT

Dementia is a progressive neurodegenerative condition characterized by cognitive decline, predominantly affecting the aging population. With the increasing global prevalence of dementia and limited efficacy of current pharmacological treatments, there is a critical need to explore alternative preventive and therapeutic strategies. This review examines the neuroprotective potential of nutraceuticals, focusing on their role in modulating neuroinflammatory processes that contribute to dementia pathogenesis. The study conducts a comprehensive review of existing literature to evaluate the impact of various nutraceuticals, bioactive dietary compounds, on neuroinflammation and cognitive decline. Emphasis is placed on the mechanisms by which these compounds influence neuroinflammatory pathways and their relevance to the pathogenesis of dementia. Current evidence supports the neuroprotective effects of several classes of nutraceuticals, including vitamins, flavonoids, non-flavonoids, carotenoids, polyunsaturated fatty acids (PUFAs), and probiotics. These compounds appear to modulate neuroinflammation by regulating microglial and astrocytic activity, suppressing proinflammatory cytokines, and reducing oxidative stress, collectively contributing to the attenuation of cognitive decline. The integration of nutraceuticals into dietary interventions may serve as a viable adjunctive strategy for mitigating cognitive decline in aging populations. A deeper understanding of their underlying mechanisms could facilitate the development of targeted, non-pharmacological approaches for preventing and caring for dementia.

Contribution/Originality: This study uniquely highlights the role of nutraceuticals in regulating neuroinflammation, providing a focused synthesis of their mechanisms and potential as non-pharmacological strategies for preventing or slowing dementia-related cognitive decline.

1. INTRODUCTION

Dementia is a progressive age-related impairment of memory, language, visual processing, problem-solving skills, and the ability to function independently. It is the leading cause of disability among older people worldwide and is expected to increase in the developing world in tandem with the aging population. In 2020, an estimated 55 million people worldwide were living with dementia. Moreover, this number is anticipated to double every 20 years, reaching 78 million in 2030 and 139 million in 2050 (Alzheimer's Disease International, 2025). Although it is far more common in the geriatric population, it may occur at any stage of adulthood. The impact of dementia on patients and

their families is significant, and the growing prevalence of dementia may substantially strain the economy and healthcare systems. Increasing public costs have become a heavy burden on society and have attracted worldwide attention. Therefore, preventive measures should be considered to reduce the incidence of dementia globally.

The number of people with cognitive decline is expected to increase exponentially in the coming decades, in parallel with the aging of the population. In the elderly, inflammatory mechanisms have been associated with the pathogenesis of dementia. Although inflammation in the body is intended to be protective, an excessive inflammatory response in the central nervous system (CNS), with the term neuroinflammation, can cause or contribute to tissue damage and disease pathology. In normal conditions, a neuroinflammation reaction is initiated in response to brain injury, infection, or a stimulus such as toxic metabolites that pass through the blood-brain barrier (BBB), or autoimmunity (DiSabato, Quan, & Godbout, 2016). Neuroinflammation, characterized by glial hyperactivation, oxidative damage, mitochondrial dysfunction, and reactive microgliosis, is a fundamental component in the pathogenesis and progression of dementia (Carson, Thrash, & Walter, 2006; DiSabato et al., 2016; Mizuno, 2015; Pasqualetti, Brooks, & Edison, 2015).

Past decades have proven that there is no cure or treatment to slow or stop the progression of dementia. The current drugs are used only to improve symptoms temporarily. After several decades of research on AD prevention, the FDA has only approved acetylcholinesterase inhibitors such as donepezil, rivastigmine, galantamine, and the N-methyl-D-aspartate (NMDA) antagonist, memantine (Colovic, Krstic, Lazarevic-Pasti, Bondzic, & Vasic, 2013; Folch et al., 2018; Schwarz, Froelich, & Burns, 2012). Other drugs, such as tacrine, which is also an acetylcholinesterase inhibitor, were discontinued due to hepatotoxicity in patients.

Due to the absence of a cure for dementia, public health priorities have recently shifted toward preventing cognitive decline. Multiple interventions, including physical activity, diet, and cognitive training, have improved various cognitive outcomes. Currently, several chemical substances, known as nutraceuticals, which belong to natural dietary classes, have gained popularity for their potential therapeutic capabilities, in addition to their nutritional and safety profiles. These may be dietary supplements or functional foods such as dietary fibers, polyunsaturated fatty acids (PUFA), probiotics, prebiotics, vitamins, polyphenols, selenium, and spices. These specific nutraceutical food groups are rich in micronutrients and vitamins, offering health or medical benefits, including disease prevention and treatment.

The impact of nutraceuticals on age-associated cognitive decline is an emerging area of research as a potential modifiable factor. Various anti-inflammatories (NSAIDs) and antioxidants are recommended to alleviate symptoms and slow the progression of dementia. Therefore, any nutraceuticals capable of crossing the blood-brain barrier (BBB) with potent antioxidant and anti-inflammatory activities could effectively slow neuronal degradation. In this paper, we review the evidence and mechanisms for the neuroprotective effects of various dietary components and nutritional approaches on the inflammatory process, which might be effective in delaying cognitive decline and the onset of dementia.

2. NEUROINFLAMMATION

Neuroinflammation is an innate cellular response to stimuli disrupting central nervous system (CNS) homeostasis. Neuroinflammation cascades are mediated by the production of cytokines (interleukin-1, interleukin-4, interleukin-6, and TNF-alpha) and chemokines (CCL2, CCL5, CXCL1), which are mainly produced by activated resident glial cells: microglia and astrocytes (DiSabato et al., 2016). Reactive oxygen species (ROS), reactive nitrogen species (RNS), and secondary messengers (prostaglandins) are also involved in the stimulation of neuroinflammation by signaling the activation of glial cells and activating intracellular pathways (Ray, Huang, & Tsuji, 2012). Several enzymes can produce reactive species, including nitric oxide synthase (NOS), cyclooxygenase (COX), and nicotinamide adenine dinucleotide phosphate oxidase (NOX) in the cell membrane, while xanthine oxidase (XO) is in the cytoplasm (DiSabato et al., 2016; Solleiro-Villavicencio & Rivas-Arancibia, 2018; Valko et al., 2007). An increase

in ROS levels may induce microglia activation (Solleiro-Villavicencio & Rivas-Arancibia, 2018). Uncontrolled reactive species may cause them to react with lipids, proteins, and nucleic acids, leading to cellular dysfunction. For example, lipid peroxidation in AD has caused the mitochondrial membrane to lose fluidity in the cerebral cortex (Ortiz et al., 2017).

2.1. Neuroinflammation in Dementia

Neuroinflammation is self-regulated and can enhance neuronal plasticity when appropriate stimuli and redox reactions are well-balanced (DiSabato et al., 2016; Pasqualetti et al., 2015; Solleiro-Villavicencio & Rivas-Arancibia, 2018). However, prolonged exposure to stimuli, activated glial cells, and oxidative stress can elicit chronic neuroinflammation, leading to progressive neuronal tissue damage and cell death (DiSabato et al., 2016; Pasqualetti et al., 2015).

The two major pathological hallmarks of AD are amyloid plaque and neurofibrillary tangle in the brain (Weller & Budson, 2018). In the aging brain, inflammatory mediators such as IL-1β and IL-6 increase, while anti-inflammatory mediators such as IL-10 and IL-4 decrease (Sierra, Gottfried-Blackmore, McEwen, & Bulloch, 2007; Xie, Morgan, Rozovsky, & Finch, 2003). In AD, IL-1β activates the MAPK-p38 signaling cascade and stimulates β-secretase (BACE-1) to initiate proteolytic cleavage of APP, leading to the production of Aβ peptides. These peptides form β-amyloid protein fragments that rapidly aggregate, creating more extensive deposits known as amyloid plaques. Continuous secretion of IL-1β by overactivated microglia and astrocytes induces tau protein phosphorylation and neurofibrillary tangles (NFTs) via the MAPK-p38 pathway. The activated MAPK pathway also mediates the transduction of signals responsible for the ongoing production of proinflammatory cytokines by activated microglia and astrocytes. Chronic secretion and overexpression of IL-1β drive the transformation of amyloid plaque deposits, accelerate progression to advanced stages of AD, and contribute to neuronal degeneration across cerebral cortex regions, leading to further cognitive impairment (Pasqualetti et al., 2015). Furthermore, IL-1β may also amplify neuroinflammation through activation of the NF-kB pathway. Increased IL-1 levels adversely affect hippocampal-dependent memory consolidation processes (Avital et al., 2003; Deak, 2007; Grau et al., 2006; McAfoose & Baune, 2009). In addition, increased levels of IL-1β and TNF-α were observed in LPS-induced activated microglia and in mice with learning and memory deficits (Tanaka et al., 2011).

Another interpretation of the increased inflammatory profile in the aging brain is due to sensitized or primed microglia (DiSabato et al., 2016). These altered microglia phenotypes with age and increased inflammatory mediators have contributed to a high inflammation profile in the aging brain. Uncontrolled activated microglia lead to neurotoxicity by secreting proinflammatory cytokines that disrupt the beneficial neuron-microglia interaction, glutamate, and reactive oxygen species. Hence, there is a rapid progression to cognitive impairment (Mizuno, 2015; Pasqualetti et al., 2015; Sawikr et al., 2017).

In AD, Aβ is also involved in activating microglia and astrocytes, thereby indirectly elevating the levels of inflammatory cytokines such as IL-6, IL-1β, and TNF-α (Agostinho, A Cunha, & Oliveira, 2010; Barger & Harmon, 1997; Ortiz et al., 2017; Pasqualetti et al., 2015; Solleiro-Villavicencio & Rivas-Arancibia, 2018). Aβ has been shown to decrease the uptake of glutamate, the neurotransmitter released during neuroinflammation under physiological conditions. Glutamate is primarily taken up by astrocytes to be converted into glutamine and then recycled back into neurons. Excessive activation of neurons due to prolonged exposure to glutamate has increased oxidative stress, mitochondrial damage, and more microglia via the MAPK pathway (Folch et al., 2018; Mizuno, 2015; Sawikr et al., 2017). Activated microglia will continuously produce proinflammatory mediators (IL-1, IL-6, CCL2, and CCL3) that induce chronic neuroinflammation, contributing to the rapid progression of AD (Sawikr et al., 2017). In the later stages of AD, tau becomes hyperphosphorylated and appears as paired helical filaments, dystrophic neurites, and NFTs (Sawikr et al., 2017). Physiologically, tau stabilizes the growing axons and is an essential contributor to the

development and growth of neurites. Hyperphosphorylated tau protein is evidence of the loss of axonal integrity and neuronal connectivity in AD (Sawikr et al., 2017; Vauzour, 2014).

Progression of cognitive decline and dementia is commonly associated with elevated oxidative stress. The nervous system, primarily the brain, is susceptible to alterations in the redox state due to its lack of an effective mechanism to remove excess pro-oxidants in the environment (Liu et al., 2018). Studies on human and experimental models have reported increased oxidative stress and neuroinflammation in the aging brain, which is highly associated with dementia (DiSabato et al., 2016; Sierra et al., 2007; Xie et al., 2003). Excess ROS in the brain will induce protein peroxidation, lipid peroxidation, and DNA damage in post-mitotic cells such as neurons and glial cells, leading to neuronal cell death (Ortiz et al., 2017; Solleiro-Villavicencio & Rivas-Arancibia, 2018; Suganthy, Devi, Nabavi, Braidy, & Nabavi, 2016). In addition, aging enhances ROS-mediated neuronal damage due to a decline in the antioxidant system in the brain. Brain tissue is susceptible to oxidative stress and has a low antioxidant capacity; therefore, it is prone to damage from neurotoxic peptides such as β-amyloid and neuroinflammation (Dominguez & Barbagallo, 2019). Moreover, Aβ peptide, the precursor of β-amyloid, is highly associated with increased oxidative stress in AD (Ortiz et al., 2017; Pasqualetti et al., 2015; Solleiro-Villavicencio & Rivas-Arancibia, 2018). It has been identified that the acute and chronic application of β-amyloid fragments into cerebral cortex cell cultures and the processes of tau protein glycation in paired helical filaments induce oxidative stress (Ortiz et al., 2017). Fragments 1-40 and 1-42 of β-amyloid can generate hydrogen peroxide via reduced Fe3+ or Cu2+ through a Fenton reaction (Ortiz et al., 2017). Oxidative stress under this condition may cause an insufficient body antioxidant response to restore redox homeostasis.

Thus, generating a new equilibrium level and altering gene expression patterns by stimulating ROS and RNS-sensitive regulatory transcription factors leads to several intracellular pathways and increased microglial activation (Farooqui, 2014; Ortiz et al., 2017; Solleiro-Villavicencio & Rivas-Arancibia, 2018). ROS and RNS-sensitive transcription factors include nuclear factor E2-related factor (Nrf2), activator protein 1 (AP1), NF-κB, HIF-1α, p53, and MAP kinase (Ortiz et al., 2017; Solleiro-Villavicencio & Rivas-Arancibia, 2018). These transcription factors activate signaling cascades that induce further secretion of proinflammatory cytokines and microglia, further exacerbating the progression to cognitive decline (Sawikr et al., 2017). These factors also lead to inadequate antioxidant responses that cannot balance the excessive ROS in the environment (Ortiz et al., 2017). Hence, uncontrolled oxidative stress results in mitochondrial dysfunction, inflammation, endoplasmic reticulum stress, and disrupted neuronal activity. These factors synergistically induce cell apoptosis and decrease synaptic plasticity, leading to cognitive impairment (Xu, Yang, & Chen, 2020). Apart from scavenging free radicals directly, oxidative stress can be regulated by inhibiting its signaling pathway and altering gene expression. Nuclear factor erythroid 2-related factor 2 (Nrf2) is mainly expressed in microglia, astrocytes, and neurons to regulate the cellular redox state (Pradeep, Yenisetti, Rajini, & Muralidhara, 2019; Saleh, Abdelhady, Khattab, & El-Hadidy, 2020). Nrf2 expression induces heme oxygenase-1 (HO-1) and increases antioxidant enzymes such as superoxide dismutase (SOD), glutathione (GSH), and glutathione S-transferase (GST). Meanwhile, activation of NF-kB, AP-1, and STAT1 induces oxidative stress (Kim, Lee, & Lee, 2014).

3. NUTRACEUTICALS

Nutraceutical is a term that combines the words 'nutrition' and 'pharmaceutics.' It refers to a bioactive compound known to improve health, delay the aging process, prevent chronic diseases, increase life expectancy, and support the structure or function of the body, especially the brain. Nutraceuticals include phytochemicals, dietary supplements, functional foods, medical foods, and specific dietary patterns (Singh, Sivanandam, Konar, & Thakur, 2021). Based on chemical constituents, nutraceuticals may be categorized as polyphenols (flavonoids; flavonols, flavones, isoflavones, and anthocyanins, and non-flavonoids; curcumin, resveratrol), isoprenoid derivatives (saponins, carotenoids, terpenoids, coumarins, tannins, and lignin), carbohydrate derivatives, polyunsaturated fatty acids (PUFA), vitamins, spices, and microbes (probiotics and prebiotics) (Das, Bhaumik, Raychaudhuri, & Chakraborty, 2012; Singh et al.,

2021). These products' consumption is generally without medical prescription or supervision by health practitioners. The frequency of nutraceutical use in developed countries is approximately 50-70%, with an increase in use with age (Télessy, 2019).

The importance of nutraceuticals has begun to gain recognition globally, and it is still developing in terms of scientific research, legal aspects, marketing strategies, and improved quality of life (Nasri, Baradaran, Shirzad, & Rafieian-Kopaei, 2014). Emerging evidence reports the effectiveness of nutraceuticals in pathological conditions such as diabetes, atherosclerosis, cardiovascular disease, cancer, and neurological disorders (Das et al., 2012; Nasri et al., 2014). Nowadays, there is a rising interest in the role of nutraceuticals in the modulation of neuroinflammation that may mitigate cognitive decline in age-related diseases, including dementia (Singh et al., 2021). Numerous studies have demonstrated the potential of nutraceuticals in regulating neuroinflammation through several mechanisms: oxidative stress, regulation of inflammatory mediators, and glial cell activation (Banerjee, Dutta, Ghosh, & Sil, 2021; Chiu, Venkatakrishnan, & Wang, 2020; Das et al., 2012; Singh et al., 2021). Table 1 summarizes the nutraceutical classes and their mechanism in regulating neuroinflammation.

3.1. Vitamins

Vitamin C (or ascorbic acid) and vitamin E (α-tocopherol) are known antioxidant vitamins commonly found in fruits and vegetables. Vitamin C is water-soluble, primarily in the aqueous phase (Banerjee et al., 2021; Saleh et al., 2020). It protects cell components by efficiently scavenging reactive oxygen and nitrogen species. For example, it eliminates hydroxyl radicals, alkoxyl radicals, hydrogen peroxide, and singlet oxygen in the aqueous phase (Saleh et al., 2020). Although it primarily acts as a protection in the aqueous phase, it can also contribute to the protection of membrane lipids by promoting the generation of vitamin E (tocopherols) (Banerjee et al., 2021; Saleh et al., 2020). Mitochondrial dysfunction in AD is one of the conditions resulting from the accumulation of ROS. Supplementation of vitamin C reduced mitochondrial dysfunction in 5XFAD mice (an AD model) (Banerjee et al., 2021; Kook et al., 2014). It was also found to inhibit the accumulation of astrocytes at a high dose and reduce neuroinflammation in a knockout mouse model that cannot produce endogenous vitamin C (Kook et al., 2014). It was demonstrated by a significant reduction in the immunoreactivity of the reactive astrocyte marker protein (GFAP) in the cortex of high-dose vitamin C-treated KO-Tg mice (Kook et al., 2014).

Loss of one hydrogen atom from ascorbic acid results in the formation of ascorbate. In the brains of mice with APP/PSEN1 and SVTC2 +/- mutations, the level of endogenous ascorbate is low, leading to increased production of mitochondrial reactive oxygen species (ROS). Administration of ascorbate to isolated mitochondria demonstrated reduced ROS production and increased oxygen consumption (Dixit, Fessel, & Harrison, 2017). Besides, ascorbic acid may promote the generation of vitamin E (α-tocopherols) by recycling the α-tocopheroxyl radicals (precursors of α-tocopherols) (Banerjee et al., 2021; Saleh et al., 2020). Meanwhile, vitamin C prevents cognitive impairment caused by ROS-induced neuronal dysfunction by reducing mitochondrial damage, inhibiting astrocyte accumulation, and attenuating neuroinflammation.

Vitamin E, or α-tocopherols, is a lipid-soluble antioxidant that donates hydrogen to alkyl or alkyl peroxyl radicals, resulting in tocopherol radicals in the reaction (Banerjee et al., 2021; Dominguez & Barbagallo, 2019; Singh et al., 2021). The oxidized tocopherols (tocopherol radicals) can be diminished by ascorbic acid. A Canadian study on health and aging reported a significantly decreased rate of cognitive decline in co-supplementation of vitamin C and E among 894 participants aged ≥65 (Dominguez & Barbagallo, 2019).

3.2. Flavonoids

Polyphenols form a large group of phytochemicals derived from plants' secondary metabolites. Approximately 8,000 different polyphenols are present, and the leading group is flavonoids, which include flavanols, flavones, isoflavones, flavanones, and anthocyanins (Das et al., 2012). Flavonoids can be found in the daily human diet, including

cocoa, green tea, grapes, apples, broccoli, celery, parsley, soy, citrus, tomatoes, berries, red wine, and *Camellia sinensis* tea. Flavonoids show potent neuroprotective properties through their antioxidant and anti-inflammatory activities. Flavonoids' primary and prominent characteristic is their potent antioxidant ability, either by directly scavenging free radicals or by directly regulating oxidative stress-mediated enzyme activity (Akinmoladun, Farombi, & Farombi, 2019; Kim et al., 2014). Some flavonoids lowered the activity of pro-oxidant enzymes while increasing the activity and expression of antioxidant enzymes via activation of antioxidant-gene encoding pathways such as Nrf2 (Kim et al., 2014; Muralidhara, 2015).

Walnuts exhibit excellent antioxidant efficacy due to their high phenolic content (flavonoids), followed by almonds, cashew nuts, and raisins (Chauhan & Chauhan, 2020; Muthaiyah et al., 2014; Rusu et al., 2019). Fifty grams (50g) of walnuts have been shown to contain higher phenolic content than an 8-ounce glass of apple juice or a 5-ounce glass of red wine. Consuming one ounce (6%) or 1.5 ounces (9%) of walnuts significantly reduced reactive oxygen species (ROS) levels and lipid peroxidation, while improving antioxidant enzyme activities in AD-Tg mice compared to the control group (non-supplemented AD-Tg mice) (Muthaiyah et al., 2014; Rusu et al., 2019). Besides, *Ginkgo biloba*, composed of flavonoids and terpenoids as the most active compounds, is also a potent antioxidant (Ekici-Günay, 2020; Howes, 2018). It protects vascular endothelial cells from oxidative damage by enhancing the Nrf2 signaling pathway and neutralizing free radicals (Ekici-Günay, 2020). Meanwhile, its anti-inflammatory properties are mediated by suppressing the COX/PEG2 pathway in LPS-induced microglial activation cells (Ekici-Günay, 2020; Vauzour, 2014).

Quercetin, one of the most studied flavonoids, is found in many plants, including onions, cocoa, tea, vegetables, and fruits (Howes, 2018; Omar, 2017). Quercetin exerts anti-inflammatory properties by attenuating the phosphorylation of transcription factors and the activity of kinases involved in neuroinflammation (Akinmoladun et al., 2019). Quercetin was also reported to suppress NO production and the overexpression of iNOS, thereby preventing inflammation mediated by 6-hydroxydopamine (6-OHDA) toxicity in PC12 cells and zebrafish models. Additionally, it was reported to downregulate iNOS expression and inhibit LPS-induced inflammation in BV-2 microglial cells (Suganthy et al., 2016). Consumption of beverages rich in green tea leaves and apple extracts for eight months showed reduced serum levels of proinflammatory IF-γ and TNF-α in the initial stage of AD (Sawikr et al., 2017).

In vitro studies have reported that quercetin increases cell resistance to oxidative stress, including H_2O_2, hydroperoxide, and neurotoxic molecules (Shokoohinia, Rashidi, Hosseinzadeh, & Jelodarian, 2015). Despite its direct antioxidant activity, quercetin also combats oxidative stress by attenuating pro-oxidant enzymes such as NOS. It also counteracts oxidative stress by activating Nrf2, enhancing the expression of γ-glutamyl-cysteine synthetase (GCS), the key enzyme in synthesizing cellular GSH (Shokoohinia et al., 2015; Suganthy et al., 2016). Besides, quercetin increased the expression of prostaglandin-endoperoxide synthase 2 (PTGS2) at both mRNA and protein levels in macrophages, neurons, and glial cells (Boesch-Saadatmandi et al., 2009; Suganthy et al., 2016). These contributed to improving the antioxidant system that can balance excess ROS in the environment, preventing neuronal damage induced by oxidative stress that can lead to cognitive impairment.

Anthocyanins (ANT) are polyphenol compounds that are rich in blueberries. These blueberry polyphenols are common in the mountain brushwood of the Northern Hemisphere; however, they are now widely distributed worldwide. Anthocyanins exhibit anti-inflammatory properties by inactivating microglia via suppression of signaling pathways. In vitro studies have shown that suppression of the p44/42 mitogen-activated protein kinase (MAPK) signaling pathway mediates the inactivation of microglia in mice (Carvalho et al., 2015; Giacalone et al., 2015). Additionally, microglia cells stimulated by LPS and pre-treated with blueberry anthocyanins have shown reduced production of proinflammatory mediators, including TNF-α, IL-1β, and ROS (NO), as well as lower NOS and COX expression. These activities are mediated by the suppression of the NF-kB pathway (Carvalho et al., 2015). Supplementation of blueberry anthocyanins in adults aged 40 to 74 for over three weeks has significantly decreased

plasma concentrations of NF-kB-mediated pro-inflammatory cytokines and chemokines such as IL-4, IL-13, IL-9, and TNF-α (Flanagan, Müller, Hornberger, & Vauzour, 2018).

In addition, the administration of anthocyanins (200 mg/kg BW, i.p. for 7 days) and cyanidin-rich berries and cherries mitigates memory deficits in the scopolamine-induced amnesic mouse model (Singh et al., 2021). Higher intake of blueberries and strawberries, which contain anthocyanins, is correlated with slower rates of cognitive decline in non-demented adults aged 70 and older (Vauzour, 2014). ANT is an efficacious scavenger that acts on ROS and RNS and restores ATP levels in energy-depleted models. Recently, studies found that ANT may promote the myelination of neurons in an in vitro mouse model of the peripheral nervous system (Stettner et al., 2013). An in vivo study was conducted to verify the benefits of anthocyanins in combating oxidative stress by administering ANT extracts from grape skin into three-month-old male Wistar rats. The antioxidant activity was assessed by reducing the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical. The results showed that ANT at 30 and 100μg/ml concentrations could suppress oxidative/nitrosative damages with an EC50 value of 24 μg/ml (Carvalho et al., 2015).

Flavanols in plants may appear as monomers (catechin and epicatechin), oligomers (proanthocyanidins), or polymers (decamers) and have been found to exhibit neuroprotective effects via modulation of neuroinflammation. Catechins are prominent in the tea plant (*Camellia sinensis*) and grape (*Vitis vinifera*). Catechins exhibit antioxidant properties due to the hydroxyl group at the ortho-position in the B-ring, contributing to direct radical scavenging activity (Omar, 2017). Meanwhile, the most abundant form of catechin, epigallocatechin-3-gallate (EGCG), exhibited a neuroprotective effect through its anti-amyloidogenic property by inhibiting Aβ1-42 amyloid fibril aggregation and suppressing Aβ-induced NF-kB activation that leads to microglial activation (Chiu et al., 2020; Jin et al., 2019; Omar, 2017; Rusu et al., 2019). Pre-treatment with 20 mg/kg (p.o.) catechins in male Wistar rats for 21 days suppressed the activation of NF-kB and redox imbalance (Ashafaq et al., 2012). The catechin-rich grape seed extract also reduced cognitive decline associated with decreased concentrations of Aβ oligomers (Chiu et al., 2020; Rusu et al., 2019; Vauzour, 2014). Besides, catechin, which is abundant in green tea, *Camellia sinensis*, and coffee, has been reported to inhibit amyloid fibril aggregation (Aβ40 and Aβ42), with IC50 values ranging from 2.9 μM to 5.3 μM (Omar, 2017). *In vivo* studies demonstrated that catechins (ranging from 10-200 mg/kg) reversed memory deficits in a dose-dependent manner (Cheruku et al., 2018).

Tannic Acid (TA), a naturally occurring flavonoid, is derived from various herbaceous and woody plants. Several studies have demonstrated the neuroprotective effects of TA by inhibiting Aβ fibrillization and reducing the expression of proinflammatory cytokines (Mori et al., 2012; Mori & Town, 2015). Oral administration of TA for six months demonstrated a significant reduction in amyloid deposits in the brains of PSAPP mice compared to the control group (Mori & Town, 2015). The decrease in plaque size may occur due to the direct inhibition of BACE-1 (β-secretase) cleavage of APP (Mori et al., 2012; Mori & Town, 2015).

3.3. Non-Flavonoids

Curcumin is a polyphenolic compound mainly obtained from turmeric (Curcuma longa L.). It is an herb widely used as a spice and additive in food, especially in tropical and subtropical countries (Banerjee et al., 2021; Chiu et al., 2020; Dominguez & Barbagallo, 2019; Howes, 2018). Curcumin exhibits a potent neuroprotective effect by improving antioxidant status and possesses anti-inflammatory properties through various mechanisms. Numerous animal models have demonstrated accelerated or normal aging, dementia, and cognitive decline, highlighting the beneficial effects of curcumin (Dominguez & Barbagallo, 2019; Javeri & Chand, 2016; Pradeep et al., 2019; Singh et al., 2021). The anti-inflammatory property of curcumin has been reported through the activation of peroxisome proliferator-activated receptor gamma (PPARγ), which hinders the production of proinflammatory cytokines and attenuates Aβ-induced neuroinflammation in AD rats (Javeri & Chand, 2016; Omar, 2017; Pradeep et al., 2019; Sawikr et al., 2017). Activation of PPARγ inhibits iNOS expression by antagonizing the activities of AP-1 and NF-κB (Kim et al., 2014; Pradeep et al., 2019). Curcumin inhibits nuclear factor-kappa B (NF-kB) activation by suppressing the

phosphorylation of inhibitory factor I-kB kinase, thereby disrupting cytokine expression (Chiu et al., 2020; Javeri & Chand, 2016; Noguchi-Shinohara, Hamaguchi, & Yamada, 2019; Pradeep et al., 2019). Curcumin can also reduce the synthesis of proinflammatory mediators such as TNF-α and interleukins and decrease the induction of iNOS and COX-2 (inflammatory enzyme systems) (Javeri & Chand, 2016; Pradeep et al., 2019). Studies have shown that incorporating curcumin has notably mitigated the mRNA and protein levels of IL-1β and iNOS expression in mice, suggesting noticeable improvements in cortical brain structure that may contribute to dementia (Pradeep et al., 2019).

Furthermore, curcumin modulates neuroinflammation by suppressing the production of prostaglandins. It inhibits the phosphorylation of cytosolic phospholipase A2 (PLA2), which is responsible for producing arachidonic acid, the precursor of prostaglandins (Kook et al., 2014; Singh et al., 2021). PLA2 is incorporated with COXs and LOXs in the cells; therefore, inhibiting PLA2 will reduce the expression of COXs and LOXs as well as inflammation (Suganthy et al., 2016).

Moreover, curcumin inhibited the formation of Aβ fibrils from Aβ140 to Aβ42 and destabilized preformed Aβ fibrils. It was reported to prevent the aggregation of Aβ40, disassemble fibrils, and reduce toxicity (Noguchi-Shinohara et al., 2019). Administration of curcumin reduced the astrocytic marker glial fibrillary acidic protein level, insoluble and soluble Aβ, and plaque burden in aged Tg mice (Javeri & Chand, 2016; Noguchi-Shinohara et al., 2019). These studies suggest that the mechanism of action of curcumin involves binding to small Aβ peptides, thereby preventing aggregation and the formation of amyloid plaques.

Curcumin also attenuates neuroinflammation by acting on oxidative stress. Curcumin scavenges free radicals by losing protons from its phenolic OH group, resulting in phenoxyl diradicals, which stabilize through the delocalization of electrons (Banerjee et al., 2021; Howes, 2018; Noguchi-Shinohara et al., 2019). Pre-treatment with 10 μg/mL curcumin for 1 hour attenuates oxidative stress, Aβ-induced damage, and tau hyperphosphorylation in PC12 cells (Noguchi-Shinohara et al., 2019). It also alleviates peroxynitrite-mediated nitrosative stress and mitochondrial dysfunction *in vitro* (Noguchi-Shinohara et al., 2019).

Another well-known non-flavonoid phytochemical that exists in nature is resveratrol. Resveratrol is a polyphenolic compound found in grapes, jackfruit, mulberry, and red wine (Chiu et al., 2020; Dominguez & Barbagallo, 2019). Resveratrol attenuates neuroinflammation by regulating NF-kB and JNK/MAPK signaling pathways (Chiu et al., 2020). Twelve-week oral administration of resveratrol (50 mg/kg/day) prevented cognitive decline, including spatial and memory deficits, in aged male Wistar rats by inhibiting neuroinflammatory signaling molecules (Singh et al., 2021). Resveratrol also prevented Aβ1-42-mediated neuroinflammation by reducing the expression of NF-kB and enhancing BBB integrity in rats with AD (Omar, 2017; Sawikr et al., 2017). A study using optical and superparamagnetic iron oxide nanoparticles (SPION) with enhanced MRI imaging has shown reduced plaque formation and microglial activation by trans-resveratrol in AβPP/PS-1 Tg mice (Solberg et al., 2014; Venigalla, Sonego, Gyengesi, Sharman, & Münch, 2016). Resveratrol enhances the antioxidant system by upregulating GSH levels, which scavenge ROS and activate the redox-sensitive transcription factor Nrf2/HO-1 to combat oxidative stress, such as H_2O_2 (Banerjee et al., 2021; Chiu et al., 2020).

3.4. Carotenoids

Carotenoids are naturally occurring lipid-soluble compounds found in yellow, orange, or red vegetables and fruits (Saleh et al., 2020; Singh et al., 2021). Carotenoids, such as β-carotene and lycopene, are characterized by simple polyene hydrocarbons, whereas xanthophylls, such as lutein, contain oxygenated groups (hydroxy, oxo, or epoxy) in their structures (Saleh et al., 2020). Oxygenated groups contribute to antioxidant properties as they can scavenge radicals by donating two electrons at a separate, distinct potential. Lutein is involved in brain function, and a low level of lutein has been associated with the severity of dementia (Muthaiyah et al., 2014). Lutein suppresses oxidative stress directly or indirectly by activating the Nrf2/ARE signaling pathway (Rusu et al., 2019). Lycopene is a carotenoid type commonly found in tomatoes, red-colored fruits, guava, grapefruit, watermelon, and papaya (Paul et

al., 2020). Lycopene can cross the blood-brain barrier (BBB) and respond to oxidative stress to modulate neuroinflammation (Paul et al., 2020; Prakash & Kumar, 2013). Lycopene enhances antioxidant status by increasing the levels of antioxidant enzymes and their markers in specific brain regions in LPS-stimulated models (Qu et al., 2011). Pre-treatment with lycopene lowered the ROS level and improved neuronal cell survival under neurotoxic conditions (Qu et al., 2011). Another study demonstrated the effectiveness of lycopene in reducing oxidative stress by decreasing oxidative markers such as malondialdehyde and nitrite concentration, and by restoring SOD levels (Prakash & Kumar, 2014). Lycopene exhibits anti-inflammatory properties by downregulating nitric oxide (NO) production and increasing brain-derived neurotrophic factor (BDNF) levels (Paul et al., 2020). Increased BDNF levels effectively protect neurons against proinflammatory cytokines and oxidative damage.

3.5. Polyunsaturated Fatty Acids (PUFA)

PUFA subtypes include omega-3 (n-3) fatty acids and omega-6 (n-6) fatty acids. Omega-3 fatty acids, which encompass alpha-linolenic acid (ALA) and derivatives such as eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA), are primarily found in fish, salmon, eggs, seafood, sunflower oil, and soybean oil. Omega-3 fatty acids help protect the brain from neuroinflammation by inactivating microglia and astrocytes through the JNK and PPAR-γ signaling pathways (Chiu et al., 2020; Mallick, Basak, & Duttaroy, 2019; Sun et al., 2018). Besides, it also mitigates amyloid β plaque by enhancing α-β-42 phagocytosis (Chiu et al., 2020; Kerdiles, Layé, & Calon, 2017). This indirectly attenuates proinflammatory mediators such as IL-1β and consequently inhibits the continuous activation of microglia and astrocytes (Mallick et al., 2019; Sawikr et al., 2017; Sun et al., 2018). Using a randomized, double-blind, placebo-controlled trial, the supplementation of fish oil (which is abundant in DHA) improved working memory in patients with mild cognitive impairment (MCI) (Lee, Shahar, Chin, & Yusoff, 2013). Besides, the omega-3-FA series showed potential anti-inflammatory properties by inhibiting the signaling pathways of proinflammatory mediators (Mallick et al., 2019; Muthaiyah et al., 2014; Ren & Chung, 2007; Sun et al., 2018). Rich in ALA, walnuts exhibit a highly potent anti-inflammatory property (Chauhan & Chauhan, 2020). Studies have shown that ALA downregulates iNOS (which inhibits NO production), COX-2, and inflammatory cytokines (IL-6, IL-1β, TNF-α) via inhibition of NF-kB in LPS-induced macrophages (Chauhan & Chauhan, 2020; Ren & Chung, 2007). The supplementation of walnuts improves cognitive, motor performance, and anxiety-related behavior in APP-transgenic mice and aged rats (Muthaiyah et al., 2014; Ren & Chung, 2007).

The omega-6 fatty acid series includes linoleic acid (LA), gamma-linolenic acid (GLA), and arachidonic acid (ARA). LA, the precursor of ARA, is primarily found in vegetable oils such as corn, safflower, soybean, and sunflower oils (Télessy, 2019). Meanwhile, GLA, commonly found in plant seed oils such as evening primrose, borage, black currant, and hemp, can scavenge reactive oxygen species (ROS), improve Aβ25-35-induced memory impairment in rats, and attenuate oxidative damage in hippocampal tissue (Youn, Lee, & Jun, 2018). GLA treatment also inhibits the production of NO and PGE in a dose-dependent manner via suppression of iNOS and COX expression (Youn et al., 2018).

3.6. Probiotics

A probiotic is a live microbial supplement that is administered in an adequate amount to provide health benefits to consumers (Das et al., 2012). Probiotic properties should be non-pathogenic, non-toxic, resistant to gastric acid, genetically stable, strongly adherent to the gut lining, and capable of producing antibacterial substances (Das et al., 2012; Pandey, Naik, & Vakil, 2015). Probiotics generally derive from the genera Lactobacillus, Bifidobacterium, and Enterococcus, which are gram-positive cocci, as well as bifidobacteria. They may consist of a single strain or a combination of a few strains. Probiotics involved in anti-dementia properties include *L. helveticus*, *L. pentosus*, and *Saccharomyces cerevisiae*.

Saccharomyces cerevisiae modulates neuroinflammation in AD by inhibiting the proteolysis of APP into Aβ peptide (precursor of β-amyloid protein). It exhibits strong BACE-1 inhibitory activity compared to other bacteria and yeast species (Lim et al., 2015). β-secretase, known as BACE-1, is the primary enzyme responsible for cleaving APP, followed by γ-secretase, which performs sequential cleavage into the Aβ peptide. Inhibition of BACE-1 offers potential evidence for the attenuation of Alzheimer's disease symptoms in patients. Additionally, an *in-vitro* study demonstrated that treatment with *L. helveticus* IDCC3801 fermented milk attenuated memory decline in mice and reduced APP levels in both cells and rat serum (Yeon et al., 2010).

4. CONCLUSION AND FUTURE PERSPECTIVE

Neuroinflammation plays a crucial role in the pathogenesis and progression of dementia. Since there is still no cure for dementia, there is a pressing need to identify dietary factors that can modulate inflammation and prevent or slow its progression. Healthy diets rich in vitamins, curcumin, and carotenoids, such as those found in pigmented fruits and vegetables, have shown promising neuroprotective activity by improving cognitive function due to their anti-inflammatory and antioxidant properties. Additionally, flavonoids, non-flavonoids, and PUFAs, abundant in berries, turmeric, and vegetable oils, enhance anti-inflammatory effects. From these reviews, we can conclude that nutraceuticals exert various mechanisms to attenuate neuroinflammation. These involve modulation of proinflammatory release and signaling cascades, attenuation of activated microglia/astrocytes, or reduction of oxidative damage.

However, a comprehensive study is necessary, including well-conducted comparative analyses of RCTs and *in-vitro* human and animal models. Since naturally occurring nutrients coexist with other phytochemicals, only a few studies have examined the effects of the mixture and combination of two separate phytochemicals on the onset of neuroinflammation. Additionally, there is a lack of research on the pharmacological properties of nutraceuticals, particularly when substances exhibit low bioavailability and a short half-life. These factors may influence the efficacy of nutraceuticals and pose challenges in progressing through clinical trials before they are officially introduced to consumers. Overall, this review provides evidence of the neuroprotective effects of certain dietary compounds, which can assist individuals in selecting more effective nutraceuticals that may help delay cognitive decline and the onset of dementia.

Table 1. Summary of the classes of nutraceuticals and their mechanisms in regulating neuroinflammation.

Nutraceuticals	Sources	Neuroprotective effects/anti-inflammatory actions	References
Vitamins	Vitamin C: Citrus fruits, kiwi, vegetables, strawberries, spinach, broccoli, red pepper, and Brussels sprouts. Vitamin E: Vegetable oils, broccoli, almonds, nuts.	i. Scavenges reactive oxygen species (hydroperoxide, alkoxyl, hydroxyl radicals). ii. Generation of tocopherols (Vitamin E) iii. Reduced mitochondrial dysfunction, modulated neuroinflammation, and decreased astrocyte marker protein (GFAP).	(Chiu et al., 2020; Dixit et al., 2017; Kook et al., 2014; Saleh et al., 2020)
Flavonoid polyphenol (Quercetin, anthocyanins, catechins, tannic acid)	Quercetin: onions, cocoa, tea, vegetables, and fruits such as apples. Anthocyanins: blueberries, blackberries, cherries Catechins: tea plant (*Camellia sinensis*) and grape (*Vitis vinifera*). Tannic acid: derived from various herbaceous and woody plants.	iv. Reduced ROS production, increased oxygen consumption v. Protects the membrane from oxidative damage and maintains cell viability. vi. Scavenges free radicals in the lipid phase. i. Modulates proinflammatory cytokines release and gene expression. ii. Inhibit NF-kB and AP-1 signaling cascades iii. Upregulates antioxidant systems by activating Nrf2/HO-1 and PI3K/Akt. iv. Exhibit anti-amyloidogenic properties that prevent Aβ-induced activation of microglia. v. Suppress α- synucleinopathies formation	(Akinmoladun et al., 2019; Chauhan & Chauhan, 2020; Cheruku et al., 2018; Ekici-Günay, 2020; Howes, 2018; Mori et al., 2012; Muralidhara, 2015; Muthaiyah et al., 2014; Rusu et al., 2019; Saleh et al., 2020; Shokoohinia et al., 2015; Stettner et al., 2013; Suganthy et al., 2016; Vauzour, 2014)
Non-flavonoid polyphenol (Curcumin and resveratrol)	Curcumin: Turmeric Resveratrol: Grape, jackfruit, mulberry, red wine	i. Enhances Nrf2/HO-1 signaling pathway ii. Scavenges reactive species and combats oxidative stress iii. Inhibit transcription factors and signaling cascades (NF-kB, JNK, ERK, MAPK). iv. Blocking prostaglandin production via inhibition of the PLA2 pathway v. Enhances phagocytosis, clearance of Aβ fibrils, and attenuates Aβ-induced neuroinflammation. vi. Ameliorate oxidative stress, elevated intracellular calcium, and tau hyperphosphorylation.	(Howes, 2018; Javeri & Chand, 2016; Noguchi-Shinohara et al., 2019; Pradeep et al., 2019; Saleh et al., 2020; Sawikr et al., 2017; Solberg et al., 2014; Venigalla et al., 2016)

Table 1. Cont.

Nutraceuticals	Sources	Neuroprotective effects/anti-inflammatory actions	References
Carotenoids (Lutein, lycopene, β- β-carotene)	Pigmented fruits (red, yellow, orange, green leaves)	i. Improve cognitive function ii. Scavenges free radicals by donating electrons iii. Activates Nrf2/ARE signaling pathway, improves antioxidant system iv. Improves brain function and reduces dementia progression v. Modulates proinflammatory cytokines expression and their release vi. Increase BDNF level	(Mohn & Johnson, 2017; Paul et al., 2020; Prakash & Kumar, 2013, 2014; Qu et al., 2011)
PUFA (Omega-3 and omega-6 series)	Omega-3 series: Fish, salmon, eggs, seafood, and vegetable oils such as corn, safflower, soybean, andsunflower Omega-6 series: Seed oils of evening primrose, borage, blackcurrant, and hemp	i. Inactivates microglia/Astrocytes via JNK and PPAR-γ signaling pathway ii. Improved working memory, immediate verbal memory, and spatial movements iii. Enhanced memory, learning skills, motor development, and anxiety-related behavior. iv. Attenuates neuroinflammation induced by the β-amyloid burden. v. Downregulating iNOS and COX expression. vi. Reduces the release of proinflammatory cytokines and gene expression.	(Banerjee et al., 2021; Dominguez & Barbagallo, 2019; Kerdiles et al., 2017; Lee et al., 2013; Sun et al., 2018; Willis, Shukitt-Hale, Cheng, & Joseph, 2008)
Probiotics	*L.helveticus* IDCC3801 fermented milk	i. Decreased APPβ level. ii. Inhibit BACE-1 and Aβ peptide production	(Kesika, Suganthy, Sivamaruthi, & Chaiyasut, 2021; Lim et al., 2015; Yeon et al., 2010)

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